CSA847998
Organizacion y Digitalizacion CSA Ltda

PCT

Industria y Comercio

SUPERINTENDENCIA

10-10473

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: DERIVADOS BICICLICOS HETEROCICLICOS O ESPIROBICICLICOS HETEROCICLICOS ENLAZADOS, DE PIRAZOLO[1,5-A]PIRIMIDINAS, PROCEDIMIENTOS PARA SU PREPARACIÓN Y USOS DE LOS MISMOS

SOLICITANTE: WYETH LLC

DIRECCIÓN: Five Giralda Farms Madison, NJ 07940 E.U.A.

APODERADO: CARLOS R. OLARTE

BOGOTÁ 24 de Agosto de 2010

P2010/000120

29-09-2010

OLARTERAISBECK

OLARTE RAISBECK MOURE & CASTRO LTDA

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-104173- -00000-0000

Fecha: 2010-08-24 16:42:33 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 218

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2010/000120**

SOLICITUD DE:

(1)

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

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: WYETH LLC
Dirección Five Giralda Farms Madison, NJ 07940 E.U.A.
Nacionalidad o Domicilio: Estadounidense
Lugar de Constitución: Estados Unidos
Teléfono: **Fax:**
E-mail:

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

REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE
Dirección: Diagonal 34 No. 5-28
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olarteraisbeck.com

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

INVENTOR (ES) (72)

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

(5) **PCT (86)**

Solicitud Internacional No. PCT/US2009/035422 Fecha Febrero 27, 2009

Publicación Internacional No. WO 2009/108338 Fecha Septiembre 3, 2009

(6) **Título (54)** **DERIVADOS BICICLICOS HETEROCICLICOS O ESPIROBICICLICOS HETEROCICLICOS ENLAZADOS, DE PIRAZOLO[1,5-A]PIRIMIDINAS, PROCEDIMIENTOS PARA SU PREPARACIÓN Y USOS DE LOS MISMOS**

Clasificación Internacional (51) C07D 491/20, A61K 31/519, A61P 35/00

Prioridad

SI [X] **NO** [ ]

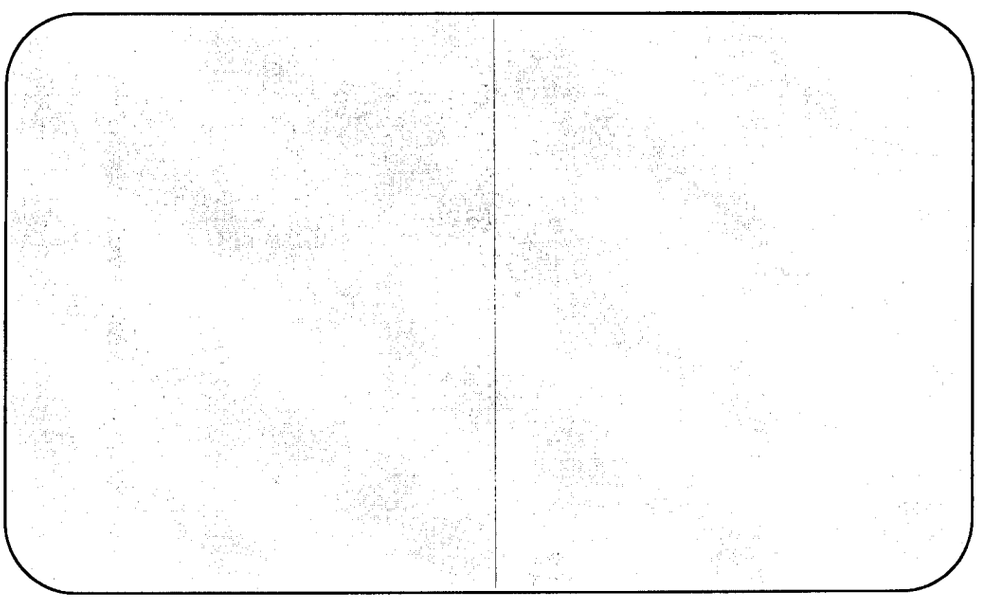
(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Febrero 29, 2008	61/067,343
US	Noviembre 21, 2008	61/116,809

(9) **Comprobante de pago No.** 10-66694 **Fecha** Agosto 12 de 2010

(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. 10-033390
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) FIGURA CARACTERÍSTICA:



(12) Solicito la concesión de la patente,

NOMBRE: CARLOS P. OLAYTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

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

LISTA DE INVENTORES

PCT/US2009/035422

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LISTA DE INVENTORES

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Nacionalidad: Estadounidense

P2012/120

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 8ov17e0e9-2

RECIBO OFICIAL DE CAJA : 10 - 66,694
FECHA : AGOSTO 12 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-104173- -00000-0000

Fecha: 2010-08-24 16:42:33 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PPRESENTACION Folios: 218

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062794387	370873101	12/08/2010	19,672,000.00

***** 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	554,000.00
		TOTAL : $	554,000.00

SON: QUINIENTOS CINCUENTA Y CUATRO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

7 700037 836803

ESCRITURA PÚBLICA NÚMERO:

CINCO MIL CIENTO UNO (5101)

FECHA DE OTORGAMIENTO:

CUATRO (4) DE JUNIO DE DOS MIL DIEZ (2010)

NOTARIA TREINTA Y OCHO (38) DEL CÍRCULO DE BOGOTA D.C.----------

CODIGO NOTARIAL 1100100038.----------

SUPERINTENDENCIA DE NOTARIADO Y REGISTRO.----------

FORMULARIO DE CALIFICACION.----------

CLASE DE ACTO: PROTOCOLIZACION DE DOCUMENTOS. ----------

PERSONAS QUE INTERVIENEN: CARLOS REINALDO OLARTE, identificado con cedula de ciudadanía numero 79,782,747 expedida en Bogotá D.C.----------

En la ciudad de Bogotá, Distrito Capital, Departamento de Cundinamarca, República de Colombia, a los CUATRO (04) días del mes de JUNIO de dos mil diez (2.010), ante mi EDUARDO DURAN GOMEZ. **NOTARIO TREINTA Y OCHO (38E) DEL CIRCULO DE BOGOTA D.C.**----------

Compareció con minuta escrita el señor **CARLOS REINALDO OLARTE,** mayor de edad, con domicilio y residencia en la ciudad de Bogotá, identificado con la cedula de ciudadanía número 79,782,747 de Bogotá D.C., de estado civil Casado, con sociedad conyugal vigente, quien manifestó su propósito de celebrar el acto que define las siguientes estipulaciones: ----------

PRIMERA.- Que presenta para su Protocolización los siguientes doçumentos:----

1º Traducción oficial de un documento que esta originalmente en ingles contenida en cuatro (4) folios utiles y es del siguiente tenor: ----------

PODER GENERAL.- WYETH LLC.- domiciliado en Five Giralda Farms Madison, NJ 07940 United States of America.- nombramos por el presente a **Carlos R. Olarte y/o J. Ian Raisbeck y/o Juan Guillermo Moure y/o Natalia Castro,** nuestros, representantes legales con facultades para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales en materia de patentes, los cuales quedan a su vez facultados para representarnos ante las autoridades de cualquier jerarquía de la República de Colombia, la República de Bolivia, la República del Ecuador, la República del Perú y la República Bolivariana de Venezuela, ya sean

administrativas, judiciales o de policia, para iniciar ante dichas autoridades todas las acciones necesarias para cumplir con el objeto indicado e intervenir en todas las instancias, grados o etapas procesales; elevar y tramitar solicitudes, declaraciones y reclamos, para demandar, reconvenir, contestar demandas y reconvenciones, formular descripciones, enmiendas, oposiciones y todo tipo de impugnaciones y escritos de cualquier naturaleza; instaurar cancelaciones y amparos administrativos; abonar todos los impuestos y cuotas y efectuar cualquier otro pago determinado por la ley; recibir todos los documentos y valores; intervenir como demandantes o demandados ante los jueces que sean competentes, pudiendo solicitar medidas cautelares de cualquier naturaleza, conciliar, transar, someter a árbitros, desistirse de la pretensión y/o el procedimiento, allanarse a la pretensión, percibir, ratificar los actos jurídicos procesales suscritos con anterioridad al otorgamiento y/o presentación del presente poder, sustituir o delegar la presentación procesal y los demás actos que exprese la ley, con todas las demás facultades que resulten necesarias; llenar cualesquiera otros requisitos y tomar, en fin, todas las medidas que creyeren conducentes al resguardo de nuestro interes.- Firma: Gregg C. Benson.- Fecha: 4 MAY 2010.- Ciudad, País: GROTON, CONNECTICUT USA.----------

CERTIFICACION NOTARIAL.- En esta fecha, May 6 2010.- el Notario Público suscrito certifica: ----------

1. Que GREGG C. BENSON mayor de edad y domiciliado en EASTERN POINT ROAD, GROTON, CONNECTICUT USA suscribó el documento que antecede.-----

2. Que el otorgante ha suscrito el referido documento en su carácter de ATTORNEY-IN-FACT de WYETH LLC.----------

3. Que WYETH LLC con sede principal ubicada en Five Giralda Farms Madison, NJ 07940 United States of America 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 está es legitima.----------

5. El fundamento de mis certificaciones contenidas en los puntos 2,3 y 4 fue la exhibición de los (del) siguiente(s) documento(s) auténticado(s): Power of Attorney executed on November 16, 2009.- NOTARY PUBLIC (Signature): (Firmado).-

Nancy M. George.- My Commission Expires 30 June 2011.- (Sellado).----------

TRADUCCION OFICIAL DE UN DOCUMENTO QUE ESTA ORIGINALMENTE EN INGLES.- Sello: "El Distrito de Columbia: SS. Suscrito y juramentado ante mi, este día 7 de mayo de 2010 (firmado) Lisa Renee Johnson, Notario Públic, Distrito de Columbia.- Mi nombramiento expira el 14 de octubre de 2011.".- (Hay otra firma ilegible).- Apostilla adjunta: Distrito de Columbia.- APOSTILLA: (Convention de La Haye du 5 octobre 1961).----------

1. País: Estados Unidos de América.- El presente documento público.----------

2. Ha sido firmado por: Lisa Renee Johnson.- Notario Público en y para el Distrito de Columbia.----------

3. Actuando en calidad de: Lisa Renee Johnson, Notario Público en y para el Distrito de Columbia.----------

4. Lleva el sello/estampilla de: Certificado.----------

5. En: Washington D.C.----------

6. El: Día 7 de mayo de 2010.----------

7. Por: El Secretario del Distrito de Columbia.----------

8. Bajo el No.: 229806.----------

9. Sello / estampilla: Distrito de Columbia.- (Firmado).----------

10. Firma: Stephanie D.Scott.- Traductor Oficial.- JORGE E. SIERRA REYES.- Licencia 376-1993 Minjusticia.- MINISTERIO DE RELACIONES EXTERIORES 160507 'JORGE SIERRA CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS.- NO ASUME RESPONSABILIDAD DEL TEXTO 2010 MAY 27 A 10:17 (FIRMADO) JEFE DE LEGALIZACIONES BOGOTA D.C.----------

DISTRICT OF COLUMBIA.- APOSTILLE.- (Convention de La Haye du 5 octobre 1961).----------

1. District of Columbia United States of America.----------

2. This public document has been sogned by LISA PENEE JOHNSON.----------

3. acting on the capacity of NOTARY PUBLIC IN AND FOR THE DISTRICT OF COLUMBIA LISA RENEE JOHNSON, NOTARY PUBLIC IN AND FOR THE.--------

4. bears the seal/stamp of DISTRICT OF COLUMBIA.- CERTIFIED.----------

5. at Washington, D.C.----------

6. the 7 day of MAY 2010.----------

7. by Secretary of the District of Columbia.----------

8. No. 229806.----------

9. Seal/Stamp.----------

10. Signature.- (Firmado) Stephanie D. Scott.----------

SEGUNDA.-Que de conformidad con lo expuesto y atendiendo a las prescripciones del artículo 47 del Decreto 960 de 1970, el documento mencionado, contenidos en cuatro (4) folios útiles, quedan legalmente protocolizados ante el Notario Treinta y Ocho (38) del Círculo Bogotá, de manera que desde ahora quedan bajo su custodia y guarda para que surtan los efectos legales a que haya lugar y los interesados puedan consultarlos y obtener las copias que de el solicite.-

---------- **HASTA AQUÍ EL CONTENIDO -DE LA MINUTA** ----------

SE ADVIRTIÓ al (a los) otorgante (s) de esta Escritura de la **obligación que tiene (n) de leer la totalidad de su texto,** a fin de verificar la exactitud de todos los datos en ella consignados con el fin de aclarar, modificar o corregir lo que le(s) pareciere; la firma de la misma demuestra su aprobación total del texto. ----------

Se advierte igualmente la necesidad de diligenciar los espacios en blanco correspondientes a la información personal y de trabajo consignados en el espacio destinado para la firma de los suscriptores del instrumento publico, con el objeto de confrontar la información solicitada con el contenido de la escritura previo a la autorización de la misma. ----------

En consecuencia, la notaria no asume ninguna responsabilidad por error o inexactitudes establecidas con posterioridad a la firma del (los) otorgante (s) y del notario. ----------

En tal caso, de la existencia de estos, deben ser corregidos mediante el otorgamiento de una nueva escritura, suscrita por el (los) que intervino (eron) en la inicial y sufragada por el (ellos) mismo (s). (Articulo 35 decreto ley 960 de 1.970).----------

ADVERTENCIA PARA TODOS LOS COMPARECIENTES QUE EXTIENDAN Y OTORGUEN INSTRUMENTOS, SEGÚN ART. 34 C.N., LEY 190 DE 1995,

LEY 333 DE 1996 Y LEY 365 DE 1997. Los comparecientes bajo la gravedad del juramento manifiestan clara y expresamente que todos los dineros, bienes muebles e inmuebles contenidos en este instrumento fueron adquiridos por medios y actividades licitas. Así como el dinero con el que se efectúa el pago de los gastos notariales. ----------

OTORGAMIENTO Y AUTORIZACIÓN. LEÍDO EL PRESENTE INSTRUMENTO POR EL OTORGANTE Y ADVERTIDO DE SU REGISTRO DENTRO DEL TÉRMINO DE LEY, ESTUVO DE ACUERDO CON ÉL LO ACEPTÓ EN LA FORMA COMO ESTÁ REDACTADO Y EN TESTIMONIO DE QUE LE DA SU ASENTIMIENTO Y APROBACIÓN LO FIRMA POR ANTE MÍ Y CONMIGO EL NOTARIO QUE DE TODO LO EXPUESTO DOY FE Y POR ELLO LO AUTORIZO.----------

CONSTANCIA: EL PRESENTE INSTRUMENTO SE EXTIENDE EN LAS SIGUIENTES HOJAS DE PAPEL NOTARIAL Nos.

/ /00005/ 8368805/ 8368810/ 8368821/

DERECHOS NOTARIALES: RESOLUCIÓN No. 10301 DEL 17 DE DICIEMBRE DE 2.009. $ 42,860

CARLOS REINALDO OLARTE

C. C. No. 79782747 de Bogotá

ESTADO CIVIL: CASADO

DIRECCIÓN RESIDENCIA:

DIRECCIÓN OFICINA: Diagonal 34 No 5-28

TELEFONO RESIDENCIA:

TELEFONO OFICINA: 601-7700

CELULAR: 315 7901625

EL(LA) NOTARIO (A) TREINTA Y OCHO (38)

DEL CIRCULO DE BOGOTA, D.C.

EDUARDO DURAN GOMEZ.

S.B

REPUBLICA DE COLOMBIA
EDUARDO DURAN GOMEZ
NOTARIO
NOTARIA
38
TREINTA Y OCHO DE BOGOTA D.C.

YanethG/201005163

9

Traducción oficial de un documento que está originalmente en inglés

Sello: "El Distrito de Columbia: SS. Suscrito y juramentado ante mí, este día 7 de mayo de 2010 (firmado) Lisa Renee Johnson, Notario Públic, Distrito de Columbia. Mi nombramiento expira el 14 de octubre de 2011."

(Hay otra firma ilegible).

Apostilla adjunta:

Distrito de Columbia

APOSTILLA:

(Convention de La Haye du 5 octobre 1961)

1. País:	Estados Unidos de América
	El presente documento público
2. Ha sido firmado por:	Lisa Renee Johnson
3. Actuando en calidad de:	Notario Público en y para el Distrito de Columbia
4. Lleva el sello/estampilla de:	Lisa Renee Johnson, Notario Público en y para el Distrito de Columbia
	Certificado
5. En:	Washington D.C.
6. El:	Día 7 de mayo de 2010
7. Por:	El Secretario del Distrito de Columbia
8. Bajo el No.:	229806
9. Sello / estampilla:	Distrito de Columbia
10. Firma:	(Firmado) Stephanie D. Scott.

Fin de la traducción

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

Apostille

(Convention de La Haye du 5 octobre 1961)

1. *District of Columbia*
   United States of America
2. This public document has been signed by LISA RENEE JOHNSON
3. acting in the capacity of NOTARY PUBLIC IN AND FOR THE DISTRICT OF COLUMBIA
4. bears the seal/stamp of LISA RENEE JOHNSON, NOTARY PUBLIC IN AND FOR THE DISTRICT OF COLUMBIA

CERTIFIED

5. at Washington, D.C.
6. the 7 day of MAY 2010
7. by *Secretary of the District of Columbia*
8. No. 229806
9. Seal/Stamp

10. Signature

Stephanie D. Scott

86 - PO138

OLARTERAISBECK
OLARTE RAISBECK MOURE & CASTRO LTDA.

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

Alexander Agudelo
Ángela Correa
Erika Rico
Carlos A. Parra
Gina Arias
Juan Felipe Acosta
Andrés Rincón
Mariana Franco
Monica Guevara
Alvaro Sabbagh

Of Counsel
Guillermo Chahín
Graciela Melo
Jacqueline Chaparro
Cruz E. de Moncaleano

The undersigned, **General Power**

El suscrito, **Poder General**

WYETH LLC

domiciled in

domiciliado en

Five Giralda Farms Madison, NJ 07940 United States of America

by means of these presents hereby grants to **Carlos R. Olarte y/o J. Ian Raisbeck y/o Juan Guillermo Moure y/o Natalia Castro** , legal representatives with faculties to receive notifications and to appoint judicial or extrajudicial agents in patent matters, who at the same time have the faculty to represent us before the administrative, judicial or police authorities of any hierarchy of the Republic of Colombia, the Republic of Bolivia, the Republic of Ecuador, the Republic of Peru, and the Bolivarian Republic of Venezuela, to initiate before said authorities all the necessary actions to accomplish said purposes and to intervene in all instances, grades and procedural levels; to file and prosecute applications, declarations, complaints, to claim, counterclaim, answer claims and counterclaims; to draw up specifications; to make amendments; oppositions and all types of objections and writings of any nature; cancellations and administrative injunction proceedings; to pay all installments and effect all other payments prescribed by law; to receive documents and monies; act as complainants as well as defendants, before the competent judges, with full powers to request preliminary injunctions of any nature, settle, make arrangements, to submit to arbitrators, to desist from claims or procedures, to accept claims, to collect, to ratify legal proceedings subscribed before the appointment and/or presentation of this Power, substitute or delegate the legal representation and other acts prescribed by law, in short, with all such further powers as may be required; to comply with all other requirements and, to take all those measures which they may deem fit for the protection of our interests.

nombramos por el presente a **Carlos R. Olarte y/o J. Ian Raisbeck y/o Juan Guillermo Moure y/o Natalia Castro,** nuestros representantes legales con facultades para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales en materia de patentes, los cuales quedan a su vez facultados para representarnos ante las autoridades de cualquier jerarquía de la República de Colombia, la República de Bolivia, la República del Ecuador, la República del Perú y la República Bolivariana de Venezuela, ya sean administrativas, judiciales o de policía, para iniciar ante dichas autoridades todas las acciones necesarias para cumplir con el objeto indicado e intervenir en todas las instancias, grados o etapas procesales; elevar y tramitar solicitudes, declaraciones y reclamos, para demandar, reconvenir, contestar demandas y reconvenciones; formular descripciones, enmiendas, oposiciones y todo tipo de impugnaciones y escritos de cualquier naturaleza; instaurar cancelaciones y amparos administrativos; abonar todos los impuestos y cuotas y efectuar cualquier otro pago determinado por la ley; recibir todos los documentos y valores; intervenir como demandantes o demandados ante los jueces que sean competentes, pudiendo solicitar medidas cautelares de cualquier naturaleza, conciliar, transar, someter a árbitros, desistirse de la pretensión y/o el procedimiento, allanarse a la pretensión, percibir, ratificar los actos jurídicos procesales suscritos con anterioridad al otorgamiento y/o presentación del presente poder, sustituir o delegar la representación procesal y los demás actos que exprese la ley, con todas las demás facultades que resulten necesarias; llenar cualesquiera otros requisitos y tomar, en fin, todas las medidas que creyeren conducentes al resguardo de nuestros intereses.

Signature/Firma: Gregg C. Benson
Attorney-in-Fact

Date/Fecha: 4 MAY 2010

City,Country/Ciudad,País: GROTON, CONNECTICUT USA

5/7 Colombia NC

OLARTERAISBECK
OLARTE RAISBECK MOURE & CASTRO LTDA.

MODEL OF NOTARIAL CERTIFICATION

Notarial Certification	**Certificación Notarial**
On this date, May 6, 2010	En esta fecha,
The undersigned Notary Public certifies:	el Notario Público suscrito certifica:
1. That GREGG C. BENSON of legal age and domiciled in EASTERN POINT ROAD, GROTON, CONNECTICUT USA signed the foregoing document.	1. Que mayor de edad y domiciliado suscribió el documento que antecede.
2. That the grantor has executed the foregoing document as ATTORNEY-IN-FACT of **WYETH LLC**	2. Que el otorgante ha suscrito el referido documento en su carácter de de
3. That **WYETH LLC** having its principal place of business located in Five Giralda Farms Madison, NJ 07940 United States of America is duly incorporated, is currently in existence, and that the purposes for which the General Power is granted are within the scope of its corporate purposes.	4. Que con sede principal ubicada en está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social.
4. That the grantor has the authority to execute the General Power and that his/her representation is legal.	4. Que el otorgante tiene la representación para suscribir el poder, y que ésta es legitima.
5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s): Power of Attorney executed on November 16, 2009	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): Nancy M George
Nancy M. George

NANCY M. GEORGE
Notary Public
My Commission Expires 30 June 2011

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 September 2009 (03.09.2009)

PCT

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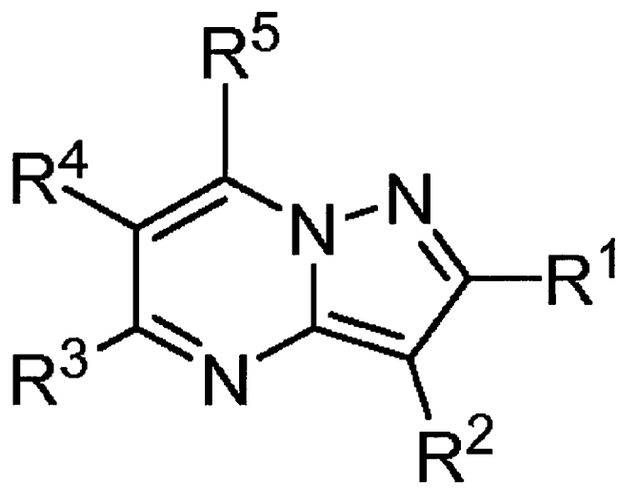
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(54) Title: BRIDGED, BICYCLIC HETEROCYCLIC OR SPIRO BICYCLIC HETEROCYCLIC DERIVATIVES OF PYRAZOLO[1,5-A]PYRIMIDINES, METHODS FOR PREPARATION AND USES THEREOF

(57) Abstract: Compounds of formula A: Formula (1) pharmaceutically acceptable salts thereof are described, which selectively inhibit Raf kinase activity and are useful for treating disorders mediated by Raf kinases.



A

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BRIDGED, BICYCLIC HETEROCYCLIC OR SPIRO BICYCLIC HETEROCYCLIC DERIVATIVES OF PYRAZOLO[1, 5-A]PYRIMIDINES, METHODS FOR PREPARATION AND USES THEREOF

FIELD OF THE INVENTION

The present invention relates to new pyrazolo[1,5-a]pyrimidine compositions that are useful for inhibiting abnormal growth of certain cell types. The invention is directed to certain bridged, bicyclic heterocyclic or spiro bicycic heterocyclic derivatives of pyrazolo[1,5-a]pyrimidines, their corresponding pharmaceutically acceptable salts and methods for their preparation and use. The bridged, bicyclic heterocyclic or spiro bicycic heterocyclic derivatives of pyrazolo[1,5-a]pyrimidines inhibit growth of tumor cells, which contain oncogenic forms of Receptor Tyrosine Kinases, K-Ras and Raf kinases.

BACKGROUND OF THE INVENTION

Raf is a multigene family expressing oncoprotein kinases: A-Raf, B-Raf and C-Raf (also known as Raf-1), as described in publications by McCubrey et al., in Leukemia, 12(12), 1903-1929 (1998); by Ikawa et al., in Mol. and Cell. Biol. 8(6), 2651-2654 (1988); by Sithanandarn et al., in Oncogene 5, 1775-1780 (1990); by Konishi et al., in Biochem. and Biophys. Res. Comm. 216(2), 526-534 (1995). All three Raf kinases are functionally present in certain human hematopoietic cells, and their aberrant expression can result in abrogation of cytokine dependency. Their regulatory mechanisms differ in that C-Raf and A-Raf appear to require additional serine and tyrosine phosphorylation within the N region of the kinase domain for full activity, as described by Mason et al., in EMBO J. 18, 2137-2148 (1999). In addition, B-Raf kinase appears to have a much higher basal kinase activity than either A-Raf kinase or C-Raf kinase. The three Raf kinases play critical roles in the transmission of mitogenic and anti-apoptotic signals. B-Raf kinase is frequently mutated in various human cancers, as described by Wan et al., in Cell 116, 855-867 (2004), indicating that specific Raf kinases are associated with cancer. The cytoplasmic serine/threonine kinase B-Raf kinases and receptor tyrosine kinases of the platelet-derived growth factor receptor (PDGFR) family are frequently activated in cancer by mutations of an equivalent amino acid. Structural studies have provided important insights into why these very different kinases share similar oncogenic hot spots and why the PDGFR juxtamembrane region is also a frequent oncogenic target, as described by Dibb in Nature Reviews, Cancer 4(9), 718-27 (2004).

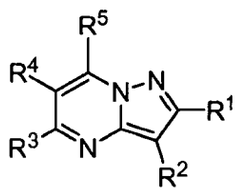
B-Raf encodes a Ras-regulated kinase that mediates cell growth and malignant transformation pathway activation that controls cell growth and survival. Activation of a Ras/Raf/MEK pathway results in a cascade of events from the cell surface to the cell nucleus, ultimately affecting cell proliferation, apoptosis, differentiation and transformation. Activating B-Raf mutations have been found in 66% of malignant melanomas and in a smaller fraction of other cancers including those of the colorectum, as reported by Davies H., *et al.* (2002) *Nature* 417:906 and by Rajagopalan H., *et al.* (2002) Nature 418, 934. Recently, B-Raf has been shown to be frequently mutated in various human cancers, as described by Wan et al. (2004) Cell 116, 855-867. B-Raf mutations also account for the MAP kinase pathway activation common in non-small cell lung carcinomas (NSCLC). Certain B-Raf mutations reported to date in NSCLC are non-V600 (89%; $P < 10^{-7}$), strongly suggesting that B-Raf mutations in NSCLC are qualitatively different from those in melanomas. Thus, there may be therapeutic differences between lung cancers and melanomas in response to Raf kinase inhibitors, as described by Karasarides et al., in Oncogene 23(37), 6292-6298 (2004) and by Bollag et al., in Current Opinion in Invest. Drugs, 4(12), 1436-1441 (2003). Although uncommon, B-Raf mutations in human lung cancers may identify a subset of tumors sensitive to targeted therapy, as described by Brose et al., in Cancer Research 62(23):6997-7000 (2002) and in U.S. Patent Application Publication No. 2005/267060.

Raf kinases are also key components of signal transduction pathways by which specific extracellular stimuli elicit precise cellular responses in mammalian cells. Activated cell surface receptors activate Ras/Rap proteins at the inner aspect of the plasma membrane, which in turn recruit and activate Raf proteins. Activated Raf proteins phosphorylate and activate the intracellular protein kinases MEK1 and MEK2. In turn, activated MEKs catalyze phosphorylation and activation of p42/p44 mitogen-activated protein kinase (MAPK). A variety of cytoplasmic and nuclear substrates of activated MAPK are directly or indirectly associated with the cellular response to cellular environmental change. In fact, B-Raf mutations have been shown to predict sensitivity to pharmacological MEK inhibition by small molecule inhibitors by limiting tumor growth in B-Raf mutant xenografts, as described by Solit et a., in Nature, Letters to Editor, Nov. 6, 2005. Three distinct genes have been identified in mammals that encode Raf proteins; A-Raf, B-Raf and C-Raf (also known as Raf-1) and isoformic variants that result from differential splicing of mRNA are known. Therefore, it is desirable to identify and characterize compounds that inhibit growth of tumor cells, which include oncogenic forms of Receptor Tyrosine Kinases, K-Ras, A-Raf kinase, B-Raf mutant kinase, B-Raf kinase and C-Raf kinase.

International Patent Publication No. WO 2004/052315 describes certain tyrosine kinase inhibitors, including certain bicyclic substituted, pyrazolo[1,5-a]pyrimidines. However, no bridged, bicyclic pyrazolo[1,5-a]pyrimidines have been described and little is known regarding how other ring systems, including bridged, bicyclic moieties, fused to the pyrazolo[5,1-a]pyrimidine ring framework influence the structure-activity relationship (SAR) of bridged, bicyclic pyrazolo[1,5-a]pyrimidines. There is a need for new compounds that selectively inhibit Raf kinase activity and that are useful for treating disorders mediated by any Raf kinase. Bridged, bicyclic pyrazolo[1,5-a]pyrimidine compositions of the present invention fulfill this unmet need and are useful in the treatment of diseases associated with Raf kinases, including cancer and inflammation, in mammals.

SUMMARY OF THE INVENTION

Accordingly, the invention provides a compound of formula A:



A

and pharmaceutically acceptable salts thereof;

wherein

R^1 is a 5-7 membered heterocyclic ring or heteroaryl ring, said ring comprising 1-3 heteroatoms selected from N, O or S, and said ring optionally substituted with one to four substituents selected from -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^9OR^7$, $-R^9NR^7R^7$, $-R^9S(O)_mR^7$, $-R^9C(O)R^7$, $-R^9C(O)OR^7$, $-R^9C(O)NR^7R^7$, $-R^9OC(O)R^7$, $-R^9OC(O)OR^7$, $-R^9OC(O)NR^7R^7$, $-R^9NR^7C(O)R^7$, $-R^9NR^7C(O)OR^7$, $-R^9NR^7C(O)NR^7R^7$, $-YR^9R^{10}$, $-YR^9NR^7R^7$ and $-YR^{10}$;

R^2 is selected from an aryl ring, a 9-14 membered bicyclic aryl ring, a 5-7 membered heteroaryl ring and a 9-14 membered bicyclic heteroaryl ring, said heteroaryl ring comprising 1-3 heteroatoms selected from N, O and S, said ring optionally substituted with one to four

substituents selected from -J, -NO_2, -CN, -N_3, -CHO, -CF_3, -OCF_3, -R^7, -OR^7, -$S(O)_mR^7$, -NR^7R^7, -$NR^7S(O)_mR^7$, -OR^9OR^7, -$OR^9NR^7R^7$, -$N(R^7)R^9OR^7$, -$N(R^7)R^9NR^7R^7$, -$NR^7C(O)R^7$, -$C(O)R^7$, -$C(O)OR^7$, -$C(O)NR^7R^7$, -$OC(O)R^7$, -$OC(O)OR^7$, -$OC(O)NR^7R^7$, $NR^7C(O)R^7$, -$NR^7C(O)OR^7$, -$NR^7C(O)NR^7R^7$, -R^8OR^7, -$R^8NR^7R^7$, -$R^8S(O)_mR^7$, -$R^8C(O)R^7$, -$R^8C(O)OR^7$, -$R^8C(O)NR^7R^7$, -$R^8OC(O)R^7$, -$R^8OC(O)OR^7$, -$R^8OC(O)NR^7R^7$, -$R^8NR^7C(O)R^7$, -$R^8NR^7C(O)OR^7$, -$R^8NR^7C(O)NR^7R^7$, -$OPO(OR^7)_2$, -YR^8R^{10}, -$YR^8NR^7R^7$ and -YR^{10};

R^3, R^4 and R^5 are each independently selected from carbon-linked R^6, –X-W-R^6, H, J, -$C(O)OR^7$, -$C(O)NR^7R^7$, -$NR^7C(O)R^7$, -CN, alkyl of 1-6 carbon atoms, branched alkyl of 1-8 carbon atoms, cycloalkyl ring of 3-10 carbons, aryl ring, 5-7 membered heterocyclic ring, and 5-10 membered heteroaryl ring, said heterocyclic ring or heteroaryl ring comprising 1-3 heteroatoms selected from N, O and S, said alkyl of 1-6 carbon atoms, branched alkyl of 1-8 carbon atoms, aryl ring, 5-7 membered heterocyclic ring, and 5-10 membered heteroaryl ring is optionally substituted with one to four substituents selected from -J, -NO_2, -CN, -N_3, -CHO, -CF_3, -OCF_3, -R^7, -OR^7, -$S(O)_mR^7$, -NR^7R^7, -$NR^7S(O)_mR^7$, -OR^9OR^7, -$OR^9NR^7R^7$, -$N(R^7)R^9OR^7$, -$N(R^7)R^9NR^7R^7$, -$NR^7C(O)R^7$, -$C(O)R^7$, -$C(O)OR^7$, -$C(O)NR^7R^7$, -$OC(O)R^7$, -$OC(O)OR^7$, -$OC(O)NR^7R^7$, $NR^7C(O)R^7$, -$NR^7C(O)OR^7$, -$NR^7C(O)NR^7R^7$, -R^8OR^7, -$R^8NR^7R^7$, -$R^8S(O)_mR^7$, -$R^8C(O)R^7$, -$R^8C(O)OR^7$, -$R^8C(O)NR^7R^7$, -$R^8OC(O)R^7$, -$R^8OC(O)OR^7$, -$R^8OC(O)NR^7R^7$, -$R^8NR^7C(O)R^7$, -$R^8NR^7C(O)OR^7$ -$R^8NR^7C(O)NR^7R^7$ and YR^{10}, wherein at least one of R^3, R^4 and R^5 comprises R^6;

R^6 is a 6-14 membered bridged, bicyclic heterocyclic ring or a 6-14 membered bicyclic spiro heterocyclic ring, said ring optionally substituted with one or more substituents selected from -J, -NO_2, -CN, -N_3, -CHO, -CF_3, -OCF_3, -R^7, -OR^7, -$S(O)_mR^7$, -NR^7R^7, -$NR^7S(O)_mR^7$, -OR^9OR^7, -$OR^9NR^7R^7$, -$N(R^7)R^9OR^7$, -$N(R^7)R^9NR^7R^7$, -$NR^7C(O)R^7$, -$C(O)R^7$, -$C(O)OR^7$, -$C(O)NR^7R^7$, -$OC(O)R^7$, -$OC(O)OR^7$, -$OC(O)NR^7R^7$, $NR^7C(O)R^7$, -$NR^7C(O)OR^7$, -$NR^7C(O)NR^7R^7$, -R^8OR^7, -$R^8NR^7R^7$, -$R^8S(O)_mR^7$, -$R^8C(O)R^7$, -$R^8C(O)OR^7$, -$R^8C(O)NR^7R^7$, -$R^8OC(O)R^7$, -$R^8OC(O)OR^7$, -$R^8OC(O)NR^7R^7$, -$R^8NR^7C(O)R^7$, -$R^8NR^7C(O)OR^7$or -$R^8NR^7C(O)NR^7R^7$ and YR^{10};

R^7 is H or is independently selected from alkyl of 1-6 carbon atoms, branched alkyl of 1-8 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, aryl ring and a 5-10 membered heteroaryl ring, optionally substituted with one to four substituents selected from -J, -NO_2, -CN, -N_3, -CHO, -CF_3, -OCF_3, -R, -OR, -$S(O)_mR$, -NRR, -$NRS(O)_mR$, -OR^9OR, -OR^9NRR, -$N(R)R^9OR$, -$N(R)R^9NRR$, -NRC(O)R, -C(O)R, -C(O)OR, -C(O)NRR, -OC(O)R, -OC(O)OR, -OC(O)NRR, NRC(O)R, -NRC(O)OR, -NRC(O)NRR, -R^8OR, -R^8NRR, -$R^8S(O)_mR$, -$R^8C(O)R$, -$R^8C(O)OR$, -$R^8C(O)NRR$, -$R^8OC(O)R$, -$R^8OC(O)OR$, -$R^8OC(O)NRR$, -$R^8NRC(O)R$, -$R^8NRC(O)OR$, -$R^8NRC(O)NRR$ and ZR^{10}, wherein R is selected from alkyl of

1-6 carbon atoms, branched alkyl of 1-3 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-10 carbon atoms, aryl of 6-10 carbon atoms and heteroaryl of 6-10 atoms, the heteroaryl comprising 1-3 heteroatoms selected from N, O and S;

R^8 is a divalent group independently selected from alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, aryl, heteroaryl, cycloalkyl, and cycloheteroalkyl;

R^9 is independently a divalent alkyl group of 2-6 carbon atoms;

R^{10} is independently selected from cycloalkyl ring of 3-10 carbons, bicycloalkyl ring of 3-10 carbons, aryl ring, heterocyclic ring, heteroaryl ring and a heteroaryl ring fused to one to three aryl or heteroaryl rings, each heterocyclic ring or heteroaryl ring comprising 1-3 heteroatoms selected from N, O and S, each optionally substituted with one to four substituents selected from –H, -aryl, $-CH_2$-aryl, -NH-aryl, -O-aryl, $-S(O)_m$-aryl, -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$-, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $-NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$, and $-R^8NR^7C(O)NR^7R^7$;

J is fluoro, chloro, bromo, or iodo;

m is an integer of 0-2;

Y is a divalent group independently selected from a bond, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, O, and $-NR^7$;

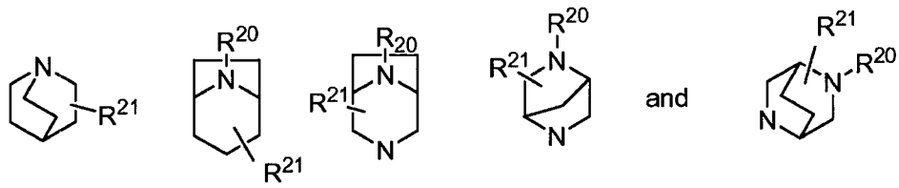
X is selected from a divalent alkyl group of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl ring of 3-10 carbons, bicycloalkyl ring of 3-10 carbons, aryl ring, heterocyclic ring and a heteroaryl ring, each heterocyclic ring or heteroaryl ring comprising 1-3 heteroatoms selected from N, O or S; optionally substituted with one to four substituents selected from –H, -aryl, $-CH_2$-aryl, -NH-aryl, -O-aryl, $-S(O)_m$-aryl, -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$-, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $-NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$,

$R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$, and $-R^8NR^7C(O)NR^7R^7$;

W is selected from a bond, Z, -OZ-, -ZO- $-S(O)_mZ-$, $-S(O)_2NR^7Z-$, $-NR^7S(O)_mZ$ -, $-NR^7Z-$, $-ZNR^7-$, -C(O)Z-; -C(O)OZ-, $-C(O)NR^7Z-$, $-NR^7C(O)Z-$, $-NR^7C(O)NR^7Z-$, -OC(O)Z-, $-NR^7C(O)OZ-$, and -OC(O) NR^7Z-; and

Z is a bond or a divalent alkyl of 1-6 carbon atoms.

The present invention also provides a compound of formula A and pharmaceutically acceptable salts thereof; wherein the bridged, bicyclic heterocyclic ring is selected from:



optionally substituted on nitrogen with R^{20} and optionally substituted on one or more carbons with R^{21}, wherein

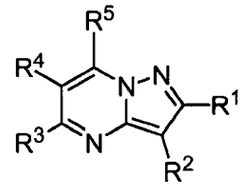
R^{20} is selected from H, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-C(O)R^7$, $-S(O)_mR^7$, alkyl of 1-6 carbon atoms, branched alkyl of 1-8 carbon atoms, cycloalkyl ring of 3-10 carbons, aryl ring, 5-7 membered heterocyclic ring and 5-10 membered heteroaryl ring, each heterocyclic ring or heteroaryl ring comprising 1-3 heteroatoms selected from N, O or S, each of the alkyl of 1-6 carbon atoms, branched alkyl of 1-8 carbon atoms, aryl ring, heterocyclic ring and heteroaryl ring optionally substituted with one to four substituents selected from -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$or $-R^8NR^7C(O)NR^7R^7$ and YR^{10}; and

R^{21} is selected from H, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, -

$R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^3OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$or $-R^8NR^7C(O)NR^7R^7$ and YR^{10}; wherein J, Y, m, and R^{7-10} are defined above.

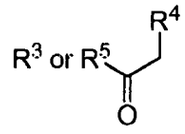
The present invention also provides a pharmaceutical composition comprising a compound of formula A or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. The present invention also provides pharmaceutical compositions comprising compounds of formula A or a pharmaceutically acceptable salt thereof in combination with other kinase-inhibiting pharmaceutical compounds or chemotherapeutic agents, and a pharmaceutically acceptable carrier.

The present invention provides a method for making a compound of formula A:



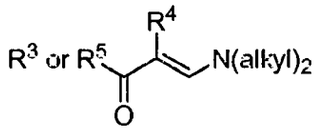
A

and pharmaceutically acceptable salts thereof; comprising the steps of: (a) reacting a substituted ketone of formula 1



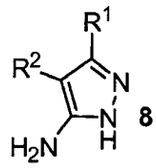
1

with an acetal of N,Ndialkylformamide or an acetal of N,N-dialkylacetamide, to provide an enaminone compound of formula 2



2 ; and

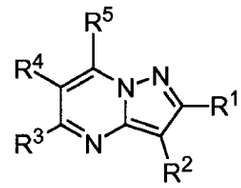
(b) reacting the compound of formula 2 with a substituted 3-aminopyrazole of formula 8,



8

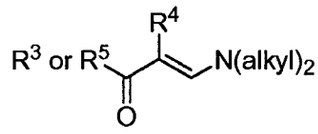
to provide a compound of formula A, wherein R^{1-10}, J, m, W, X, Y and Z are as defined above.

The present invention also provides a method for making a compound of formula A:



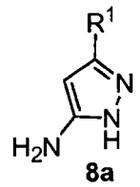
A

and pharmaceutically acceptable salts thereof; comprising the steps of: (a) reacting an enaminone compound of formula 2



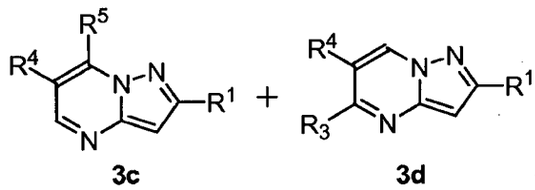
2

with an aminopyrazole of formula 8a



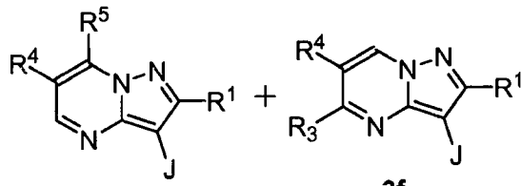
8a

to provide compounds of formula 3c and 3d



3c 3d ;

(b) halogenating one or both of the compounds of formula 3c and 3d to provide one or both of compounds of formula 3e and 3f



3e 3f ; and

(c) subjecting one or both of the compounds of formula 3e and 3f to a palladium catalyzed, Suzuki coupling using aryl or heteroaryl boronic acids or corresponding boronate esters to provide one or both of the compounds of the invention.

The present invention provides additional independent steps of separating compounds of formula 3c and 3d prior to the halogenation step, separating compounds of formula 3e and 3f prior to the palladium catalyzed, Suzuki coupling step and separating compounds of formula A after the palladium catalyzed, Suzuki coupling step, respectively.

The invention also provides methods for inhibiting Raf kinase activity in a cell comprising contacting a cell with a compound of formula A, whereby the compound inhibits activity of a Raf kinase selected from A-Raf kinase, B-Raf kinase, mutant B-Raf kinase and C-Raf kinase.

The present invention also provides a method of treating an A-Raf kinase, B-Raf kinase, mutant B-Raf kinase or C-Raf kinase dependent condition, said condition comprising cancer or inflammation, by administering to a patient a pharmaceutically effective amount of a compound of formula A.

The present invention provides methods of treating mammalian diseases associated with a Raf kinase selected from A-Raf kinase, B-Raf kinase, mutant B-Raf kinase and C-Raf kinase, by administering to a patient a compound of formula A.

The present invention provides methods of treating a cancer associated with Raf kinase wherein the cancer is selected from breast, kidney, bladder, thyroid, mouth, larynx, esophagus, stomach, colon, ovary, lung, pancreas, skin, liver, prostate and brain cancer.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The following definitions are used in connection with pyrazolo[1,5-a]pyrimidines of the invention. The term "alkyl" refers to saturated aliphatic groups of 1 to 8 carbon atoms, including straight-chain alkyl groups and branched-chain alkyl groups. In one embodiment, a straight chain or branched chain alkyl has 6 or fewer carbon atoms in its backbone. The term "alkyl" can be used alone or as part of a chemical name, such as "alkylamine". The terms "alkenyl" and "alkynyl" refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one double or triple carbon-carbon bond, respectively. The term "cycloalkyl" refers to saturated or partially unsaturated cycloaliphatic rings of 3 to 10 carbon atoms, including unbranched cycloalkyl rings and branched cycloalkyl rings. Unless otherwise defined, the term "aryl", as used herein, refers to an aromatic carbocyclic moiety, e.g. having from 6-20 carbon atoms, including from 6-10 carbon atoms, which may be a single ring (monocyclic) or multiple rings fused together or linked covalently, wherein at least one of the rings is aromatic. Any suitable ring position of the aryl moiety may be covalently linked to the defined chemical structure. Examples of aryl include phenyl and napthyl. The aryl group may be optionally substituted. In addition to other optional substituents, the aryl group may be substituted by an oxo substituent meaning one of the ring carbon atoms is part of a carbonyl group.

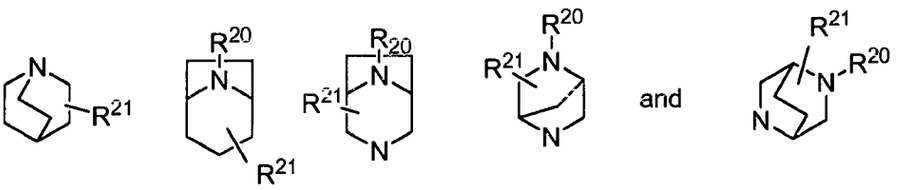
Unless otherwise defined, the term "heteroaryl" as used herein means an aromatic heterocyclic ring system, e.g. having from 5-20 ring atoms, which may be a single ring or multiple rings fused together or linked covalently, wherein at least one of the rings is aromatic. The rings may contain one or more heteroatoms, e.g. 1 to 3 heteroatoms, selected from nitrogen, oxygen, or sulfur, wherein the nitrogen or sulfur atom(s) are optionally oxidized, or the nitrogen atom(s) are optionally quaternized. Any suitable ring position of the heteroaryl moiety may be covalently linked to the defined chemical structure. Suitable examples of heteroaryl include 3-pyridinyl, 4-pyridinyl, 1-*H*-indazol-4-yl or indol-1-yl. The heteroaryl group may be optionally substituted. In addition to other optional substituents, the heteroaryl group may be substituted by an oxo substituent meaning one of the ring carbon atoms is part of a carbonyl group.

The term "heterocyclic", "heterocycle" or "heterocyclyl" as used herein can be used interchangeably to refer to a stable, saturated or partially unsaturated monocyclic or multicyclic heterocyclic ring system, including a spirocyclic and bridged heterocyclic ring system, e.g. having from 5 to 7 ring members. The heterocyclic ring members are carbon

atoms and one or more heteroatoms, e.g. 1 to 3 heteroatoms, selected from nitrogen, oxygen, and sulfur atoms, wherein the nitrogen or sulfur atom(s) are optionally oxidized, or the nitrogen atom(s) are optionally quaternized. The heterocyclic, heterocycle or heterocyclyl group may be optionally substituted. In addition to other optional substituents, the heterocyclic, heterocycle or heterocyclyl group may be substituted by an oxo substituent meaning one of the ring carbon atoms is part of a carbonyl group. The heterocyclic, heterocycle or heterocyclyl group may contain one of more fused rings.

The term "spiro heterocyclic" refers to at least one heterocyclic ring system bonded to another ring system at the same atom.

The term "bridged, bicyclic" refers to a heterocyclic ring system fused to another ring system on non-adjacent atoms, where at least one the ring systems is a heterocyclic ring. Suitable examples of "bridged, bicyclic" ring systems are provided in the Examples section of the specification and include, but are not limited to:

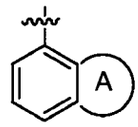


optionally substituted on nitrogen with R^{20} and optionally substituted on one or more carbons with R^{21}, wherein

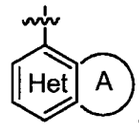
R^{20} is selected from H, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-C(O)R^7$, $-S(O)_mR^7$, alkyl of 1-6 carbon atoms, branched alkyl of 1-8 carbon atoms, cycloalkyl ring of 3-10 carbons, aryl ring, 5-7 membered heterocyclic ring and 5-10 membered heteroaryl ring, each heterocyclic ring or heteroaryl ring comprising 1-3 heteroatoms selected from N, O or S, each of the alkyl of 1-6 carbon atoms, branched alkyl of 1-8 carbon atoms, aryl ring, heterocyclic ring and heteroaryl ring optionally substituted with one to four substituents selected from -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$ or $-R^8NR^7C(O)NR^7R^7$ and YR^{10}; and

R^{21} is selected from H, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$or $-R^8NR^7C(O)NR^7R^7$ and YR^{10}; wherein $R^{7\text{-}10}$ are defined above.

The term "bicyclic aryl ring or heteroaryl ring" refers to a ring framework of formula



or

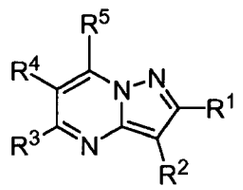


The symbol  refers to a 5-7 membered heteroaryl ring comprising 1-3 heteroatoms selected from N, O or S. The term "Het" refers to a 6 membered heteroaryl ring containing 1-2 nitrogen atoms. Each of the bicyclic aryl ring or bicyclic heteroaryl ring are optionally substituted with substituents selected from -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$, $-R^8NR^7C(O)NR^7R^7$, $-YR^8R^{10}$, $-YR^8NR^7R^7$ and $-YR^{10}$.

As used herein, the term "pharmaceutically acceptable carrier" includes pharmaceutically acceptable diluents and excipients.

As used herein, the term "individual", "subject" or "patient," used interchangeably, refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

According to an exemplary embodient, the invention provides a compound of formula A:



A

and pharmaceutically acceptable salts thereof;

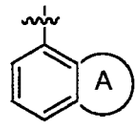
wherein R^1-R^{10}, J, m, W, X, Y and Z are as defined above.

[0001] Suitable examples of R^1 include, but are not limited to, thienyl, furyl, indolyl, pyrrolyl, thiophenyl, benzofuryl, benzothiophenyl, quinolyl, isoquinolyl, imidazolyl, thiazolyl, oxazolyl, pyridinyl, pyrrolidyl, oxolanyl, thiolanyl, piperidinyl, piperazinyl, thiazolyl, triazolyl, pyrazolyl, pyrazinyl, pyridazinyl, pyrimidinyl, and morpholinyl. The heterocyclic ring or heteroaryl ring may be substituted to the pyrazolo[1, 5-a]pyrimidine ring framework in any acceptable position. According to one embodiment, R^1 is 4-pyridinyl or 4-morpholinyl, optionally substituted with one to four substituents selected from -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^9OR^7$, $-R^9NR^7R^7$, $-R^9S(O)_mR^7$, $-R^9C(O)R^7$, $-R^9C(O)OR^7$, $-R^9C(O)NR^7R^7$, $-R^9OC(O)R^7$, $-R^9OC(O)OR^7$, $-R^9OC(O)NR^7R^7$, $-R^9NR^7C(O)R^7$, $-R^9NR^7C(O)OR^7$, $-R^9NR^7C(O)NR^7R^7$, $-OPO(OR^7)_2$, $-YR^9R^{10}$, $-YR^8NR^7R^7$ and $-YR^{10}$.

Suitable examples of R^2 include, but are not limited to, halogen substituted phenyl, C_1-C_6 alkylsulfonamido substituted phenyl, carbamate substituted phenyl, C_1-C_6 alkoxy substituted phenylcarbamate, benzonitrile, hydroxyl substituted benzonitrile, C_1-C_6 alkoxy substituted benzonitrile, hydroxyphenyl (phenol), C_1-C_6 alkyl substituted hydroxyphenyl (phenol), halogen substituted hydroxyphenyl (phenol), C_1-C_6 alkoxyphenyl, halogen substituted C_1-C_6 alkoxyphenyl, hydroxypyridinyl, C_1-C_6 alkoxypyridinyl, amino phenyl (aniline), halogen substituted amino phenyl (aniline), hydroxyl substituted amino phenyl (aniline), formamide substituted phenyl, hydroxyl substituted phenylformamide, C_1-C_6 alkoxy substituted phenylformamide, C_1-C_6 alkoxy substituted amino phenyl (aniline), urea substituted phenyl, benzamido, C_1-C_6 alkyl substituted benzamido, halogen substituted benzamido, indazolyl, C_1-C_6 alkyl substituted indazolyl, halogen substituted indazolyl, halo

C_1-C_6 alkyl substituted indazolyl, perfluoro C_1-C_6 alkyl substituted indazolyl, benzamidazolyl, halogen substituted benzamidazolyl, oxo-dihydro-benzamidazolyl, dihydro-pyrrolodinyl, substituted dihydro-pyrrolodinyl, dihydro-indolyl, substituted dihydro-indolyl, and oxadiazolyl substituted phenyl. Other suitable examples of R^2 include, but are not limited to, indolyl, benzotriazolyl, oxindolyl, benzothiazolonyl and benzooxazolonyl. The monocyclic aryl ring and the bicyclic heteroaryl ring may be substituted to the pyrazolo[1,5-a]pyrimidine ring framework in any acceptable position.

According to one embodiment, R^2 is an aryl ring or a bicyclic aryl ring of formula



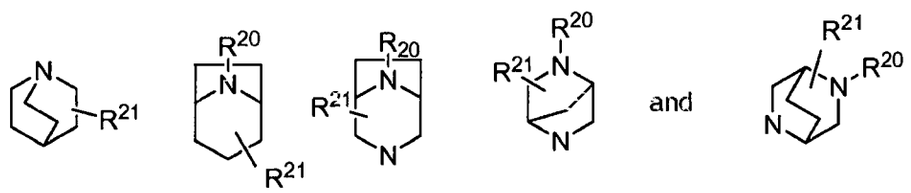
wherein  refers to a 5-7 membered heteroaryl ring comprising 1-3 heteroatoms selected from N, O and S, said ring optionally substituted with one to four substituents selected from -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$, $-R^8NR^7C(O)NR^7R^7$, $-YR^8R^{10}$, $-YR^8NR^7R^7$ and $-YR^{10}$.

According to a separate embodiment, R^2 is a phenyl ring or an indazolyl ring, optionally substituted with one to four substituents selected from -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$, $-R^8NR^7C(O)NR^7R^7$, $-YR^8R^{10}$, $-YR^8NR^7R^7$ and $-YR^{10}$.

According to a separate embodiment, R^2 is selected from halogen substituted phenyl, C_1-C_6 alkylsulfonamido substituted phenyl, carbamate substituted phenyl, C_1-C_6 alkoxy substituted phenylcarbamate, benzonitrile, hydroxyl substituted benzonitrile, C_1-C_6 alkoxy substituted benzonitrile, hydroxyphenyl, C_1-C_6 alkyl substituted hydroxyphenyl, halogen substituted hydroxyphenyl, C_1-C_6 alkoxyphenyl, halogen substituted C_1-C_6

alkoxyphenyl, hydroxypyridinyl, C_1-C_6 alkoxypyridinyl, amino phenyl, halogen substituted amino phenyl, hydroxyl substituted amino phenyl, formamide substituted phenyl, hydroxyl substituted phenylformamide, C_1-C_6 alkoxy substituted phenylformamide, C_1-C_6 alkoxy substituted amino phenyl, urea substituted phenyl, benzamido, C_1-C_6 alkyl substituted benzamido, halogen substituted benzamido, indazolyl, C_1-C_6 alkyl substituted indazolyl, halogen substituted indazolyl, halo C_1-C_6 alkyl substituted indazolyl, perfluoro C_1-C_6 alkyl substituted indazolyl, benzamidazolyl, halogen substituted benzamidazolyl, dihydro-pyrrolodinyl, substituted dihydro-pyrrolodinyl, dihydro-indolyl, substituted dihydro-indolyl and oxadiazolyl substituted phenyl.

Suitable examples of R^6 include, but are not limited to bridged, bicyclic heterocyclic rings selected from:



optionally substituted on nitrogen with R^{20} and optionally substituted on one or more carbons with R^{21}, wherein

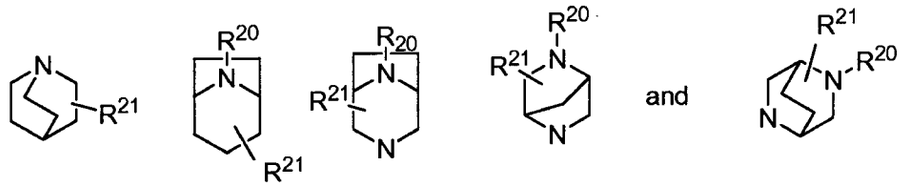
R^{20} is selected from H, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-C(O)R^7$, $-C(O)R^{10}$, $-S(O)_mR^7$, alkyl of 1-6 carbon atoms, branched alkyl of 1-8 carbon atoms, cycloalkyl ring of 3-10 carbons, aryl ring, 5-7 membered heterocyclic ring and 5-10 membered heteroaryl ring, each heterocyclic ring or heteroaryl ring comprising 1-3 heteroatoms selected from N, O or S, each of the alkyl of 1-6 carbon atoms, branched alkyl of 1-8 carbon atoms, aryl ring, heterocyclic ring and heteroaryl ring optionally substituted with one to four substituents selected from -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$ or $-R^8NR^7C(O)NR^7R^7$ and YR^{10}; and

R^{21} is selected from H, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, -

$R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$or $-R^8NR^7C(O)NR^7R^7$ and YR^{10}; wherein $R^{7\text{-}10}$ are defined above.

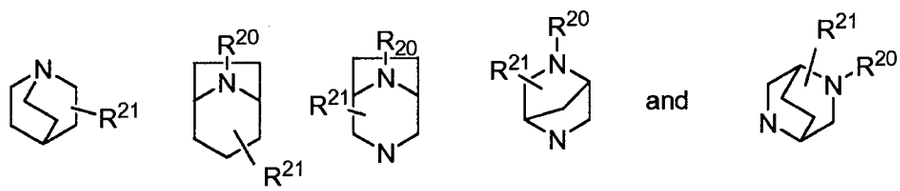
R^6 may be directly bonded, via a carbon (referred to as carbon-linked), to the pyrazolo[1,5-a]pyrimidine ring framework in a number of acceptable positions. R^6 also may be indirectly bonded to the pyrazolo[1,5-a]pyrimidine ring framework in a number of acceptable positions, as joined together using spacer groups defined by X-W-R^6. According to one embodiment, at least one of R^3, R^4 and R^5 are each independently selected from carbon-linked R^6. According to a separate embodiment, at least one of R^3, R^4 and R^5 are each independently selected from X-W-R^6.

According to one embodiment, R^5 is carbon-linked R^6 and comprises a bridged, bicyclic heterocyclic ring selected from:



optionally substituted on nitrogen with R^{20} and optionally substituted on one or more carbons with R^{21}.

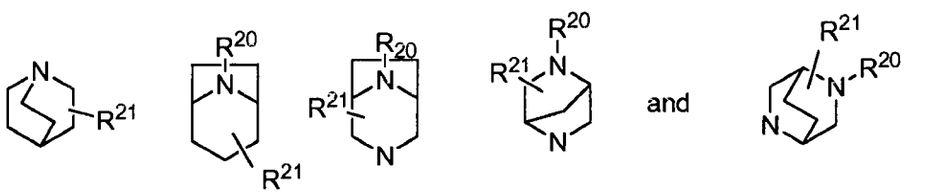
According to a separate embodiment, R^5 is X-W-R^6, wherein R^6 comprises an aryl ring or a heteroaryl ring substituted with a bridged, bicyclic heterocyclic ring selected from:



optionally substituted on nitrogen with R^{20} and optionally substituted on one or more carbons with R^{21}, X is aryl or heteroaryl, each further optionally substituted with one to four substituents selected from -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, -

$R^9C(O)NR^7R^7$, $-R^9OC(O)R^7$, $-R^9OC(O)OR^7$, $-R^9OC(O)NR^7R^7$, $-R^9NR^7C(O)R^7$, $-R^9NR^7C(O)OR^7$ or $-R^9NR^7C(O)NR^7R^7$ and YR^{10} and W is a bond.

According to a separate embodiment, R^6 is R^5 is X-W-R^6, wherein R^6 comprises a bridged, bicyclic heterocyclic ring selected from:

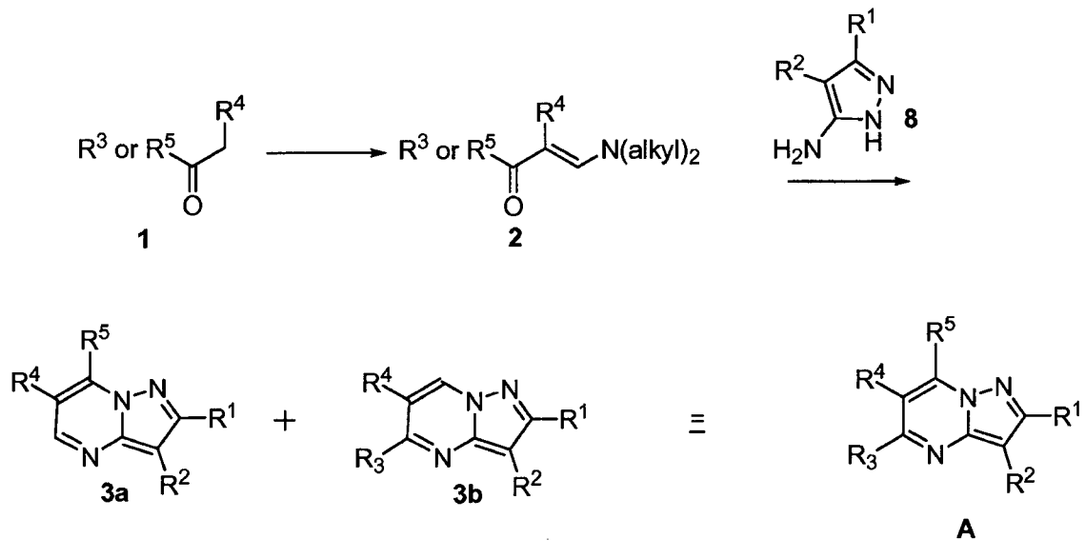


optionally substituted on nitrogen with R^{20} and optionally substituted on one or more carbons with R^{21}, X is aryl or heteroaryl, each further optionally substituted with one to four substituents selected from -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^9OR^7$, $-R^9NR^7R^7$, $-R^9S(O)_mR^7$, $-R^9C(O)R^7$, $-R^9C(O)OR^7$, $-R^9C(O)NR^7R^7$, $-R^9OC(O)R^7$, $-R^9OC(O)OR^7$, $-R^9OC(O)NR^7R^7$, $-R^9NR^7C(O)R^7$, $-R^9NR^7C(O)OR^7$ or $-R^9NR^7C(O)NR^7R^7$ and YR^{10} and W is ZN R^7 or NR^7Z.

According to a separate embodiment, R^6 is a bicyclic spiro heterocyclic ring comprising 1-3 heteroatoms selected from N, O and S, optionally substituted with one to four substituents selected from -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^9OR^7$, $-R^9NR^7R^7$, $-R^9S(O)_mR^7$, $-R^9C(O)R^7$, $-R^9C(O)OR^7$, $-R^9C(O)NR^7R^7$, $-R^9OC(O)R^7$, $-R^9OC(O)OR^7$, $-R^9OC(O)NR^7R^7$, $-R^9NR^7C(O)R^7$, $-R^9NR^7C(O)OR^7$ or $-R^9NR^7C(O)NR^7R^7$ and YR^{10}.

The compounds of this invention may be prepared from: (a) commercially available starting materials (b) known starting materials which may be prepared as described in literature procedures or (c) new intermediates described in the schemes and experimental procedures herein. Reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformation being effected. It is understood by those skilled in the art of organic synthesis that the various functionalities present on the molecule must be consistent with the chemical transformation proposed. This may necessitate judgement as to the order of synthetic steps.

Compounds of the present invention may be prepared as illustrated in the examples and in following reaction Schemes 1 to 5:

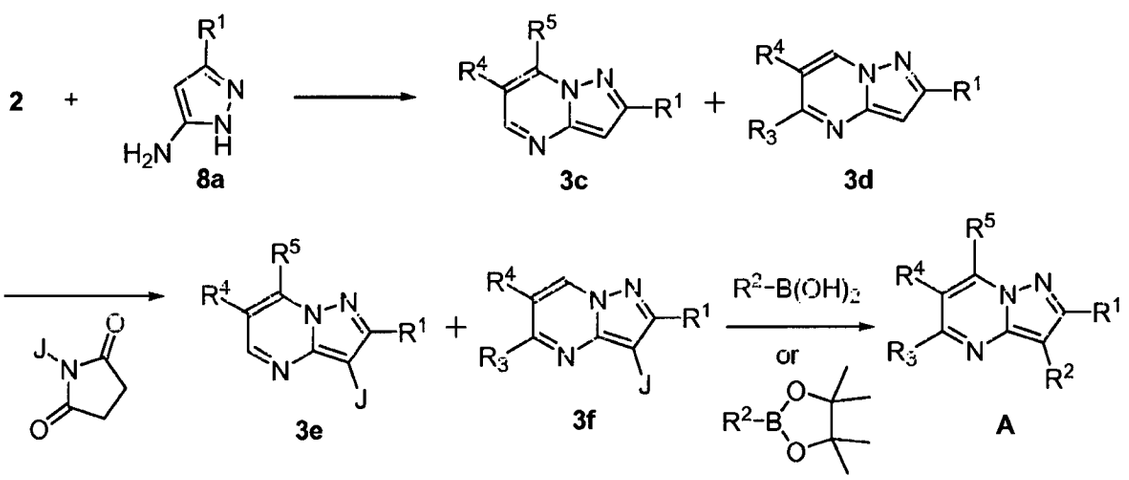


Scheme 1

Referring to Scheme 1, the reaction of a ketone of formula **1**, optionally substituted with R^3, R^4 and R^5 with an acetal of N,Ndialkylformamide or an acetal of N,N-dialkylacetamide, carried out in an inert solvent or without a solvent provides an enaminone, namely a 3-dialkylamino-2-propen-1-one, of formula **2**. The reaction of the substituted 3-aminopyrazole of formula **8**, where R^1 and R^2 are defined above or are hydrogen, with an appropriately substituted 3-dialkylamino-2-propen-1-one in weak acid such as glacial acetic acid or in an inert solvent such as toluene, acetonitrile or dimethoxyethane, at reflux temperature for several hours, or without solvent at 50-150°C, provides the desired compounds of formula **3a** and **3b**. In some cases, chemical modification of compounds of formula **3a** and **3b**, according to methods known by those skilled in the art of organic synthesis, may be performed by those of skill in the art to provide additional compounds of the invention. For example, where any of R^3, R^4, or R^5 in compounds of formula **3a** and **3b** is a halogen, or halo aryl group, or the like, palladium catalyzed, Suzuki or Buchwald coupling reactions provide additional compounds of the invention. Furthermore, when any of R^3, R^4, or R^5 in compounds of formula **3a** and **3b** is a 2-bromopyridyl moiety, reaction of such a compound at elevated temperature, from 50-150° C with an amine, alcohol, or thiol, in DMSO or other polar, aprotic solvent, in the presence of a tertiary amine base such as Hunig's base, or sodium hydride or the like, provides compounds of the invention.

Compounds of the invention may also be synthesized according to the route shown in Scheme 2. Thus, the enaminone of formula **2**, can react with aminopyrazole

compound of formula **8a** in weak acid such as glacial acetic acid or in an inert solvent such as toluene, acetonitrile or dimethoxyethane, at reflux temperature for several hours, or without solvent at 50-150° C, to provide one or both of compounds of formula **3c** and **3d**. Compounds of formula **3c** and **3d** can be separated, chromatographically or via recrystallization, and halogenated to afford the corresponding halo-pyrazole derivatives, using *N*-halosuccininmides at room temperature to 50° C in chlorinated hydrocarbon solvents, to give one or both of compounds of formula **3e** or **3f**. Alternatively, the mixture of compounds of formula **3c** and **3d** can be halogenated under these conditions with subsequent separation of compounds of formula **3e** or **3f**. The halopyrazole compounds of formula **3e** or **3f** can then undergo palladium catalyzed, Suzuki coupling reactions with aryl or heteroaryl boronic acids or corresponding boronate esters to provide the compounds of the invention.

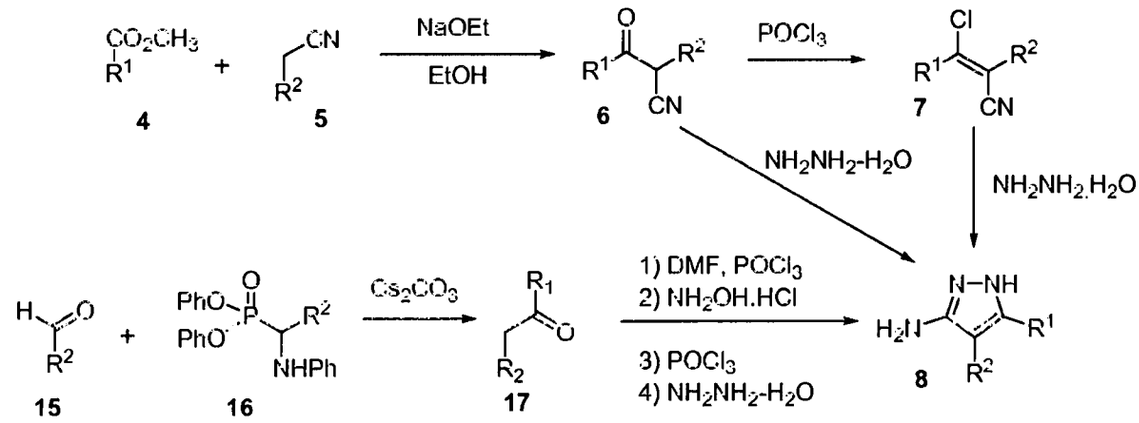


Scheme 2

Substituted 3-dimethylamino-1-(3-heteroaryl)-2-propen-1-ones are described in U.S. Patent Nos. 4,281,000 and 4,521,422 and 3-dialkylamino-1-phenyl-2-propen-1-ones are disclosed in U.S. Patent Nos. 4,178,449 and 4,236,005. Various 3-amino-4-pyrazoles are disclosed in U.S. Patent Nos. 4,236,005; 4,281,000; 4,521,422; 4,626,538; 4,654347; and 4,900,836. Pyrazolo[1,5-a]pyrimidines are prepared by condensation of 3-aminopyrazoles and substituted 3-aminopyrazoles with 1,3-dicarbonyl compounds as described in *J. Med. Chem., 18*, 645 (1974); *J. Med. Chem. 18*, 460 (1975); *J. Med. Chem., 20*, 386 (1977); *Synthesis*, 673 (1982) and references contained therein.

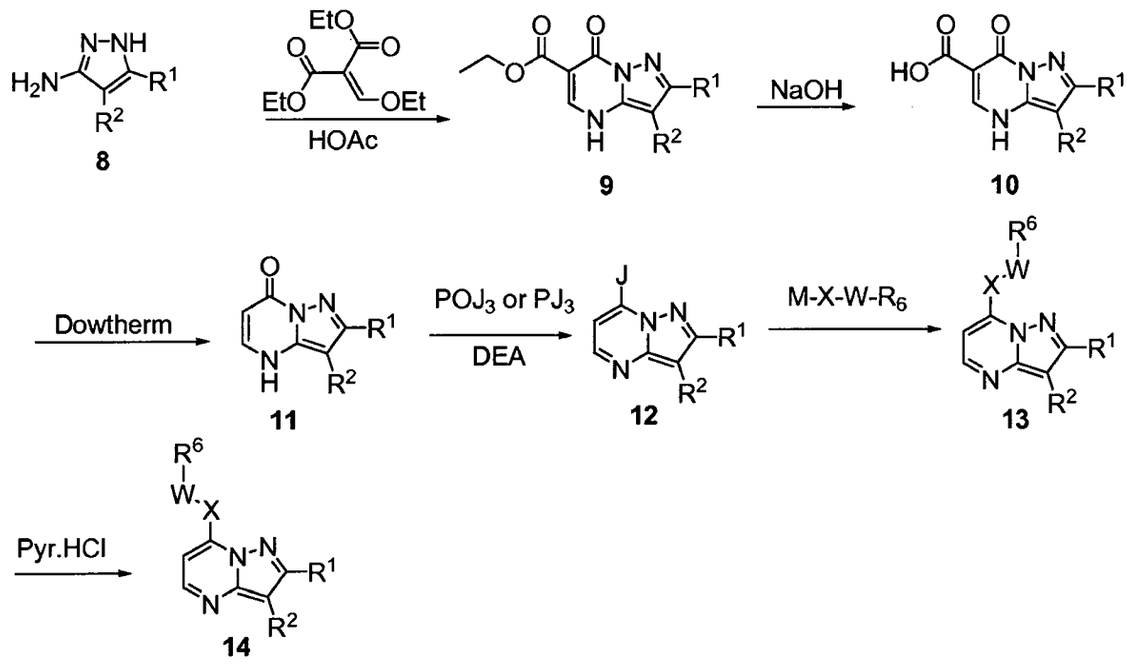
Additional aminopyrazole intermediate compounds of formula **8**, are available according to the route shown in Scheme 3. Referring to Scheme 3, the condensation

reaction of substituted acetonitrile compounds of formula **5**, wherein R^2 is as defined above or is hydrogen, with substituted ester compounds of formula **4** can be carried out in the presence of a base such as, but not limited to sodium ethoxide, in a suitable solvent such as ethanol to provide intermediate compounds of formula **6**. Intermediate compounds of formula **6** can subsequently be reacted with hydrazine hydrate in a suitable solvent such as ethanol to provide aminopyrazole compounds of formula **8** where R^1 and R^2 are defined above. For certain substituted intermediate compounds of formula **6**, it is necessary to first react with phosphorus oxychloride at elevated temperatures, typically at reflux, to provide intermediate compounds of formula **7**. Intermediate compounds of formula **7** can be converted to substituted aminopyrazole compounds of formula **8** by subsequent reaction with hydrazine hydrate in a suitable solvent such as ethanol. Substituted ester compounds of formula **4** and substituted acetonitrile compounds of formula **5** can be obtained from commercial sources or readily prepared by numerous literature procedures by those skilled in the art. Aminopyrazolecompounds of formula **8** can also be prepared from an alternative route starting from aldehyde compounds of formula **15**, as shown in Scheme 3. In the first step of this alternative route, aldehyde compounds **15**, which are commercially available or can be prepared by known methods, are reacted typically at room temperature with phosphonate compounds of formula **16** (which can be prepared according to the procedure of Tet. Lett., **1988**, *39*, 1717-1720) in a suitable solvent such as tetrahydrofuran, using an appropriate base such as, but not limited to, cesium carbonate to provide intermediate compounds of formula **17**. Intermediate compounds of formula **17** are subsequently heated, typically at 80°C, in a mixture of chloroform, phosphorus oxychloride or the like, and dimethylformamide to give the corresponding substituted 3-chloropropenals. The crude 3-chloropropenals are treated with hydroxylamine in a suitable solvent such as dimethylformamide, typically at room temperature, to provide the corresponding 3-chloropropenal oximes, which are then treated with a suitable dehydrating agent such as, but not limited to, phosphorus oxychloride, typically at room temperature, to give the corresponding 3-chloroacrylonitriles. The intermediate 3-chloroacrylonitriles can then be converted into the desired substituted aminopyrazole compounds of formula **8** by subsequent reaction with hydrazine hydrate in a suitable solvent such as ethanol.



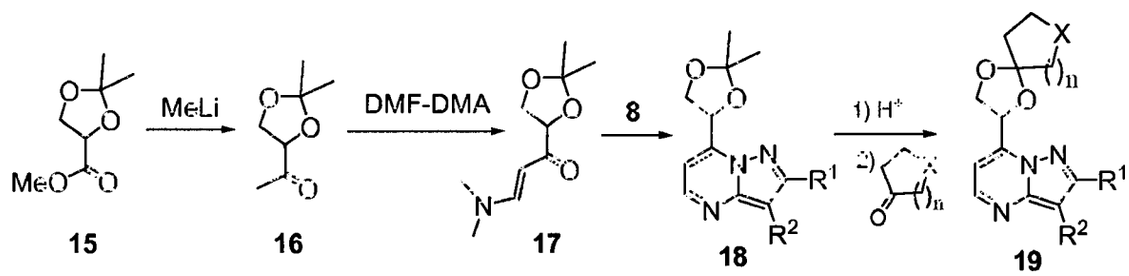
Scheme 3

Referring to Scheme 4, compounds of the invention are also available via condensation of the desired aminopyrazole compounds of formula **8**, with alkoxymethylene malonates in weak acid such as acetic acid at elevated temperature, typically at reflux, to provide the dihydropyrazolo[1,5-a]pyrimidine derivative compounds of formula **9**. Hydrolysis of the ester functionality of compounds of formula **9** mediated by aqueous base such as sodium hydroxide provides pyrimidone compounds of formula **10,** that is then decarboxylated at elevated temperature to form compounds of formula **11**. Transformation of the pyrimidone compounds of formula **11** into the corresponding halo-pyrimidine compounds of formula **12**, is carried out with phosphorus oxychloride, or similar halogenating agent, at elevated temperature in the presence of an amine base such as *N,N*-diethylaniline. Reaction of halo-pyrimidine compounds of formula **12** with M-X-W-R^6, where M is a hydrogen, boronic acid, boronate ester, stannane, or silane, in the presence of a transition metal catalyst then gives compounds of formula **13** of the invention which may be further functionalized according to methods known to those skilled in the art. Halo-pyrimidine compounds of formula **12** can similarly be converted into compounds of formula **13** of the invention by reaction with M-X-W-R^6 where M is a metal including but not limited to zinc, lithium, and magenesium. In the case of compounds wherein R^2 is a methoxyphenyl moiety, the corresponding phenol (compounds of formula **14**, R_2 =PhOH) is provided by reaction with pyridine hydrochloride at elevated temperature, or boron tribromide.



Scheme 4

Referring to Scheme 5, certain compounds of the invention wherein R^6 is a spiro-bicyclic moiety are available starting from ketone-ketal compounds of formula **16**, prepared in one step from commercially available methyl ester compounds of formula **15** [D. Tanner, P. Somfai, Syn. Commun., 16(12), 1517-1522 (1986)]. Conversion of methyl ketone compounds of formula **16** into enaminone compounds of formula **17** is carried out by reaction with acetals of N,N-dialkylformamide or acetals of N,N-dialkylacetamide, in an inert solvent or without a solvent at a temperature of 50-100° C. The reaction of the substituted 3-aminopyrazole compounds of formula **8**, where R^1 and R^2 are defined above or are hydrogen, with enaminone compounds of formula **17** in weak acid such as glacial acetic acid or in an inert solvent such as toluene, acetonitrile or dimethoxyethane, at reflux temperature for several hours, or without solvent at 50-150° C, produces the desired ketal compounds of formula **18**. Hydrolysis of the ketal compounds of formula **18** under acidic conditions, such as aqueous acetic acid, trifluoroacetic acid, tosic acid, or camphorsulfonic acid at room temperature to 100° C, followed by reaction of the resulting diol with carbocyclic and heterocyclic ketones under acidic conditions provides invented compounds of formula **19**.



Scheme 5

Exemplary compounds of Formula A prepared by methods of the present invention include the following compounds: 3-(7-{6-[(1-azabicyclo[2.2.2]oct-4-ylmethyl)amino]pyridin-3-yl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol, 3-(7-{6-[(3*S*)-1-azabicyclo[2.2.2]oct-3-ylamino]pyridin-3-yl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol, 3-(7-{6-[(3*R*)-1-azabicyclo[2.2.2]oct-3-ylamino]pyridin-3-yl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol, (3*R*)-*N*-{4-[3-(3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]pyridin-2-yl}quinuclidin-3-amine, (3*R*)-*N*-{5-[3-(4-chloro-3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]pyridin-2-yl}quinuclidin-3-amine, 3-{7-[(1-azabicyclo[2.2.2]oct-4-ylmethyl)amino]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl}phenol, ethyl 3-[3-(3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate, ethyl 3-[3-(3-hydroxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]-octane-8-carboxylate, 3-[7-(8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]phenol, ethyl 3-[3-(4-chloro-3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate, ethyl 3-[3-(4-chloro-3-hydroxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate, 5-[7-(8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]-2-chlorophenol, 5-[7-(8-acetyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]-2-chlorophenol, 2-chloro-5-{7-[8-(methylsulfonyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl}phenol, 5-[7-(8-acetyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]-2-chlorophenyl acetate, 7-(8-azabicyclo[3.2.1]oct-3-yl)-3-(4-chloro-3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(4-chloro-3-methoxyphenyl)-7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 2-chloro-5-[7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]phenol, 7-(8-azabicyclo[3.2.1]oct-3-yl)-3-(3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-3-(2-methoxypyridin-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 4-[7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]pyridin-2-ol, 4-[7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]aniline, 1-{4-[7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]phenyl}urea, 3-(3-methoxyphenyl)-7-[4-(8-methyl-3,8-

diazabicyclo[3.2.1]oct-3-yl)phenyl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-{7-[4-(8-methyl-3,8-diazabicyclo[3.2.1]oct-3-yl)phenyl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl}phenol, 3-(4-chloro-3-methoxyphenyl)-7-[4-(8-methyl-3,8-diazabicyclo[3.2.1]oct-3-yl)phenyl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 2-chloro-5-{7-[4-(8-methyl-3,8-diazabicyclo[3.2.1]oct-3-yl)phenyl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl}phenol, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol, 3-(7-{4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol, 3-(4-chloro-3-methoxyphenyl)-7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(4-fluoro-3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 5-(7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)-2-fluorophenol, 3-(1*H*-indazol-4-yl)-7-{6-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]pyridin-3-yl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-7-{4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(3-methoxyphenyl)-7-{4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]-hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(4-fluoro-3-methoxyphenyl)-7-{4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 5-(7-{4-[(1*S*,4*S*)-5-ethyl-2,5-diazabicyclo[2.2.1]-hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)-2-fluorophenol, 5-(7-{4-[(1*S*,4*S*)-5-acetyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)-2-fluorophenol, 7-{6-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]pyridin-3-yl}-3-(7-methyl-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(7-chloro-1*H*-indazol-4-yl)-7-{6-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]pyridin-3-yl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(7-fluoro-1*H*-indazol-4-yl)-7-{6-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]pyridin-3-yl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(7-{6-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]pyridin-3-yl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)benzamide, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-methylphenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-7-{2-methyl-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-4-fluorophenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-fluoro-2-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, *tert*-butyl (1*S*,4*S*)-5-{2-[3-(4-chloro-3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-5-fluorophenyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate, 3-(4-chloro-3-methoxyphenyl)-7-{2-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-4-fluorophenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(4-chloro-3-methoxyphenyl)-7-{4-fluoro-2-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-

[(1*S*,4*S*)-2,5-diazabicyclo-[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-fluorophenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2-fluoro-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 2-fluoro-5-(7-{4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol, 3-(4-fluoro-3-methoxyphenyl)-7-{2-methyl-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 2-fluoro-5-(7-{2-methyl-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol, 3-(7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-methylphenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol, 3-(7-{2-methyl-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol, 3-(7-{2-chloro-4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol, 3-(7-{2-chloro-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol, 7-{2-chloro-4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2-chloro-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, ethyl 3-[3-(3-hydroxy-4-methylphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate, 5-[7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]-2-fluorophenol, ethyl 3-[3-(2,3-difluorophenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate, ethyl 3-(3-{3-[(methylsulfonyl)amino]-phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate, methyl {4-[7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]phenyl}carbamate, 4-[7-(8-ethyl-8-azabicyclo[3.2.1]-oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]-2-hydroxybenzonitrile, tert-butyl {4-[7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]-2-methoxyphenyl}carbamate, 4-[7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]-2-methoxyaniline, 2-amino-5-[7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]phenol, *N*-{4-[7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]-2-hydroxyphenyl}formamide, *N*-{4-[7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]-2-methoxyphenyl}formamide, ethyl 3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate, 7-(8-azabicyclo[3.2.1]oct-3-yl)-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo-[1,5-a]pyrimidine, ethyl 3-[3-(7-chloro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate, ethyl 3-{2-pyridin-4-yl-3-[7-(trifluoromethyl)-1*H*-indazol-4-yl]pyrazolo[1,5-a]pyrimidin-7-yl}-8-azabicyclo[3.2.1]-octane-8-carboxylate, 7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-3-(7-methyl-1H-indazol-4-yl)-2-pyridin- 4-ylpyrazolo[1,5-

a]pyrimidine, ethyl 3-[3-(7-methyl-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate, 3-(7-chloro-1*H*-indazol-4-yl)-7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-yl-3-[7-(trifluoromethyl)-1*H*-indazol-4-yl]pyrazolo[1,5-a]pyrimidine, ethyl 3-[3-(7-fluoro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate, 3-(7-chloro-6-fluoro-1*H*-indazol-4-yl)-7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, ethyl 3-[3-(2-oxo-2,3-dihydro-1*H*-benzimidazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]-octane-8-carboxylate, ethyl 3-[3-(1*H*-indol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate, ethyl 3-[3-(1*H*-indol-6-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate, ethyl 3-[3-(2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-b]pyridin-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate, 7-(8-ethyl-8-azabicyclo-[3.2.1]oct-3-yl)-3-(1*H*-indol-6-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, ethyl 3-[3-(2-oxo-2,3-dihydro-1*H*-indol-6-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate, 2-chloro-5-[7-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]phenol, 7-(8-Ethyl-8-azabicyclo[3.2.1]-octan-3-yl)-3-(1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine, Ethyl 3-(3-(3-(1,3,4-oxadiazol-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate, *tert*-Butyl (1S,4S)-5-{3-fluoro-4-[3-(1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl}-2,5-diazabicyclo-[2.2.1]heptane-2- carboxylate, 7-{4-[(1S,4S)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-fluorophenyl}-3-(1H-indazol-4- yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2-Fluoro-4-[(1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2-fluoro-4-[(1S,4S)-5-methyl-5-oxido-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo-[1,5-a]pyrimidine, (1S,4S)-5-{3-Chloro-4-[3-(1H-indazol-4-yl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester, 7-[2-Chloro-4-((1S,4S)-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-phenyl]-3-(1H-indazol-4-yl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine bis-hydrochloride salt, 7-[2-Chloro-4-((1S,4S)-5-methyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-phenyl]-3-(1H-indazol-4-yl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine, *tert*-butyl (1S,4S)-5-{3,5-difluoro-4-[3-(1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2- carboxylate, 7-(4-((1S,4S)-2,5-diazabicyclo[2.2.1]-heptan-2-yl)-2,6-difluorophenyl)-3-(1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine, 7-{2,6-difluoro-4-[(1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3- (1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, *tert*-Butyl (1S,4S)-5-{4-[3-(7-fluoro-1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate, 7-[4-(2,5-Diaza-bicyclo[2.2.1]hept-2-yl)-phenyl]-3-(7-fluoro-1H-indazol-4-yl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine, 3-(7-fluoro-1H-indazol-4-yl)-7-{4-[(1S,4S)-5-methyl-

2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine hydrochloride, *tert*-Butyl (1S,4S)-5-{3-fluoro-4-[3-(7-fluoro-1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2- carboxylate, 7-{4-[(1S,4S)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-fluorophenyl}-3-(7-fluoro-1H- indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(7-fluoro-1H-indazol-4-yl)-7-{2-fluoro-4-[(1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, *tert*-Butyl (1S,4S)-5-{3,5-difluoro-4-[3-(7-fluoro-1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2- carboxylate, 7-{4-[(1S,4S)-2,5-Diazabicyclo[2.2.1]hept-2-yl]-2,6-difluorophenyl}-3-(7-fluoro-1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2,6-Difluoro-4-[(1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3- (7-fluoro-1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, ethyl 3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-5-yl]-8-azabicyclo[3.2.1]-octane-8-carboxylate, 2-{3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]oct-8-yl}ethanol, 3-(1*H*-indazol-4-yl)-7-(8-isopropyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-7-[8-(methylsulfonyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxamide, 2-{3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]oct-8-yl}-*N*,*N*-dimethyl-2-oxoethanamine, {3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]oct-8-yl}acetonitrile, *N*-ethyl-3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxamide, 7-(8-acetyl-8-azabicyclo[3.2.1]oct-3-yl)-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-*N*,*N*-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxamide, *tert*-butyl (1*S*,4*S*)-5-{[3-(4-chloro-3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]methyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate, *tert*-butyl (1*S*,4*S*)-5-{4-[3-(7-fluoro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-5-yl]phenyl}-2,5-diazabicyclo-[2.2.1]heptane-2-carboxylate, *tert*-butyl (1*S*,4*S*)-5-{3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate, 7-{3-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, *tert*-butyl (1*S*,4*S*)-5-{4-[3-(7-chloro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate, 3-(1*H*-indazol-4-yl)-7-{3-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(7-chloro-1*H*-indazol-4-yl)-7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, *tert*-butyl (2*S*)-2-({3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]oct-8-yl}carbonyl)pyrrolidine-1-carboxylate, 3-(1*H*-indazol-4-yl)-7-(8-L-prolyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 1-{3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]oct-8-yl}propan-2-

one, ethyl 3-[3-(7-fluoro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-5-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-fluorophenyl}-3-(3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-fluorophenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol, 3-(7-{2-fluoro-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-methylphenyl}-3-(7-fluoro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(7-fluoro-1*H*-indazol-4-yl)-7-{2-methyl-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo-[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-(8-azabicyclo[3.2.1]oct-3-yl)-3-(7-fluoro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, {3-[3-(7-fluoro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]oct-8-yl}acetonitrile, 3-(7-chloro-1*H*-indazol-4-yl)-5-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-7-[6-(8-methyl-3,8-diazabicyclo[3.2.1]oct-3-yl)pyridin-3-yl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(7-chloro-1*H*-indazol-4-yl)-7-{4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-(1,4-dioxaspiro[4.5]dec-8-yl)-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-7-{4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.2]oct-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo-[2.2.2]oct-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-4,6-difluorophenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 5-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-*N*,*N*-dimethylaniline, 7-{2,4-difluoro-6-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 2-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-*N*,*N*-dimethyl-5-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]aniline, 7-{*cis*-4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]cyclohexyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-7-[*cis*-4-(3-oxa-8-azabicyclo[3.2.1]oct-8-yl)cyclohexyl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-7-[*trans*-4-(3-oxa-8-azabicyclo[3.2.1]-oct-8-yl)cyclohexyl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-7-[*cis*-4-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)cyclohexyl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-7-[*trans*-4-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)cyclohexyl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-7-{*cis*-4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl]cyclohexyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-7-{*trans*-4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl]cyclohexyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{*trans*-4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]cyclohexyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-3-(trifluoromethyl)phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-1-naphthyl}-3-(1*H*-

indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-7-{4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]-3-(trifluoromethyl)phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-7-{4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]-1-naphthyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-3,5-difluorophenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2,3-difluorophenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2,5-difluorophenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{3,5-difluoro-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2,3-difluoro-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2,5-difluoro-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-[(1*S*,4*S*)-5-ethyl-2,5-diazabicyclo[2.2.1]-hept-2-yl]-2,6-difluorophenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2,6-difluoro-4-[(1*S*,4*S*)-5-isobutyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2,6-difluoro-4-[(1*S*,4*S*)-5-isopropyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-[(1*S*,4*S*)-5-cyclobutyl-2,5-diazabicyclo[2.2.1]hept-2-yl]-2,6-difluorophenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-(1,4-dioxaspiro[4.5]dec-8-yl)-3-(7-fluoro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.2]oct-2-yl]-2-fluorophenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2-fluoro-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.2]oct-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-2-pyridin-4-yl-7-{2,3,5,6-tetrafluoro-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}pyrazolo[1,5-a]pyrimidine, *tert*-butyl (1*S*,4*S*)-5-{3-chloro-4-[3-(7-fluoro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate, 7-{*cis*-4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]cyclohexyl}-3-(7-fluoro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(7-fluoro-1*H*-indazol-4-yl)-7-{*cis*-4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl]cyclohexyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(7-fluoro-1*H*-indazol-4-yl)-7-{*trans*-4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl]cyclohexyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(7-fluoro-1*H*-indazol-4-yl)-7-[*cis*-4-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)cyclohexyl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(7-fluoro-1*H*-indazol-4-yl)-7-[*trans*-4-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)cyclohexyl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(7-fluoro-1*H*-indazol-4-yl)-7-[*cis*-4-(3-oxa-8-azabicyclo[3.2.1]oct-8-yl)cyclohexyl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(7-fluoro-1*H*-indazol-4-yl)-7-[*trans*-4-(3-oxa-8-azabicyclo[3.2.1]oct-8-yl)cyclohexyl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{*trans*-4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]cyclohexyl}-3-(7-fluoro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2-chloro-4-[(1*S*,4*S*)-

2,5-diazabicyclo[2.2.1]-hept-2-yl]phenyl}-3-(7-fluoro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-3-fluorophenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-(trifluoromethyl)phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2-bromo-4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{3-fluoro-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-7-{4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-(trifluoromethyl)phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2-bromo-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2,6-difluoro-4-[(1*S*,4*S*)-5-methyl-5-oxido-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-7-{5-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-ylmethyl]furan-3-yl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, *tert*-butyl (1*S*,4*S*)-5-({4-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]furan-2-yl}methyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate, 7-{5-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]furan-3-yl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, *tert*-butyl (1*S*,4*S*)-5-({5-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]thiophen-2-yl}methyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate, 3-(1*H*-indazol-4-yl)-7-{5-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-ylmethyl]thiophen-2-yl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{5-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]thiophen-2-yl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, ethyl (3-endo)-3-[3-(1*H*-indazol-4-yl)-6-methyl-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate, 3-(1*H*-indazol-4-yl)-7-[6-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)pyridin-3-yl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-7-{6-[(1*S*,4*S*)-2-oxa-5-azabicyclo-[2.2.1]hept-5-yl]pyridin-3-yl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, *tert*-butyl (1*S*,4*S*)-5-{3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]benzyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate, *tert*-butyl (1*S*,4*S*)-5-{4-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]benzyl}-2,5-diazabicyclo[2.2.1]-heptane-2-carboxylate, 3-(1*H*-indazol-4-yl)-7-{4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]-hept-5-ylmethyl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-2-fluorophenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2-fluoro-4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-ylmethyl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2-fluoro-4-[(1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]hept-5-ylmethyl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{3-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]phenyl}-3-(1*H*-indazol-4-

yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 9-{3-fluoro-4-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]benzyl}-3,7-dioxa-9-azabicyclo[3.3.1]nonane and pharmaceutically acceptable salts thereof.

Compounds of Formula A may be obtained as inorganic or organic salts using methods known to those skilled in the art, for example Richard C. Larock, Comprehensive Organic Transformations, VCH publishers, 411-415, 1989. It is well known to one skilled in the art that an appropriate salt form is chosen based on physical and chemical stability, flowability, hydroscopicity and solubility.

Pharmaceutically acceptable salts of the compounds of Formula A with an acidic moiety may be formed from organic and inorganic bases. For example with alkali metals or alkaline earth metals such as sodium, potassium, lithium, calcium, or magnesium or organic bases and N- tetraalkylammonium salts such as N-tetrabutylammonium salts. Similarly, when a compound of this invention contains a basic moiety, salts may be formed from organic and inorganic acids. For example salts may be formed from acetic, propionic, lactic, citric, tartaric, succinic, fumaric, maleic, malonic, mandelic, malic, phthalic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, naphthalenesulfonic, benzenesulfonic, toluenesulfonic, camphorsulfonic, and similarly known acceptable acids. Suitable examples of pharmaceutically acceptable salts include, but are not limited, to sulfate; citrate, acetate; oxalate; chloride; bromide; iodide; nitrate; bisulfate; phosphate; acid phosphate; isonicotinate; lactate; salicylate; acid citrate; tartrate; oleate; tannate; pantothenate; bitartrate; ascorbate; succinate; maleate; gentisinate; fumarate; gluconate; glucaronate; saccharate; formate; benzoate; glutamate; methanesulfonate; ethanesulfonate; benzenesulfonate; p-toluenesulfonate; pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)); and salts of fatty acids such as caproate, laurate, myristate, palmitate, stearate, oleate, linoleate, and linolenate salts.The compounds can also be used in the form of esters, carbamates and other conventional prodrug forms, which when administered in such form, convert to the active moiety *in-vivo*.

The present invention accordingly provides a pharmaceutical composition, which comprises an effective amount of a compound of Formula A in combination or association with a pharmaceutically acceptable carrier. Pharmaceutical compositions are prepared in accordance with acceptable pharmaceutical procedures, such as described in Remingtons Pharmaceutical Sciences, 17th edition, ed. Alfonoso R. Gennaro, Mack Publishing Company, Easton, Pa. (1985). Pharmaceutically acceptable carriers are those that are compatible with the other ingredients in the formulation and biologically acceptable. As used herein, the term "effective amount" refers to the amount of active compound or pharmaceutical agent that

elicits the biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following: (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease; (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting or slowing further development of the pathology and/or symptomatology); and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology).

The compounds of this invention may be formulated neat or may be combined with one or more pharmaceutically acceptable carriers for administration. Suitable carriers include but are not limited to, for example, solvents, diluents and the like, and may be administered orally in such forms as tablets, capsules, dispersible powders, granules, or suspensions containing, for example, from about 0.05 to 5% of suspending agent, syrups containing, for example, from about 10 to 50% of sugar, and elixirs containing, for example, from about 20 to 50% ethanol, and the like, or parenterally in the form of sterile injectable solution or suspension containing from about 0.05 to 5% suspending agent in an isotonic medium. Such pharmaceutical preparations may contain, for example, from about 0.05 up to about 90% of the active ingredient in combination with the carrier, more usually between about 5% and 60% by weight.

In some embodiments, the formulations are administered transdermally which includes all methods of administration across the surface of the body and the inner linings of body passages including epithelial and mucosal tissues. Such administration may be in the form of a lotion, cream, colloid, foam, patch, suspension, or solution.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration and the severity of the condition being treated. However, in general, satisfactory results are obtained when the compounds of the invention are administered at a daily dosage of from about 0.5 to about 1000 mg/kg of animal body weight, optionally given in divided doses two to four times a day, or in sustained release form. For most large mammals the total daily dosage is from about 1 to 1000 mg, preferably from about 2 to 500 mg. Dosage forms suitable for internal use comprise from about 0.5 to 1000 mg of the active compound in intimate admixture with a solid or liquid

pharmaceutically acceptable carrier. This dosage regimen may be adjusted to provide the optimal therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

The compounds of this invention may be administered orally as well as by intravenous, intramuscular, or subcutaneous routes. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvants customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules. Oral administration of the compounds is sometimes desirable. In some cases it may be desirable to administer the compounds directly to the airways in the form of an aerosol.

The compounds of this invention may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt may be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier may be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

For the treatment of cancer, the compounds of this invention may be administered in combination with other antitumor substances or with radiation therapy. These other substances or radiation treatments may be given at the same or at different times as

the compounds of this invention. These combined therapies may effect synergy and result in improved efficacy. For example, the compounds of this invention may be used in combination with mitotic inhibitors such as taxol or vinblastine, alkylating agents such as cisplatin or cyclophosamide, antimetabolites such as 5-fluorouracil or hydroxyurea, DNA intercalators such as adriamycin or bleomycin, topoisomerase inhibitors such as etoposide or camptothecin, antiangiogenic agents such as angiostatin, and antiestrogens such as tamoxifen. As used in accordance with this invention, the term an "effective amount" of a compound means either directly administering such compound, or administering a prodrug, derivative, or analog which will form an effective amount of the compound within the body.

As used in accordance with this invention, the term an "effective amount" of a compound means either directly administering such compound, or administering a prodrug, derivative, or analog which will form an effective amount of the compound within the body.

Methods of administration of a pharmaceutical composition of the invention are not specifically restricted, and can be administered in various preparations depending on the age, sex, and symptoms of the patient. For example, tablets, pills, solutions, suspensions, emulsions, granules and capsules may be orally administered. Injection preparations may be administered individually or mixed with injection transfusions such as glucose solutions and amino acid solutions intravenously. If necessary, the injection preparations are administered singly intramuscularly, intracutaneously, subcutaneously or intraperitoneally. Suppositories may be administered into the rectum.

The amount of the compound of formula A contained in a pharmaceutical composition according to the present invention is not specifically restricted, however, the dose should be sufficient to treat, ameliorate, or reduce the targeted symptoms. The dosage of a pharmaceutical composition according to the present invention will depend on the method of use, the age, sex, and condition of the patient.

The present invention also provides methods of inhibition and treatment further comprising administering an additional inhibitor of an oncoprotein kinase of the Ras/Raf/MEK pathway.

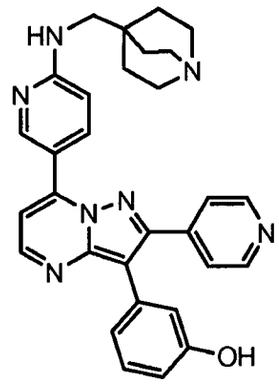
The pharmaceutical compositions of the present invention may comprise the compound of the present invention alone or in combination with other oncoprotein kinase-inhibiting compounds or chemotherapeutic agents. Chemotherapeutic agents include, but are not limited to exemestane, formestane, anastrozole, letrozole, fadrozole, taxane and

derivatives such as paclitaxel or docetaxel, encapsulated taxanes, CPT-11, camptothecin derivatives, anthracycline glycosides, e.g., doxorubicin, idarubicin, epirubicin, etoposide, navelbine, vinblastine, carboplatin, cisplatin, estramustine, celecoxib, tamoxifen, raloxifen, Sugen SU-5416, Sugen SU-6668, and Herceptin.

Having described the invention, the invention is further illustrated by the following non-limiting examples.

EXAMPLES

Example 1: 3-(7-{6-[(1-Azabicyclo[2.2.2]oct-4-ylmethyl)amino]pyridin-3-yl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol



Step 1: A slurry of 5-acetyl-2-bromopyridine (5 g, 0.025 mol) in 45 mL of dimethylformamide dimethyl acetal was heated to 110° C for 2.5 hrs. The reaction mixture was cooled to room temperature to precipitate a yellow solid, which was filtered, rinsed with ether, and dried at 40° C under vacuum overnight to provide 5.20 g (82% yield) of (2E)-1-(6-bromopyridin-3-yl)-3-(dimethylamino)prop-2-en-1-one, which was used without further purification.

Step 2: To 5 mL of dry ethanol was added 0.73 g (31.84 mmol) of sodium metal (after removal of mineral oil with hexane) and the mixture was stirred at 45°C for 1 hour until the solution turned clear. A mixture of 3 g (20.38 mmol) of 3-(methoxyphenyl)acetonitrile and 3.9 g (28.66 mmol) of methyl isonicotinate in 26 mL of dry ethanol was then added and the resulting brown solution was heated at reflux for 3 hours. After cooling, the residue was evaporated and purified by silica gel chromatography eluting with 9:1 to 4:1 methylene

chloride/methanol to provide 1.75 g (34% yield) of 2-(3-methoxyphenyl)-3-oxo-3-pyridin-4-yl-propionitrile.

A mixture of 1.7 g (6.74 mmol) of 2-(3-methoxyphenyl)-3-oxo-3-pyridin-4-yl-propionitrile and 17 mL $POCl_3$ was heated at 80°C for 18 hours. After cooling, the $POCl_3$ was evaporated off. To the resulting residue was added toluene, and the mixture was then evaporated to dryness. This step was repeated to fully remove $POCl_3$. Ice and saturated sodium bicarbonate were added to the residue, and a solid precipitated out, providing 1 g (57% yield) of 3-chloro-2-(3-methoxyphenyl)-3-pyridin-4-yl-acrylonitrile as a white solid. MS: 271.1 [M+H].

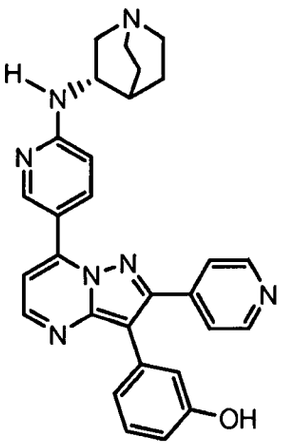
A mixture of 1 g (3.69 mmol) of 3-chloro-2-(3-methoxyphenyl)-3-pyridin-4-yl-acrylonitrile and 0.9 mL (18.6 mmol) hydrazine hydrate in 30 mL of ethanol was heated at reflux for 6.5 hours. The mixture was allowed to cool to room temperature and the solvent was removed by evaporation. Aqueous sodium bicarbonate was stirred into the residue, and the resulting solid was collected by filtration. The solid was washed with water, and then dried under vacuum to provide 0.92 g (94% yield) of 4-[3-methoxy-phenyl]-5-pyridin-4-yl-1H-pyrazol-3-amine. MS: 267.2 [M+H].

A mixture of 4-(3-methoxyphenyl)-5-pyridin-4-yl-1H-pyrazol-3-amine (3.0g, 11.27 mmol) and pyridine hydrochloride (6.0g, 51.92 mmol) was heated at 202° C for one hour. The reaction was then cooled to room temperature, diluted with 10 mL of ammonium hydroxide, stirred for 30 min, and then the solvent was removed under vacuum. The resulting residue was washed with 15% methanol/dichloromethane and the collected washings were dried over sodium sulfate, filtered, and evaporated to a residue that was purified via silica flash chromatography eluting with 5%-12% methanol/dichloromethane to provide 2.21g (78% yield) of 3-(3-amino-5-pyridin-4-yl-1H-pyrazol-4-yl)phenol as a beige solid.

Step 3: 1-(6-Bromo-pyridin-3-yl)-3-dimethylamino-propenone (258 mg, 1.0 mmol), 3-(3-amino-5-pyridin-4-yl-1H-pyrazol-4-yl)phenol (254 mg, 1.0 mmol), and 3 mL glacial acetic acid were combined and heated in the microwave at 120° C for 3000 sec. Upon cooling, obtained yellow precipitate which was filtered, rinsed with 10% ethyl acetate/ether then with ether, and dried at 40° C under reduced pressure to give 575 mg (94% yield) of 3-[7-(6-bromopyridin-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]phenol as an acetic acid salt, a yellow orange solid. MS: 444.1 [M+H].

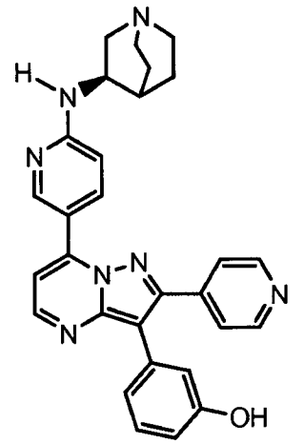
Step 4: To a stirred suspension of 3-[7-(6-bromopyridin-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]phenol (117 mg, 0.25 mmol) in 1.2 mL of DMSO was added diisopropylethylamine (0.13 mL, 0.75 mmol) followed by 1-(1-azabicyclo[2.2.2]oct-4-yl)methanamine (74 mg, 0.5 mmol). The mixture was heated at 125° C for 16 hours, cooled to room temperature, and purified by RP-HPLC on a Gemini™ C18 column eluted with 5-95% acetonitrile/water (0.02% TFA) to give 18 mg of 3-(7-{6-[(1-azabicyclo[2.2.2]oct-4-ylmethyl)amino]pyridin-3-yl}-2-pyridin-4- ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol as a yellow-orange solid, 11% yield. MS: 504.4 [M+H].

Example 2: 3-(7-{6-[(3S)-1-Azabicyclo[2.2.2]oct-3-ylamino]pyridin-3-yl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol



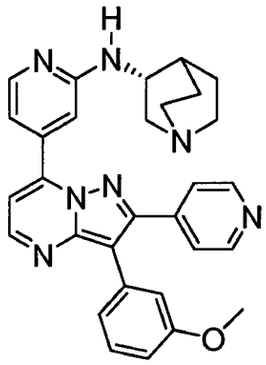
To a stirred suspension of 3-[7-(6-bromopyridin-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]phenol (117 mg, 0.25 mmol) in 1.0 mL DMSO was added diisopropylethylamine (0.23 mL, 1.35 mmol) and 3-(S)-aminoquinuclidine dihydrochloride (60 mg, 0.3 mmol) and the resulting mixture was microwaved at 150 °C for 1 hour and then purified by RP-HPLC on a Gemini™ C18 column, eluting with 5-95% acetonitrile/water (0.02% TFA) to give 21 mg (14% yield) of 3-(7-{6-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]pyridin-3-yl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol as a yellow-orange solid. MS: 490.4 [M+H].

Example 3: 3-(7-{6-[(3R)-1-Azabicyclo[2.2.2]oct-3-ylamino]pyridin-3-yl}-2-pyridin-4- ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol



Following the procedure for Example 2, 3-[7-(6-bromopyridin-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]phenol and 3-(R)-aminoquinuclidine dihydrochloride reacted to give 29 mg (14% yield) of 3-(7-{6-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]pyridin-3-yl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol as a yellow solid. MS: 490.4 [M+H].

Example 4: (3R)-N-{4-[3-(3-Methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]pyridin-2-yl}quinuclidin-3-amine



Step 1: To a solution of acetylpyridine (2.2 mL, 20 mmol) in 22 mL dichloromethane was added 3-chloroperoxybenzoic acid (3.45 g, 20 mmol) and the resulting mixture was heated to reflux for 16 hours. The solvent was then evaporated and the crude residue was chromatographed on silica gel, eluting with 0-40% methanol/ethyl acetate to provide 1 g (38% yield) of 1-(1-oxy-pyridin-4-yl)-ethanone as a white solid which was used directly in the next step.

Step 2: A solution of 1-(1-oxy-pyridin-4-yl)-ethanone (231 mg, 1.7 mmol) in 2.2 mL dimethylformamide dimethyl acetal in a 5 mL Smith process vial was microwaved at 110°C for one hour. The resulting mixture was cooled to RT, and the precipitate was collected by

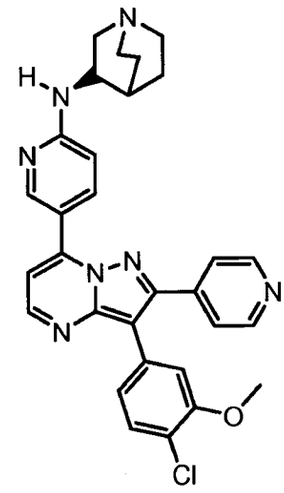
filtration and then rinsed with 2% ethyl acetate/ether followed by ether. The solid was dried at 40° C under reduced pressure to give 222 mg (68% yield) of 3-dimethylamino-1-(1-oxy-pyridin-4-yl)-propenone as a beige solid that was used directly in the next step.

Step 3: A mixture of 3-dimethylamino-1-(1-oxy-pyridin-4-yl)-propenone (222 mg, 1.15 mmol) and 4-(3-methoxyphenyl)-5-pyridin-4-yl-1H-pyrazol-3-amine (308 mg, 1.15 mmol) in 2 mL of glacial acetic acid was heated in the microwave at 120° C for one hour. The reaction mixture was then cooled to room temperature, and the resulting yellow precipitate was collected by filtration, and rinsed with 10% ethyl acetate/ether and then with ether. The solid was dried at 40°C under reduced pressure to give 330 mg (65% yield) of 3-(3-methoxyphenyl)-7-(1-oxidopyridin-4-yl)-2-pyridin-4-ylpyrazolo[1,5- a]pyrimidine as yellow solid that was used directly in the next step. MS: 396.1 [M+H].

Step 4: A solution of 3-(3-methoxyphenyl)-7-(1-oxidopyridin-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine (264 mg, 0.67 mmol) was refluxed in $POCl_3$ for one hour and then cooled to room temperature. The mixture was then evaporated with toluene, quenched with cold saturated $NaHCO_3$, and extracted into ether. The organic phase was dried and evaporated under vacuum to give 272 mg (99% yield) of 7-(2-chloropyridin-4-yl)-3-(3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5- a]pyrimidine as a yellow solid that was used directly in the next step. MS: 414.1 [M+H].

Step 5: A mixture of 7-(2-chloropyridin-4-yl)-3-(3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine (272 mg, 0.66 mmol), 3-(S)-aminoquinuclidine dihydrochloride (654 mg, 3.29 mmol), and DIPEA (1.28 g, 9.9 mmol), in 2.0 mL anhydrous DMSO was microwaved at 170° C for one hour. The resulting crude reaction mixture was purified by HPLC to give 43 mg (13% yield) of (3R)-N-{4-[3-(3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]pyridin-2-yl}quinuclidin-3-amine as a yellow solid. MS: 504.5 [M+H].

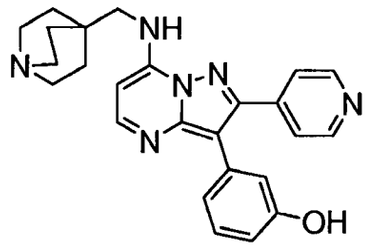
Example 5: 5-(7-{6-[(3R)-1-Azabicyclo[2.2.2]oct-3-ylamino]pyridin-3-yl}-3-(4-chloro-3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine



Step 1: A mixture of (2E)-1-(4-bromophenyl)-3-(dimethylamino)prop-2-en-1-one (125mg, 0.5mmol), (4-chloro-3-methoxyphenyl)-5-pyridin-4-yl-1H-pyrazol-3-amine (150mg, 0.5mmol; prepared following the procedure of Example 1, Step 2, starting with (4-chloro-3-methoxyphenyl)acetonitrile), and 1.5 mL glacial acetic acid was heated in the microwave at 120° C for 1 hour. The acetic acid was then removed under reduced pressure, saturated $NaHCO_3$ was added and the resulting mixture was extracted with dicloromethane with 3% MeOH. The organic phase was dried and evaporated under vacuum and the recovered crude product was chromatographed on silica gel to give 98 mg (40% yield) of 7-(6-bromopyridin-3-yl)-3-(4-chloro-3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine as a yellow solid. MS: 494.1 [M+H].

Step 2: A mixture of 7-(6-bromopyridin-3-yl)-3-(4-chloro-3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine (90 mg, 0.18 mmol), 3-(R)-aminoquinuclidine dihydrochloride (35 mg, 0.22 mmol), DIPEA (47 mg, 0.36 mmol), and 1.0 mL anhydrous DMSO was heated in the microwave at 150° C for 3900 sec. The crude reaction mixture was then purified by HPLC to give 48 mg (44% yield) of 5-(7-{6-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]pyridin-3-yl}-3-(4-chloro-3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine as a yellow solid. MS: 538.3 [M+H].

Example 6: 3-{7-[(1-Azabicyclo[2.2.2]oct-4-ylmethyl)amino]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl}phenol



Step 1: A mixture of 4-[3-(methoxy)phenyl]-5-pyridin-4-yl-1H-pyrazol-3-amine (1.5 g, 5.63 mmol) and diethyl ethoxymethylene malonate (1.4 mL, 6.9 mmol) in glacial acetic acid (15 mL) was heated under reflux for 2.5 hours. The mixture was cooled and triturated with ether. The solid was collected by filtration, washed with ether and dried. The crude product was purified by silica gel flash chromatography (methanol/methylene chloride) to give 1.28 g (58% yield) of ethyl 3-(3-methoxyphenyl)-7-oxo-2-pyridin-4-yl-4,7-dihydropyrazolo[1,5-a]pyrimidine-6-carboxylate as a brown solid. MS: 391.2 [M+H].

Step 2: A mixture of ethyl 3-(3-methoxyphenyl)-7-oxo-2-pyridin-4-yl-4,7-dihydropyrazolo[1,5-a]pyrimidine-6-carboxylate (1.2 g, 3.07 mmol) and 2.5 N solution of sodium hydroxide (5.5 mL) was heated at reflux for 4 hours. The mixture was cooled, acidified with 2N HCl and the solid was collected by filtration, then washed with water and dried to yield 1.03 g (92%) of 3-(3-methoxyphenyl)-7-oxo-2-pyridin-4-yl-4,7-dihydropyrazolo[1,5-a]pyrimidine-6- carboxylic acid as a beige solid, 220°-225° C. MS: 363.2 [M+H].

Step 3: To a refluxing Dowtherm™ (30 mL) was added 3-(3-methoxyphenyl)-7-oxo-2-pyridin-4-yl-4,7-dihydropyrazolo[1,5-a]pyrimidine-6-carboxylic acid (1.0 g, 2.76 mmol) in one portion and the resulting mixture was heated at 250° C for 45 minutes. After cooling to room temperature, the solid was collected by filtration, washed with ether and dried to provide 0.86 g (98% yield) of 3-(3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7(4H)-one as yellow solid, 110°-115° C. MS: 319.2 [M+H].

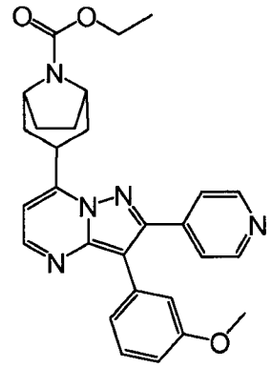
Step 4: A mixture of 3-(3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7(4H)-one (0.85g , 2.6 mmol), N,N-diethylaniline (0.9 mL) and phosphorous oxychloride (9.0 mL) was heated at 110° C for 2 hours. The mixture was allowed to cool and the excess phosphorous oxychloride was evaporated to dryness, followed by re-evaporation twice from toluene. The residue was cooled in an ice bath, neutralized with saturated solution of sodium bicarbonate and extracted with 10% methanol in methylene chloride. The organic layer was dried over anhydrous sodium sulfate, filtered and the filtrate was evaporated to yield an oil. The crude product was purified by silica gel flash chromatography, eluting with 1% methanol

in methylene chloride, to give 1.28 g (58% yield) of 7-chloro-3-(3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine as a yellow solid, 135°-140° C. MS: 337.2 [M+H].

Step 5: To a cold (0°-5° C) solution of 1-(1-azabicyclo[2.2.2]oct-4-yl)methanamine (0.13g, 0.9 mmol) and N,N-diisopropylethylamine (0.3 mL, 1.76 mmol) in acetonitrile (5 mL) was added 7-chloro-3-(3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine (0.15 g, 0.44 mmol) in portions over a period of 5 minutes, and the resulting mixture was stirred at 5° C for 2 hours. The solvent was evaporated and the residue was stirred with a saturated solution of sodium bicarbonate. The solid was collected by filtration, washed with water and dried. The resulting crude solid was purified by preparative reverse phase HPLC (acetonitrile/water/trifluroacetic acid) to give 0.12g (49% yield) of (1-aza-bicyclo [2,2,2]oct-4ylmethyl)-3-(3-methoxy-phenyl)-2-pyridin-4-yl-pyrazolo [1,5,a]pyrimidin-7-yl]-amine as a yellow solid. MS: 441.3 [M+H].

Step 6: A mixture of (1-aza-bicyclo [2,2,2]oct-4ylmethyl)-3-(3-methoxy-phenyl)-2-pyridin-4-yl-pyrazolo [1,5,a]pyrimidin-7-yl]-amine (0.092 g, 0.21 mmol) and pyridine hydrochloride (1.2 g, 10.4 mmol) was heated a 205°C for 1 hour. After cooling, the mixture was basified with a solution of ammonium hydroxide and the solvent was evaporated to dryness to yield a crude residue. The residue was washed with 10% methanol in methylene chloride and the filtrate was dried over anhydrous sodium sulfate, filtered and the filtrate was evaporated to yield an oil. The crude oil was purified by preparative reverse phase HPLC (acetonitrile/water/trifluroacetic acid) to provide 0.025g (28% yield) of 3-{7-[(1-azabicyclo[2.2.2]oct-4-ylmethyl)amino]-2-pyridin-4-ylpyrazolo[1,5- a]pyrimidin-3-yl}phenol as a yellow solid. MS: 427.3 [M+H].

Example 7: Ethyl 3-(3-(3-methoxyphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate



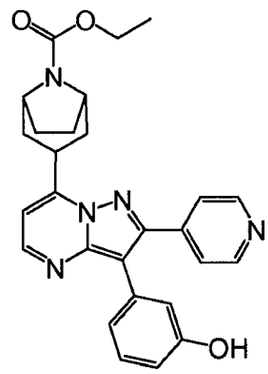
Step 1: A mixture of tosylmethylisocyanide (5 g, 25.6 mmol) and ethyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (3.8 g, 19.7 mmol) in DME (60 mL) and Ethanol (1.85 mL) was stirred at -10° C while adding potassium *tert*-butoxide portionwise over the course of 1 hour that the temperature was maintained at < 5° C. Once the addition was complete the reaction was stirred at -10° C for 1 hour and then stirred for additional 2 hours at room temperature. The solvents were then removed under reduced pressure to give an orange brown solid. To this solid was added water (200 mL) and extracted with ether (4 x, 150 mL). The organics extract was dried over anhydrous magnesium sulfate, filtered and the filtrate was evaporated to yield a brown oil. The crude mixture was purified on a silica column eluting with 30% ethylacetate in hexanes to give 2.43 g of ethyl 3-cyano-8-azabicyclo[3.2.1]octane-8-carboxylate (60% yield). MS: 209.2 [M+H].

Step 2: A 1.4M solution of methyl magnesium bromide (35.4 mL) in THF/toluene was added to a solution of ethyl 3-cyano-8-azabicyclo[3.2.1]octane-8-carboxylate (2.4 g, 11.5 mmol) in THF (50 mL) at rt. The reaction was stirred for 3 hours and quenched with ammonium chloride (100 mL). The mixture was then extracted with ether (4 x, 100 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, then filtered and the filtrate was evaporated to yield ethyl 3-acetyl-8-azabicyclo[3.2.1]octane-8-carboxylate as an oil. MS: 226.2 [M+H].

Step 3: A mixture of ethyl 3-acetyl-8-azabicyclo[3.2.1]octane-8-carboxylate (1.7 g, 7.68 mmol) in 25 mL of dimethylformamide dimethyl acetal was heated to 110° C for 48 hours. The reaction mixture was then cooled to room temperature and the solvent was evaporated to provide an orange oil. The crude product was purified by silica gel flash chromatography, eluting with 50% acetone in dichloromethane to give 0.86 g (50% yield) of (*E*)-ethyl 3-(3-(dimethylamino)acryloyl)-8-azabicyclo[3.2.1]octane-8-carboxylate, which was used without further purification. MS: 281.2 [M+H].

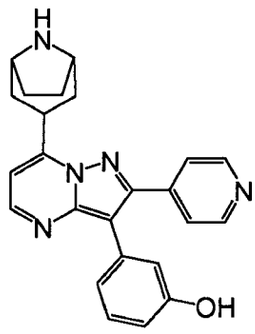
Step 4: A mixture of (E)-ethyl 3-(3-(dimethylamino)acryloyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (0.37 g, 1.3 mmol) and 4-(3-methoxyphenyl)-3-(pyridin-4-yl)-1H-pyrazol-5-amine (0.35 g, 1.3 mmol) in acetic acid (5 mL) was stirred at 80° C for 2 h. The reaction was cooled to room temperature and the solvent was evaporated. The crude mixture was purified on silica eluting with 50% acetone in dicholormethane to give ethyl 3-(3-(3-methoxyphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate as a yellow solid. MS: 484.4 [M+H].

Example 8: Ethyl 3-(3-(3-hydroxyphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate



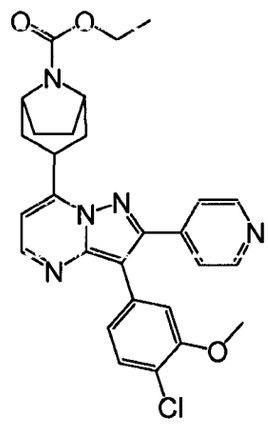
A solution of ethyl 3-(3-(3-methoxyphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (0.3 g, 0.6 mmol) in dichloromethane was cooled to 0° C. A 1 M solution of boron tribromide in dichloromethane (3.7 mL) was then added while keeping the temperature at 0° C. The reaction was stirred at 0° C for 3 hours then allowed to warm to room temperature. The reaction was next quenched with ice water and the pH was adjusted to about 7, followed by extraction using dichloromethane (3 x, 100 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and the filtrate was evaporated. The crude mixture was purified on silica eluting with 20 % acetone in dichloromethane to give ethyl 3-(3-(3-hydroxyphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J=4.4 Hz, 1H), 8.41 (d, J= 4.8 Hz, 2H), 7.64 (d, J=6 Hz, 2H), 7.38 (t, J=8 Hz, 1H), 7.21 (d, J=7.6 Hz, 1H), 6.92 (m, 2H), 6.74 (d, J=4.4 Hz, 1H), 4.19 (m, 3H), 2.18-1.97 (m, 8H), 1.60 (brs, 2H), 1.26 (t, J=7.2 Hz, 3H). MS: 470.3 [M+H].

Example 9: 3-(7-(8-Azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)phenol



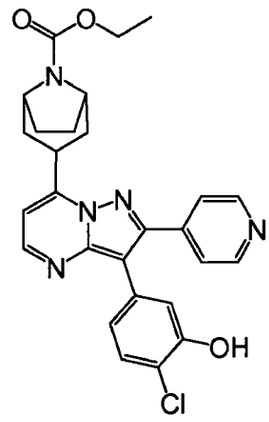
A solution of ethyl 3-(3-(3-hydroxyphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (0.1 g, 0.21 mmol) and iodotrimethylsilane (0.64 g, 3.2 mmol) in chloroform was stirred at reflux for 5 hours. The reaction was cooled to room temperature and solvent was evaporated. The crude mixture was purified using prep HPLC to give the trifluoroacetate (TFA) salt of 3-(7-(8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)phenol as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 9.49 (s, 1H), 8.75 (s, 1H), 8.67 (d, J=4.8 Hz, 2H), 8.62 (d, J=4 Hz, 1H), 7.68 (d, J=4.8 Hz, 2H), 7.22 (t, J=8 Hz, 1H), 7.08 (d, J=4 Hz, 1H), 6.89 (d, J=4 Hz, 1H), 6.83 (d, J=6 Hz, 1H), 6.77 (d, J=6.8 Hz, 1H), 4.10 (dt, J=4.8 Hz, 7.6 Hz, 1H), 2.48 (m, 2H), 2.30 (m, 2H), 2.15 (m, 6H). MS: 398.3 [M+H].

Example 10: Ethyl 3-(3-(4-chloro-3-methoxyphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate



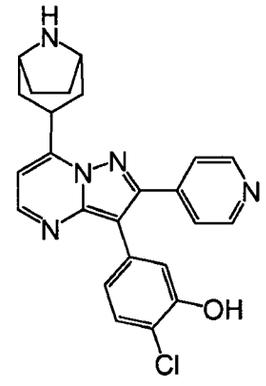
Ethyl 3-(3-(4-chloro-3-methoxyphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate was synthesized according to the procedure for Example 7, Step 4, starting from (E)-ethyl 3-(3-(dimethylamino)acryloyl)-8-azabicyclo[3.2.1]octane-8-carboxylate and (4-chloro-3-methoxyphenyl)-5-pyridin-4-yl-1H-pyrazol-3-amine. MS: 518.3 [M+ H].

Example 11: Ethyl 3-(3-(4-chloro-3-hydroxyphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate



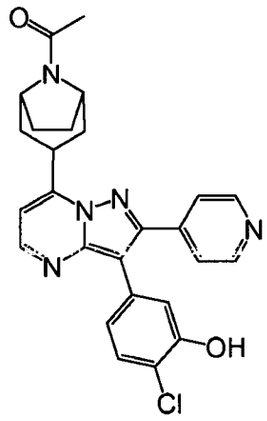
Ethyl 3-(3-(4-chloro-3-hydroxyphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate was synthesized starting from ethyl 3-(3-(4-chloro-3-methoxyphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate, the product of Example 10, by reaction with boron tribromide according to the procedure for Example 8. MS: 504.3 [M+H].

Example 12: 5-(7-(8-Azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-chlorophenol



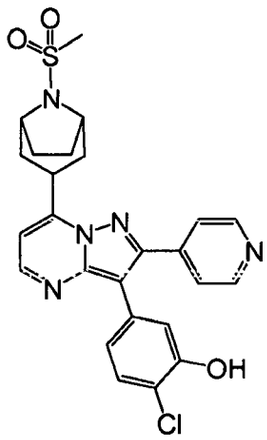
The reaction of ethyl 3-(3-(4-chloro-3-hydroxyphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate, the product of Example 11, with iodotrimethylsilane, according to the procedure for Example 9, provided 5-(7-(8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-chlorophenol. ^{1}H NMR (400 MHz, DMSO) δ 10.28 (s, 1H) 8.80 (s, 1H), 8.73 (d, J=8 Hz, 2H), 8.65 (d, J=4 Hz, 1 Hz), 7.76 (d, J=4 Hz, 2H), 7.39 (d, J=8 Hz, 1H), 7.12 (m, 2H), 6.87 (d, J=8 Hz, 1H), 4.10 (dt, J=5.2 Hz, 7.2 Hz, 1H), 2.48 (m, 2H), 2.30 (m, 2H), 2.15 (m, 6H). MS: 432.3 [M+H].

Example 13: 5-[7-(8-Acetyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]-2-chlorophenol



A solution of 5-(7-(8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-chlorophenol (0.15 g, 0.35 mmol), the product of Example 12, and triethylamine (140 μL, 1.05 mmol) in 1-methyl-2-pyrrolidinone was cooled to 0° C. Acetyl chloride (23 μL, 0.33 mmol) was then added and the reaction was stirred at 0° C for 1 hour. The reaction was warmed to room temperature and diluted with water and dichloromethane followed by extraction with saturated sodium bicarbonate (2 x 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and the filtrate was evaporated. The crude mixture was purified by reverse phase HPLC (acetonitrile/water/trifluoroacetic acid) to provide 0.015 g (7% yield) of 5-[7-(8-acetyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]-2-chlorophenol. MS: 474.3 [M+H].

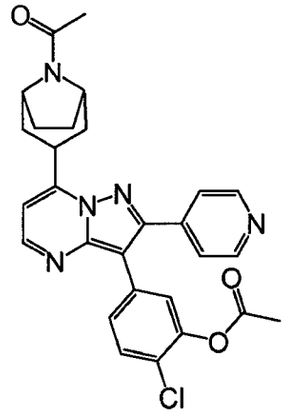
Example 14: 2-Chloro-5-{7-[8-(methylsulfonyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl}phenol



A solution of 5-(7-(8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-chlorophenol (0.15 g, 0.35 mmol), the product of Example 12, and triethylamine (140 μL, 1.05 mmol) in 1-methyl-2-pyrrolidinone was cooled to 0° C. Methylsulfonyl chloride (25 μL, 0.33 mmol) was then added and the reaction was stirred at 0° C for 1 hour. The reaction was warmed to room temperature and diluted with water and

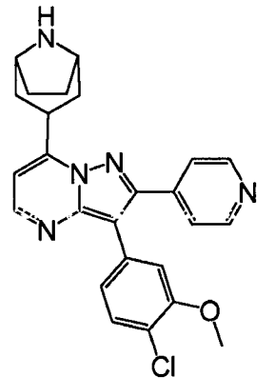
dichloromethane followed by extraction with saturated sodium bicarbonate (2 x 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and the filtrate was evaporated. The crude mixture was purified by reverse phase HPLC (acetonitrile/water/trifluoroacetic acid) to provide 0.017 g (9% yield) of 2-chloro-5-{7-[8-(methylsulfonyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl}phenol. MS: 510.3 [M+H].

Example 15: 5-[7-(8-Acetyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]-2-chlorophenyl acetate



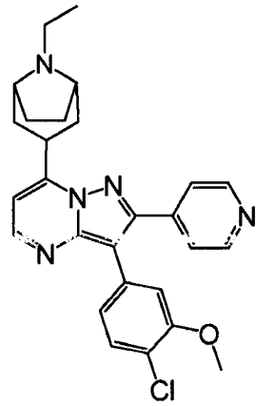
To a solution of 5-(7-(8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-chlorophenol (0.10 g, 0.23 mmol), the product of Example 12, in dichloromethane was added triethylamine (200 μL, 1.4 mmol). Acetyl chloride (36 μL, 0.51 mmol) was then added and the reaction was stirred for 1 hour. The reaction was extracted with saturated ammonium chloride (2 x 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and the filtrate was evaporated. The crude mixture was purified by preparatory TLC using 5% methanol/dichloromathane to provide 0.058 g (48% yield) of 5-[7-(8-acetyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]-2-chlorophenyl acetate. MS: 516.4 [M+H].

Example 16: 7-(8-Azabicyclo[3.2.1]oct-3-yl)-3-(4-chloro-3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine



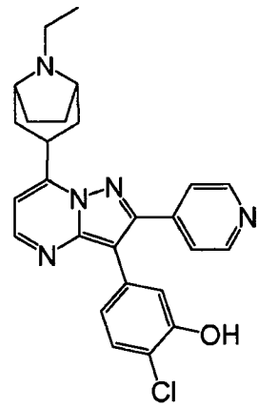
7-(8-Azabicyclo[3.2.1]oct-3-yl)-3-(4-chloro-3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine was prepared from ethyl 3-(3-(4-chloro-3-methoxyphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo-[3.2.1]octane-8-carboxylate, the product of Example 10, using iodotrimethylsilane according to the procedure for Example 9. MS 446: [M+H].

Example 17: 3-(4-Chloro-3-methoxyphenyl)-7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine



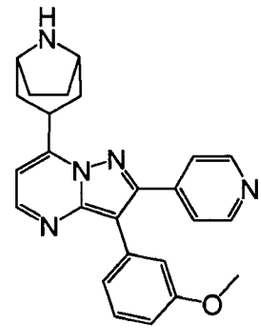
To a solution of 7-(8-azabicyclo[3.2.1]oct-3-yl)-3-(4-chloro-3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine (0.258 g, 0.58 mmol), the product of Example 16, and potassium carbonate (321 mg, 2.3 mmol) in N,N-dimethylformamide was added iodoethane (92 µL, 1.16 mmol) and the reaction was stirred for 3 hours. The reaction was then added to water (25 mL) and the resulting crude solid was filtered and dried. The crude solid was purified by silica gel chromatography eluting with a 5%-10%-15%-20% gradient of methanol in dichloromathane to provide 0.172 g (63% yield) of 3-(4-chloro-3-methoxyphenyl)-7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine. MS: 474.3 [M+H].

Example 18: 2-Chloro-5-[7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]phenol



A solution of 3-(4-chloro-3-methoxyphenyl)-7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine (0.09 g, 0.19 mmol), the product of Example 17, in dichloromethane was cooled to 0°C. A 1 M solution of boron tribromide in dichloromethane (1.12 mL) was then added while keeping the temperature at 0°C. The reaction was stirred at 0° C for 3 hours, then was allowed to warm to room temperature. The reaction was next quenched with ice water and the pH was adjusted to about 7 followed by extraction with dichloromethane (3 x 100 mL). The combined organic extracts were extracted with aqueous 10% HCl (2 x 15 mL). The pH of the combined aqueous extracts was adjusted to about pH 10 with sodium carbonate. The resulting solid was filtered and dried to give the crude product. The remaining aqueous extracts were concentrated and the resulting solid was washed with 10% methanol/dichloromethane. The organics were concentrated *in-vacuo* to give additionl crude product. The crude products were combined and purified on silica gel eluting with 10% methanol/dichloromethane to give 56 mg (64% yield) of 2-chloro-5-[7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]phenol. MS: 460.4 [M+H].

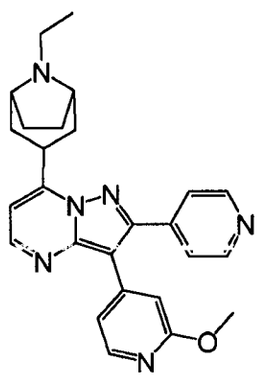
Example 19: 7-(8-Azabicyclo[3.2.1]oct-3-yl)-3-(3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5- a]pyrimidine



Ethyl 3-(3-(3-methoxyphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (0.4 g, 0.8 mmol), the product of Example 7, was

heated to reflux in chloroform. Iodotrimethylsilane was added in two aliquots (0.8 g + 0.4 g, 6.0 mmol total) as the reaction was monitored to completion within 5 hours. The resultant orange solid was collected by filtration, dissolved in dichloromethane/methanol (9:1), adsorbed onto silica, and chromatographed in 5-15% methanol/dichloromethaneto provide 0.11 g (33% yield) of 7-(8-azabicyclo[3.2.1] oct-3-yl)-3-(3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5- a]pyrimidine as a yellow solid. MS: 412.4 [M+H].

Example 20: 7-(8-Ethyl-8-azabicyclo[3.2.1]octan-3-yl)-3-(2-methoxypyridin-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine



Step 1: Ethyl 3-(2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate was synthesized according to the procedure for Example 7, Step 4, staring from (*E*)-ethyl 3-(3-(dimethylamino)acryloyl)-8-azabicyclo[3.2.1]octane-8-carboxylate and 3-(pyridin-4-yl)-1H-pyrazol-5-amine. MS: 378.4 [M+ H].

Step 2: 7-(8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine was synthesized according to the procedure for Example 9 starting from ethyl 3-(2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate. MS: 306.3 [M+ H].

Step 3: A mixture of 7-(8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine (3.1 g, 10.2 mmol), trifluoroacetic anhydride (1.48 mL, 10.7 mmol) and triethylamine (4.26 mL, 30.6 mmol) in dicholoromethane (100 mL) was stirred for 1 hour. The reaction was then extracted once with saturated sodium bicarbonate (200 mL) and saturated ammonium chloride (200 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and the filtrate was evaporated to yield a solid. The crude product was purified by silica gel flash chromatography, eluting with 5-20% methanol in dichloromethane, to give 2.1 g (51% yield) of 2,2,2-trifluoro-1-(3-(2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octan-8-yl)ethanone. MS: 402.3 [M+H].

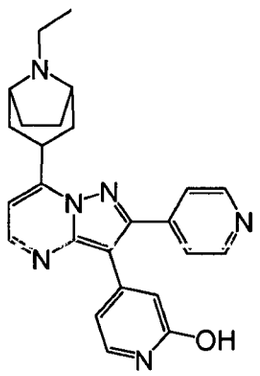
Step 4: To solution of 2,2,2-trifluoro-1-(3-(2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octan-8-yl)ethanone (2.1 g, 5.2 mmol) in dichloromethane (125 mL) was added N-iodosuccinamide (17 g, 52.3 mmol) in three portions over a 3 hour period and the reaction was then stirred for an additional 16 hours. The reaction was extracted with saturated sodium thiosulfate (2 x 200 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and the filtrate was evaporated to give 3.0 g of 2,2,2-trifluoro-1-(3-(3-iodo-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octan-8-yl)ethanone as a yellow solid. This product was used in the next step without further purification. MS: 528.1 [M+H].

Step 5: A mixture of 2,2,2-trifluoro-1-(3-(3-iodo-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octan-8-yl)ethanone (3.0 g, 5.7 mmol), potassium carbonate (3.5 g, 25 mmol), methanol (50mL) and water (10 mL) was stirred for 4 days. The solvent was then removed and the remaining crude solid was stirred in 10% methanol in dichloromethane. The remaining solids were removed by filtration and washed with dichloromethane. The filtrate was concentrated in vacuo to give 7-(8-azabicyclo[3.2.1]octan-3-yl)-3-iodo-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine as a yellow solid that was used directly in the next step.

Step 6: Following the procedure of Example 17, 7-(8-azabicyclo[3.2.1]octan-3-yl)-3-iodo-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine (2.9 g, 5.7 mmol) was reacted with potassium carbonate and iodoethane in dimethylformamide to provide 2.3 g (86% yield) of 7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-3-iodo-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine as a yellow solid. MS: 460.3 [M+H].

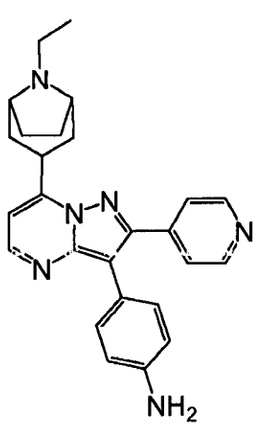
Step 7: 7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-3-iodo-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine (150 mg, 0.32 mmol) and 2-methoxypyridin-4-ylboronic acid (100 mg, 0.65 mmol) were dissolved in ethylene glycol dimethyl ether (3 mL) and to the resulting solution was added (1,1'-bis(diphenylphosphino)ferrocene) dichloropalladium(II) dichloromethane complex (53 mg). A solution of potassium carbonate (90 mg, 2.24 mmol) in water (0.5 mL) was next added to the reaction mixture, and the reaction was heated to 80° C for 3 hours. The reaction was then cooled and saturated sodium bicarbonate (20 mL) was added. The mixture was then extracted with dichloromethane (2 x 50 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and the filtrate was evaporated to yield a solid. The crude solid was purified by silica gel flash chromatography, eluting with 15% methanol in dichloromethane, to give 0.07 g (50% yield) of 7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-3-(2-methoxypyridin-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine. MS: 441.3 [M+H].

Example 21: 4-(7-(8-Ethyl-8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-ol



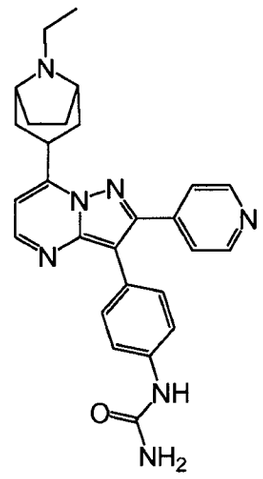
A mixture of 7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-3-(2-methoxypyridin-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine (0.68 g, 0.15mmol) and pyridine hydrochloride (0.68 g) was stirred at 180° C for 30 minutes. The reaction was then cooled and diluted with saturated sodium bicarbonate. The solvent was removed and the remaining crude solid was washed with 10% methanol in dichloromethane. The organic layer was dried over anhydrous sodium sulfate, filtered and the filtrate was evaporated to give .049 g (75% yield) of 4-(7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-ol as a yellow solid. MS: 427.3 [M+H].

Example 22: 4-(7-(8-Ethyl-8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)aniline



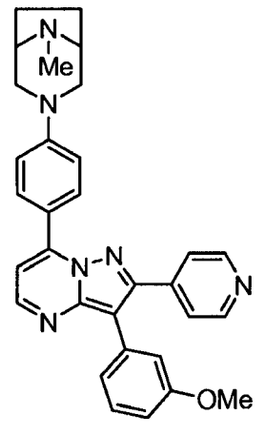
Following the procedure of Example 20, Step 7, 7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-3-iodo-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine was reacted with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline to provide 81mg (60% yield) of 4-(7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)aniline as a yellow solid. MS: 425.3 [M+H].

Example 23: 1-(4-(7-(8-Ethyl-8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)phenyl)urea



A mixture of 4-(7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)aniline (23 mg, 0.05 mmol), the product of Example 22, and triethylamine (22 μL, 0.16 mmol) in dichloromethane (1.5 mL) was added to a solution of triphosgene (8 mg, 0.025 mmol) in dichloromethane (0.5 mL) and stirred for 10 minutes. To this mixture was added a 2M solution of ammonia in dioxane (2 mL) and the resulting mixture was stirred for an additional 30 minutes. The reaction was diluted with dichloromethane (5 mL) and extracted with saturated sodium bicarbonate (2 x, 5 ml). The organic layer was dried over anhydrous sodium sulfate, filtered, and the filtrate was evaporated to give a solid. The crude solid was purified by silica gel flash chromatography, eluting with 15% methanol in dichloromethane, to give 5.1 mg (20% yield) of 1-(4-(7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)phenyl)urea as a yellow solid. MS: 468.3 [M+H].

Example 24: 3-(3-Methoxy-phenyl)-7-[4-(8-methyl-3,8-diaza-bicyclo[3.2.1]oct-3-yl)-phenyl]-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine

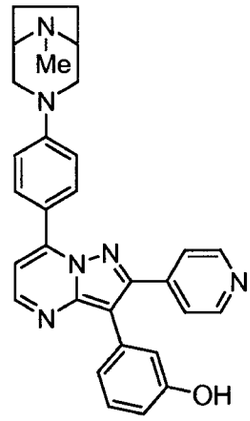


Step 1: Following the procedure of Example 1, Step 1, 1-(4-bromo-phenyl)-ethanone was reacted with dimethylformamide dimethyl acetal to provide 1-(4-bromo-phenyl)-3-dimethylamino-propenone. MS: 254.2 [M+H].

Step 2: Following the procedure of Example 7, Step 4, 1-(4-bromo-phenyl)-3-dimethylamino-propenone was reacted with 4-(3-methoxyphenyl)-3-(pyridin-4-yl)-1H-pyrazol-5-amine to provide 7-(4-bromo-phenyl)-3-(3-methoxy-phenyl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine. MS: 457.3 [M+H].

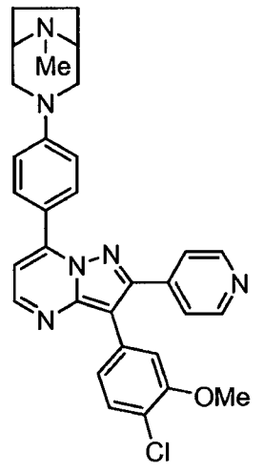
Step 3: A sealed tube was charged with 7-(4-bromo-phenyl)-3-(3-methoxy-phenyl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine (65 mg, 0.14 mmol), 8-methyl-3,8-diaza-bicyclo[3.2.1]octane dihydrochloride (25 mg, 0.13 mmol), sodium tert-butoxide (37 mg, 0.39 mmol), tris(dibenzylideneacetone)dipalladium(0) (25 mg, 0.027 mmol,), BINAP (66 mg, 0.1 mmol), and THF (3 mL) under nitrogen. The tube was heated to 100° C overnight. The solution was then allowed to cool to room temperature, concentrated, dissolved in DMSO, filtered, and purified by HPLC to give 3-(3-methoxy-phenyl)-7-[4-(8-methyl-3,8-diaza-bicyclo[3.2.1]oct-3-yl)-phenyl]-2-pyridin-4-yl-pyrazolo[1,5-]pyrimidine TFA salt as a yellow solid. MS: 503.5 [M+H].

Example 25: 3-{7-[4-(8-Methyl-3,8-diaza-bicyclo[3.2.1]oct-3-yl)-phenyl]-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidin-3-yl}-phenol



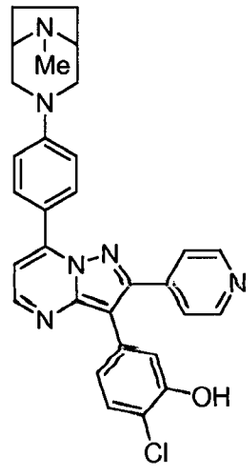
Following the procedure of Example 8, 3-(3-methoxy-phenyl)-7-[4-(8-methyl-3,8-diaza-bicyclo[3.2.1]oct-3-yl)-phenyl]-2-pyridin-4-yl-pyrazolo[1,5-]pyrimidine was reacted with boron tribromide and then purified using HPLC to provide 3-{7-[4-(8-methyl-3,8-diaza-bicyclo[3.2.1]oct-3-yl)-phenyl]-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidin-3-yl}-phenol. MS: 489.5 [M+H].

Example 26: 3-(4-Chloro-3-methoxy-phenyl)-7-[4-(8-methyl-3,8-diaza-bicyclo[3.2.1]oct-3-yl)-phenyl]-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine



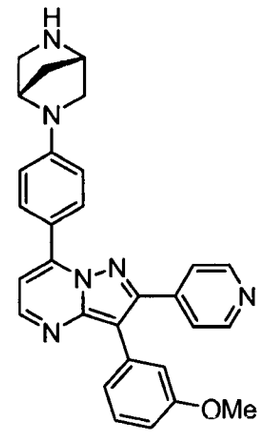
Following the procedure of Example 24, starting from 4-(4-chloro-3-methoxy-phenyl)-5-pyridin-4-yl-2H-pyrazol-3-ylamine, 3-(4-chloro-3-methoxy-phenyl)-7-[4-(8-methyl-3,8-diaza-bicyclo[3.2.1]oct-3-yl)-phenyl]-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine in the form of the TFA salt was obtained as a yellow solid. MS: 537.5 [M+H].

Example 27: 2-Chloro-5-{7-[4-(8-methyl-3,8-diaza-bicyclo[3.2.1]oct-3-yl)-phenyl]-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidin-3-yl}-phenol



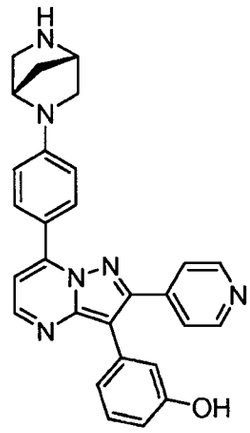
Following the procedure of Example 8, 3-(4-chloro-3-methoxy-phenyl)-7-[4-(8-methyl-3,8-diaza-bicyclo[3.2.1]oct-3-yl)-phenyl]-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine was reacted with boron tribromide and then purified using HPLC to provide 2-chloro-5-{7-[4-(8-methyl-3,8-diaza-bicyclo[3.2.1]oct-3-yl)-phenyl]-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidin-3-yl}-phenol. MS: 523.5 [M+H].

Example 28: 7-[4-((1S,4S)-2,5-Diaza-bicyclo[2.2.1]hept-2-yl)-phenyl]-3-(3-methoxy-phenyl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine



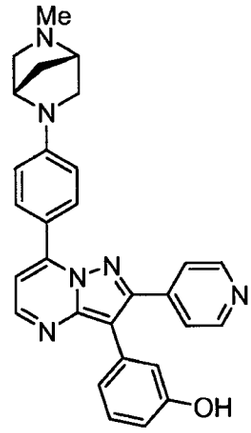
Following the procedure of Example 24, starting from 4-(3-methoxy-phenyl)-5-pyridin-4-yl-2H-pyrazol-3-ylamine and (1S,4S)-2,5-diaza-bicyclo[2.2.1]heptane dihydrobromide, 7-[4-((1S,4S)-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-phenyl]-3-(3-methoxy-phenyl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine trifluoroacetate salt was obtained as a yellow solid. MS: 475.5 [M+H].

Example 29: 3-{7-[4-((1S,4S)-2,5-Diaza-bicyclo[2.2.1]hept-2-yl)-phenyl]-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidin-3-yl}-phenol



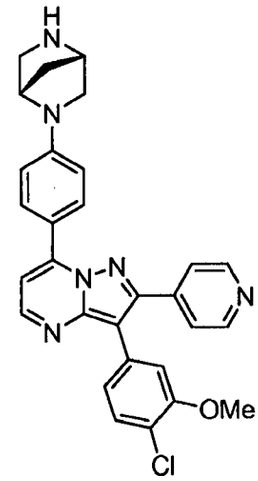
Following the procedure of Example 8, 7-[4-((1S,4S)-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-phenyl]-3-(3-methoxy-phenyl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine was reacted with boron tribromide and then purified using HPLC to provide 3-{7-[4-((1S,4S)-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-phenyl]-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidin-3-yl}-phenol trifluoroacetate salt. MS: 461.4 [M+H].

Example 30: 3-{7-[4-((1S,4S)-5-Methyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-phenyl]-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidin-3-yl}-phenol



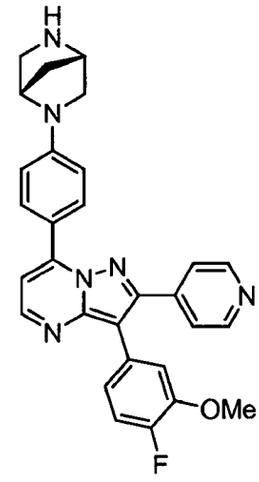
Three drops of formaldehyde (37% in water) was added to a solution of 3-{7-[4-((1S,4S)-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-phenyl]-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidin-3-yl}-phenol (18 mg), the product of Example 25, and excess sodium triacetoxyborohydride in 2 mL of DMF. After 3 hours, the reaction mixture was filtered and the crude product was purified by HPLC to provide 3-{7-[4-((1S,4S)-5-methyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-phenyl]-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidin-3-yl}-phenol trifluoroacetate salt. MS: 475.5 [M+H].

Example 31: 7-(4-((1S,4S)-2,5-Diaza-bicyclo[2.2.1]heptan-2-yl)phenyl)-3-(4-chloro-3-methoxyphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine



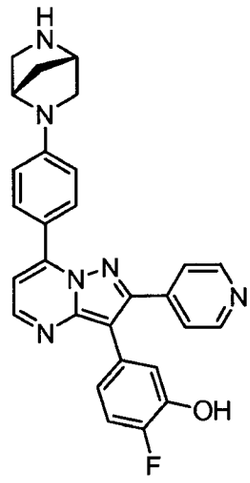
Following the procedure of Example 24, Steps 1-3, 4-(4-chloro-3-methoxyphenyl)-5-pyridin-4-yl-2H-pyrazol-3-ylamine and (1S,4S)-2,5-diaza-bicyclo[2.2.1]heptane dihydrobromide gave 7-(4-((1S,4S)-2,5-diaza-bicyclo[2.2.1]heptan-2-yl)phenyl)-3-(4-chloro-3-methoxyphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine as a trifluoroacetate salt. MS: 509.3 [M+H].

Example 32: 7-(4-((1S,4S)-2,5-Diaza-bicyclo[2.2.1]heptan-2-yl)phenyl)-3-(4-fluoro-3-methoxyphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine



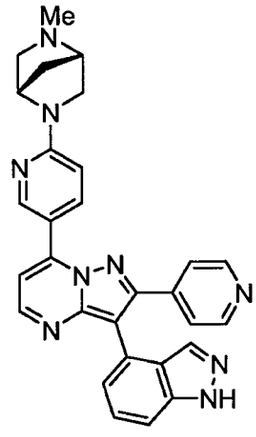
The compound 4-(4-fluoro-3-methoxyphenyl)-5-pyridin-4-yl-2H-pyrazol-3-ylamine was prepared according to the procedure of Example 1, Step 2, starting from 4-fluoro-3-methoxy-benzeneacetonitrile. Following the procedure of Example 24, Steps 1-3, and using (1S,4S)-2,5-diaza-bicyclo[2.2.1]heptane dihydrobromide in step 3, 4-(4-fluoro-3-methoxyphenyl)-5-pyridin-4-yl-2H-pyrazol-3-ylamine, gave 7-(4-((1S,4S)-2,5-diaza-bicyclo[2.2.1]heptan-2-yl)phenyl)-3-(4-fluoro-3-methoxyphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine trifluoroacetate salt. MS: 493.5 [M+H].

Example 33: 5-(7-(4-((1S,4S)-2,5-Diazabicyclo[2.2.1]heptan-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-fluorophenol



Following the procedure of Example 8, 7-(4-((1S,4S)-2,5-diaza-bicyclo[2.2.1]heptan-2-yl)phenyl)-3-(4-fluoro-3-methoxyphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine was reacted with boron tribromide and the resulting product was purified by HPLC to provide 5-(7-(4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-fluorophenol trifluoroacetate salt. MS: 479.5 [M+H].

Example 34: 3-(1H-Indazol-4-yl)-7-(6-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine



Step 1: Following the procedure of Example 1, Step 3, 1-(6-bromo-pyridin-3-yl)-3-dimethylamino-propenone was reacted with 3-(pyridin-4-yl)-1H-pyrazol-5-amine to give 7-(6-bromopyridin-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine as a yellow solid.

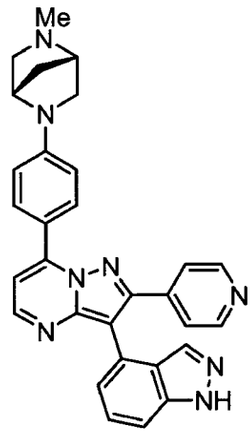
Step 2: Following the procedure of Example 1, Step 4, 7-(6-bromopyridin-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine was reacted with (1S,4S)-2,5-diaza-bicyclo[2.2.1]heptane dihydrobromide and purified by silica gel chromatography to give 7-(6-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine. MS: 370.4 [M+H].

Step 3: 7-(6-((1S,4S)-2,5-Diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine (100 mg, 0.27 mmol) was dissolved in 5 mL of DMF, and then 37% formaldehyde (0.10 mL, 1.35 mmol) and a drop of acetic acid were added. The solution was stirred for 5 minutes and then sodium triacetoxyborohydride (286 mg, 1.35 mmol) was added. The reaction was quenched with 2mL of a solution of methanolic ammonia after one hour. Then the mixture was concentrated and purified by silica gel chromatography to give 7-(6-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine. MS: 384.4 [M+H].

Step 4: 7-(6-((1S,4S)-5-Methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine (200 mg, 0.52 mmol) was dissolved in 10 mL of dichloromethane and 1 mL of acetic acid and then *N*-iodosuccinimide (175 mg, 0.78 mmol) was added. The resulting reaction was quenched with a solution of methanolic ammonia after one hour, concentrated and purified by silica gel chromatography to give 3-iodo-7-(6-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine. MS: 510.4 [M+H].

Step 5: To a suspension of 3-iodo-7-(6-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine (110 mg, 0.22 mmol) in 3 mL of dimethoxyethane was added 2M sodium carbonate (0.22 mL, 0.44 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (100 mg [79% purity], 0.32 mmol) and catalytic amount of tetrakis(triphenylphosphine)palladium(0). The mixture was heated to 130° C for 50 minutes in a microwave reactor. The crude product was purified by HPLC and then silica gel chromatography to give the desired product as a free base. The free base was dissolved in methanol and then 1 mL of 1.25 M methanolic HCl was added. The solution was concentrated in vacuo and dried to give 3-(1H-indazol-4-yl)-7-(6-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine hydrochloride salt. MS: 500.3 [M+H].

Example 35: 3-(1H-indazol-4-yl)-7-(4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine

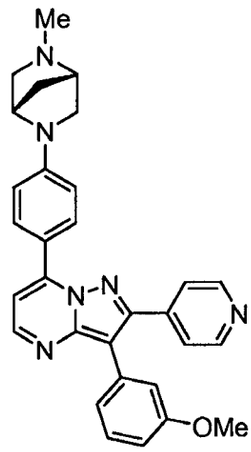


Step 1: Following the procedure of Example 1, Step 3, (E)-1-(4-bromophenyl)-3-(dimethylamino)prop-2-en-1-one was reacted with 3-(pyridin-4-yl)-1H-pyrazol-5-amine to give 7-(4-bromophenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine as a yellow solid.

Step 2: Following the procedure of Example 24, Step 3, 7-(4-bromophenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine was coupled with (1S,4S)-2,5-diaza-bicyclo[2.2.1]heptane dihydrobromide to give 7-(4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine. MS: 369.4 [M+H].

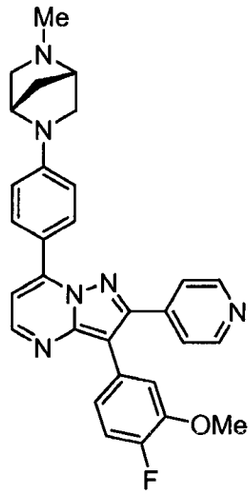
Steps 3-5: Following the procedure of Example 34, Steps 3-5, 7-(4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine was converted into 3-(1H-indazol-4-yl)-7-(4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine hydrochloride salt, obtained as a deep red solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73-8.70 (m, 2H), 8.57 (d, J = 4.4 Hz, 1H), 8.41–8.36 (m, 2H), 8.26–8.21 (m, 2H), 7.73–7.67 (m, 2H), 7.58 (dd, J = 7.0, 8.2 HZ, 1H), 7.38 (d, J = 4.8 Hz, 1H), 7.35–7.31 (m, 1H), 6.99–6.93 (m, 2H), 4.51–4.47 (m, 1H), 3.92–3.82 (m, 2H), 3.60 (d, J = 11.2 Hz, 1H), 3.04 (s, 3H), 2.55-2.49 (m, 1H), 2.41–2.34 (m, 1H). MS: 499.5 [M+H].

Example 36: 3-(3-Methoxyphenyl)-7-(4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine



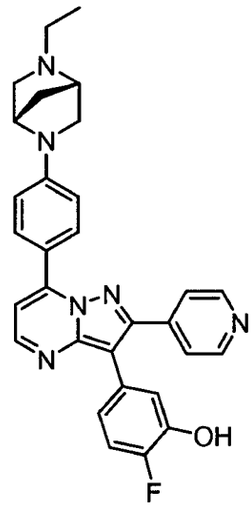
Following the procedure of Example 30, 7-[4-((1S,4S)-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-phenyl]-3-(3-methoxy-phenyl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine was converted into 3-(3-methoxyphenyl)-7-(4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine, obtained as a trifluoroacetate salt. MS: 489.5 [M+H].

Example 37: 3-(4-Fluoro-3-methoxyphenyl)-7-(4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine



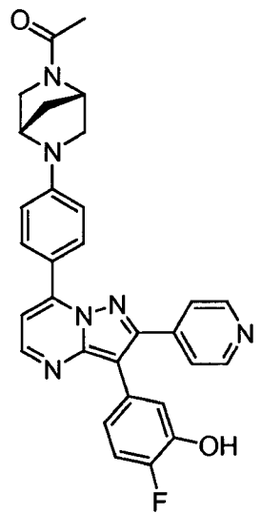
Following the procedure of Example 30, 7-(4-((1S,4S)-2,5-diaza-bicyclo[2.2.1]heptan-2-yl)phenyl)-3-(4-fluoro-3-methoxyphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine was converted into 3-(4-fluoro-3-methoxyphenyl)-7-(4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine, obtained as a trifluoroacetate salt. MS: 507.5 [M+H].

Example 38: 5-(7-(4-((1S,4S)-5-Ethyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-fluorophenol



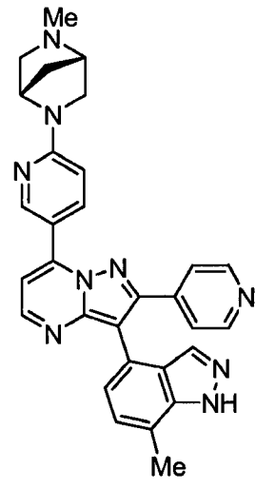
Following the procedure of Example 30, acetaldehyde and 5-(7-(4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-fluorophenol provided 5-(7-(4-((1S,4S)-5-ethyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-fluorophenol as a trifluoroacetate salt. MS: 507.3 [M+H].

Example 39: 1-((1S,4S)-5-(4-(3-(4-Fluoro-3-hydroxyphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)phenyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)ethanone



The compound 5-(7-(4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-fluorophenol was acetylated to give 1-((1S,4S)-5-(4-(3-(4-fluoro-3-hydroxyphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)phenyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)ethanone. MS: 521.5 [M+H].

Example 40: 3-(7-Methyl-1H-indazol-4-yl)-7-(6-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine



Step 1: A mixture of nitro-m-xylene (3.02 g, 20.0 mmol), iodine (2.04 g, 8.0 mmol), periodic acid (4.1 g, 18.0 mmol), and concentrated sulfuric acid (1.2 mL) in acetic acid (2.4 mL) was heated at 90° C for 3 days. The reaction was then cooled, poured in to water and extracted with dichloromethane. The combined organics were cooled and washed with a cold solution of 2N sodium hydroxide, and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue was triturated with hexanes and the solid was collected by filtration, washed with hexanes and dried to yield 2.3 g (42%) of 1-iodo-2,4-dimethyl-3-nitrobenzene as a white solid. MS: 278.1 $[M+H]^+$

Step 2: To a hot suspension of iron powder (2.3 g, 8.3 mmol), ammonium chloride (2.16 g, 38.7 mmol) and water (18 mL) in ethanol (50 mL) was added 1-iodo-2,4-dimethyl-3-nitrobenzene in portions over a period of 10 minutes. The resulting mixture was heated at reflux for 1 hour, and filtered hot through a pad of Celite™. The Celite was washed with ethanol and ethyl acetate and the filtrate was concentrated in vacuo. The residue was extracted with dichloromethane, the organics were dried over anhydrous sodium sulfate and filtered and the filtrate was evaporated to yield 2.0g (98%) of 3-iodo-2,6-dimethyl-phenylamine as a white solid. MS: 248.1 $[M+H]^+$

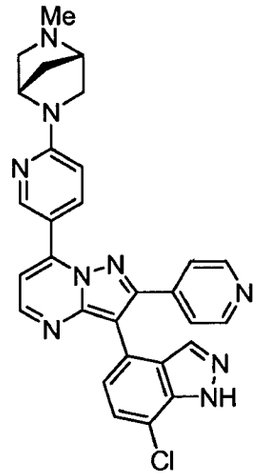
Step 3: To a cold (0°-5°C) solution of 3-iodo-2,6-dimethyl-phenylamine (2.0 g, 8.09 mmol) in chloroform (20 mL) was dropwise added acetic anhydride (1.8 mL, 18.63 mmol) and the resulting mixture was stirred for 5 minutes. The reaction was allowed to warm to room temperature and stirred for 1 hour and then potassium acetate (0.24 g, 2.45 mmol) and isoamyl nitrite (2.3 mL, 17.4 mmol) were added. The reaction was then heated at reflux for 20 hours. After cooling to room temperature the solvent was evaporated to yield a brown solid that was then diluted with water. After evaporating the water, the resulting brown solid residue was treated with concentrated hydrochloric acid and the mixture was heated at 50°C for 2 hours and then cooled in an ice bath and basified to pH 14 with 50% potassium hydroxide solution. The solid was collected by filtration, washed with water and dried to yield

1.96 g of solid as 1:1 mixture of two isomers. The isomers were separated and purified by RP-HPLC to give 0.35g (17%) of the desired isomer, 4-iodo-7-methyl-1H-indazole, as a white solid, MS: 259.0 $[M+H]^+$

Step 4: To a solution of 4-iodo-7-methyl-1H-indazole (0.113 mg, 0.44 mmol) in DMSO (5 mL) was added potassium acetate (0.17 g, 1.73 mmol), 1,1'-bis(diphenyl phosphino)ferrocene palladium chloride (11 mg, 0.013 mmol) and bis(pinacolato)diboron (0.14 g, 0.55 mmol). The mixture was degassed and heated in a microwave reactor at 120° C for 1.5 hours. The reaction mixture was then filtered through a pad of celite, and the filtrate was diluted with water and then extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in-vacuo*. The residue was purified by silica gel chromatography to provide 7-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-indazole as a white solid in 79% yield. MS: 259.2 $[M+H]^+$

Step 5: Following the procedure of Example 34, Step 5, 3-iodo-7-(6-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine and 7-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole provided 3-(7-methyl-1H-indazol-4-yl)-7-(6-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine as a hydrochloride salt. MS: 514.7 [M+H].

Example 41: 3-(7-Chloro-1H-indazol-4-yl)-7-(6-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine



Step 1: To a solution of 2,2,6,6-tetramethylpiperidine (811 mg, 5.8 mmol) in THF (10 mL) at -78°C was added a solution of 2.5 M butyllithium in hexanes (2.31 mL, 5.8 mmol) and 4-bromo-1-chloro-2-fluoro-benzene (1.0 g, 4.8 mmol). The mixture was warmed to –

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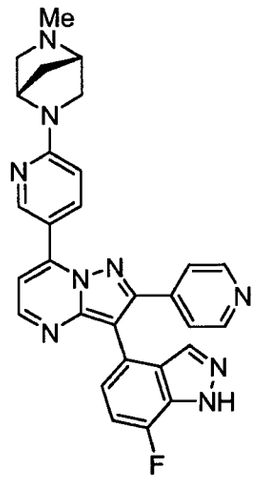
20°C for 2 hours, then DMF (0.54 mL, 6.9 mmol) was added and the reaction was then stirred for 2 hours at room temperature. The reaction was quenched with water (100 mL) and the mixture was neutralized with 1M HCl and then extracted with ether (3 x 30 mL). The combined organic extracts were dried over sodium sulfate, filtered, concentrated *in-vacuo*. The residue was purified by silica gel chromatography to provide 6-bromo-3-chloro-2-fluorobenzaldehyde in 85% yield. MS: 270.0 [M+H].

Step 2: To a solution of 6-bromo-3-chloro-2-fluorobenzaldehyde (1.0 g, 4.24 mmol) in DME (5 mL) was added hydrazine hydrate (5 mL). The mixture was refluxed for 3 hours and then cooled to room temperature. The solvent was evaporated, water (100 mL) was added, and the organic product was extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in-vacuo*. The resulting residue was purified by silica gel chromatography to provide 4-bromo-7-chloro-1H-indazole in 51% yield. MS: 230.9 [M+H].

Step 3: To a solution 4-bromo-7-chloro-1H-indazole (500 mg, 2.16 mmol) in dimethylsulfoxide, DMSO (2 mL) was added potassium acetate (697 mg, 7.12 mmol), 1,1'-bis(diphenyl phosphino)ferrocene palladium chloride (77 mg, 0.10 mmol) and bis(pinacolato)diboron (1.1 g, 4.32 mmol). The mixture was degassed and heated in a microwave reactor for 2 hours at 120° C. The solvent was then filtered through a pad of celite, water (60 mL) was added, and the product was extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were dried over sodium sulfate, concentrated *in-vacuo*, and the resulting 7-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole was used in the next step without further purification.

Step 4: Following the procedure of Example 34, Step 5, 3-iodo-7-(6-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine and 7-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole provided 3-(7-chloro-1H-indazol-4-yl)-7-(6-((1S,4S)-5-methyl-2,5-diazabicyclo-[2.2.1]heptan-2-yl)pyridin-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine as a hydrochloride salt. MS: 534.3 [M+H].

Example 42: 3-(7-Fluoro-1H-indazol-4-yl)-7-(6-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine



Step 1: To a solution of 2,2,6,6-tetramethylpiperidine (3.12 mL, 18.4 mmol) in THF (35 mL) at -78°C was added a solution of 1.6M butyl lithium in hexanes (11.5 mL, 18.4 mmol) and 1-bromo-3,4-difluorobenzene (3.38 g, 17.5 mmol). The mixture warmed to –20 °C for 2 hours, and then DMF (1.42 mL, 18.4 mmol) was added and the reaction was warmed to room temperature and stirred for for 2 hours. The reaction was quenched with water (5 mL), neutralized with 1M HCl and extracted with ether (3 x 30 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in-vacuo*. The crude material 6-bromo-2,3-difluorobenzaldehyde was used as is in the next step.

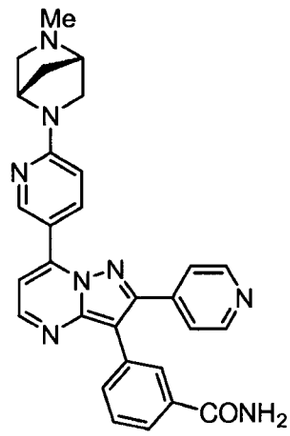
Step 2: To a solution of 6-bromo-2,3-difluorobenzaldehyde (5.0 g, 22.6 mmol) in DME (20 mL) was added hydrazine hydrate (20 mL). The mixture was refluxed for 3 hours, and cooled to room temperature. The solvent was evaporated, water (100 mL) was added and the mixture was extracted with ethyl acetate (3 x 40 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was recrystallized from hot dichloromethane to provide 4-bromo-7-fluoro-1H-indazole as a white solid in 21% yield. MS: 215.0 [M+H].

Step 3: According to the procedure of Example 40, Step 4, 4-bromo-7-fluoro-1H-indazole provided 7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole as a white solid in 74% yield. MS: 263.1 [M+H].

Step 4: Following the procedure of Example 34, Step 5, 3-iodo-7-(6-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine and 7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole provided 3-(7-fluoro-1H-indazol-4-yl)-7-(6-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine as a hydrochloride salt. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (d, J = 2Hz, 1H), 8.81–8.75 (m, 3H), 8.69 (d, J = 4 Hz, 1H), 8.30–8.25

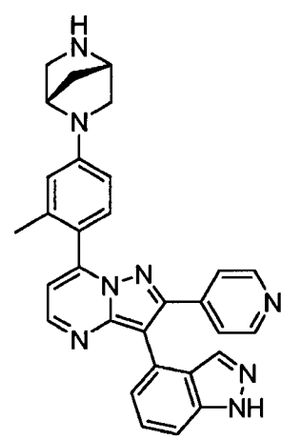
(m, 2H), 7.75 (d, J = 3.2 Hz, 1H), 7.57 (d, J = 4.4 Hz, 1H), 7.34–7.24 (m, 3H), 5.34 (s, 1H), 4.64 (s, 1H), 4.10–3.95 (m, 3H), 3.10 (s, 3H), 2.64 (d, J = 11.6, 1H), 2.45 (d, J = 11.6, 1H). MS: 518.7 [M+H].

Example 43: 3-(7-(6-((1S,4S)-5-Methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)benzamide



Following the procedure of Example 34, Step 5, 3-iodo-7-(6-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine and 3-carbamoylphenylboronic acid provided 3-(7-(6-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)benzamide as a hydrochloride salt. MS: 503.3 [M+H].

Example 44: 7-(4-((1S,4S)-2,5-Diazabicyclo[2.2.1]heptan-2-yl)-2-methylphenyl)-3-(1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine



Step 1: To a solution of (1S,4S)-tert-butyl 2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (200 mg, 1.3 mmol) in 2 mL of 1-methylpyrrolidin-2-one, 1-(4-fluoro-2-

methylphenyl)ethanone (387 mg, 1.95 mmol) and N-ethyl-N-isopropylpropan-2-amine (0.45 mL, 2.6 mmol) were added. This solution was heated at 240° C for 1 hour in a microwave reactor. The mixture was then cooled down to room temperature and then 0.54 g di-tert-butyl dicarbonate and 0.2 mL triethylamine were added. After stirring for 30 minutes, this mixture was diluted with 80 mL of dichloromethane and the organics were washed with water twice. The organic layer was dried and concentrated and the residue was purified by silica gel chromatography to give (1S,4S)-tert-butyl 5-(4-acetyl-3-methylphenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate. MS: 331.2 [M+H].

Step 2: A mixture of (1S,4S)-tert-butyl 5-(4-acetyl-3-methylphenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (95 mg, 0.29 mmol) and 2 mL of 1,1-dimethoxy-N,N-dimethylmethanamine were heated at 190° C for 1 hour in a microwave reactor. The reaction mixture was then diluted with 80 mL dichloromethane and the organics were washed with water twice. The organic layer was dried and concentrated and the residue was purified by silica gel chromatography to give (1S,4S)-tert-butyl 5-(4-((E)-3-(dimethylamino)acryloyl)-3-methylphenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate. MS: 386.2 [M+H].

Step 3: To a cold (0°-5° C) suspension of sodium hydride (0.6 g, 15.0 mmol) in DMF (20 mL) was added methyl 1H-indazole-4-carboxylate (2.4 g, 13.62 mmol) [D.Batt, et al. J. Med. Chem., 2000, *43*, 41-58] in portions over a period of 5 minutes and the resulting mixture was stirred at 5° C for 15 minutes. A solution of benzene sulfonyl chloride (1.9 mL, 15.0 mmol) was then added dropwise and the resulting mixture was stirred at 5° C for 30 minutes and then at room temperature for 3 hours. The mixture was poured on to ice and the solid was collected by filtration, washed with water and dried to yield 3.91 g (91%) of methyl 1-(phenylsulfonyl)-1H-indazole-4-carboxylate as a beige solid. MS: 317.1 $[M+H]^+$

Step 4: To a suspension of methyl 1-(phenylsulfonyl)-1H-indazole-4-carboxylate (3.11g, 9.83 mmol) in mixture of THF (30 mL) and toluene (15 mL) was added lithium borohydride as a 2.0M solution in THF(2.7 mL, 5.5 mmol) and the resulting mixture was stirred and heated at 70°C for 30 minutes. Additional 2.0 M lithium borohydride solution (2.0 mL. 4.0 mmol) was added in portions over a period of 2.5 hours until all of the starting ester was consumed. The mixture was then cooled and poured on to ice water and the resulting two layers were separated. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography to yield 2.0 g (71%) of [1-(phenylsulfonyl)-1H-indazol-4-yl]methanol as a white solid. MS: 289.1 [M+H].

Step 5: A mixture of [1-(phenylsulfonyl)-1H-indazol-4-yl]methanol (13.0 g, 45.08 mmol) and Dess-Martin periodinane (22.9 g, 54.0 mmol) in dichloromethane (420 mL) was stirred at room temperature for 1 hour. The reaction was quenched by stirring for 20 minutes with a saturated sodium thiosulfate solution (100 mL) and a saturated solution of sodium bicarbonate (75 mL). The two layers were separated and the aqueous layer was extracted with methylene chloride. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The resulting crude solid was purified by silica gel chromatography to yield 12.65 g (98%) of 1-(phenylsulfonyl)-1H-indazole-4-carbaldehyde as a white solid. MS: 287.1 [M+H].

Step 6: A mixture of 1-(phenylsulfonyl)-1H-indazole-4-carbaldehyde (6.4 g, 22.4 mmol) and 8.5 g (20.3 mmol) of diphenyl(phenylamino)(pyridin-4-yl)methylphosphonate (prepared according to the procedure of Tet. Lett., 1988, *39*, 1717-1720) in THF (50 mL) and isopropyl alcohol (10 mL) was stirred at room temperature and cesium carbonate (8.6 g, 26.4 mmol) was added in portions. After the reaction was stirred for 15 hours, 3N HCl (20 mL) was added and the mixture was stirred for an additional 4 hours. The reaction was then diluted with ether (150 mL) and extracted with 10% HCl (3 x, 150 mL). The aqueous layer was neutralized to pH 7-8 using NaOH. The aqueous layer was next extracted with ethyl acetate (3X, 150 mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in-vacuo* to give 4.6 g (55% yield) of 2-(1-(phenylsulfonyl)-1H-indazol-4-yl)-1-(pyridin-4-yl)ethanone as a white solid. MS: 378.1 [M+ H].

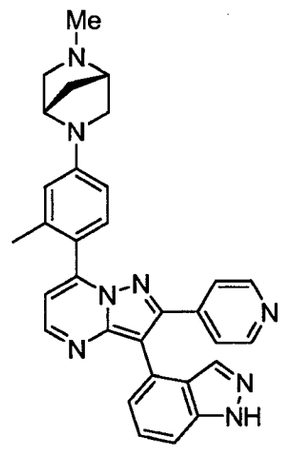
Step 7: Phosphorus oxychloride (1.4 mL, 14.9 mmol) was added to DMF (1.84 mL) at 0°C and the mixture was stirred for 15 minutes. To this solution was added 2-(1-(phenylsulfonyl)-1H-indazol-4-yl)-1-(pyridin-4-yl)ethanone (1.13 g, 3.0 mmol) in dichloromethane (10 mL), and the reaction was then heated to 80° C for 15 hours. The reaction was then cooled to room temperature, quenched with saturated sodium bicarbonate (300 mL), and extracted with 2% methanol in dichloromethane (4x250 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and then concentrated *in-vacuo*. The resulting residue was dissolved in dimethyl formamide, DMF (3 mL), hydroxylamine hydrochloride (0.15 mL, 3.6 mmol) was added and the reaction was stirred for 12 hours. The reaction was then cooled to 0° C, phosphorus oxychloride (0.64 mL, 6.0 mmol) was added and the mixture was stirred overnight at room temperature. The reaction was quenched with saturated sodium bicarbonate and extracted with 3% methanol in dichloromethane (4 x 200 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and then concentrated *in-vacuo* to give crude (E)-3-chloro-2-(1H-indazol-4-yl)-3-(pyridin-4-yl)acrylonitrile. The crude (E)-3-chloro-2-(1H-indazol-4-yl)-3-(pyridin-4-yl)acrylonitrile was dissolved in ethanol (16 mL) and hydrazine monohydrate (0.44 mL, 9.0 mmol) was added

and the resulting reaction was stirred at 80° C for 6 hours. The reaction was cooled to room temperature and the solvent was removed by evaporation. The crude product was purified by silica gel flash chromatography, eluting with 2-12% methanol in dichloromethane, to give 0.58 g (71% yield) of 4-(1H-indazol-4-yl)-3-(pyridin-4-yl)-1H-pyrazol-5-amine. MS: 277.2 [M+H].

Step 8: Following the procedure of Example 7, Step 4, (1S,4S)-tert-butyl 5-(4-((E)-3-(dimethylamino)acryloyl)-3-methylphenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (41 mg, 0.11 mmol) and 4-(1H-indazol-4-yl)-3-(pyridin-4-yl)-1H-pyrazol-5-amine (34mg, 0.12 mmol) provided (1S,4S)-tert-butyl 5-(4-(3-(1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-3-methylphenyl)-2,5-diazabicyclo-[2.2.1]heptane-2-carboxylate, which was used as a crude product for the next step. MS: 599.8 [M+H].

Step 9: Crude 5-(4-(3-(1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-3-methylphenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate was dissolved in 3 mL of 4 N HCl (diluted from concentrated HCl with methanol) and stirred for 1 hour at room temperature. The mixture was then concentrated, basified with methanolic ammonia solution, and purified by HPLC. The free base was dissolved in methanol and then 1 mL of 1.25 M methanolic HCl was added. The solution was concentrated *in-vacuo* and then dried to give 7-(4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-2-methylphenyl)-3-(1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine-hydrochloride salt. MS: 499.4 [M+H].

Example 45: 3-(1H-Indazol-4-yl)-7-(2-methyl-4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine

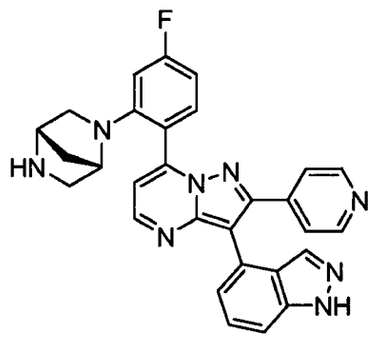


Following the procedure of Example 30, 7-(4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-2-methylphenyl)-3-(1H-indazol-4-yl)-2-(pyridin-4-

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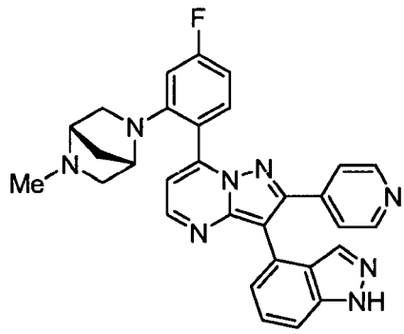
yl)pyrazolo[1,5-a]pyrimidine provided 3-(1H-indazol-4-yl)-7-(2-methyl-4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]-heptan-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine as a hydrochloride salt. MS: 513.4 [M+H].

Example 46: 7-(2-((1S,4S)-2,5-Diazabicyclo[2.2.1]heptan-2-yl)-4-fluorophenyl)-3-(1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine



Following the procedure of Example 44, 1-(2,4-difluorophenyl)ethanone provided 7-(2-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-4-fluorophenyl)-3-(1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine as a hydrochloride salt. ^{1}H NMR (400 MHz, CD_3OD) δ 8.73–8.68 (m, 3H), 8.19–8.14 (m, 2H), 7.75–7.66 (m, 3H), 7.59 (dd, J = 7.4, 8.2 Hz, 1H), 7.38–7.28 (m, 2H), 7.00 (dd, J = 2.2, 11.8 Hz, 1H), 6.85 (dt, J = 2.0, 8.0 Hz, 1H), 4.65 (s, 1H), 4.22 (s, 1H), 3.57–3.5 (m, 1H), 2.20–2.08 (m, 1H), 2.02–1.94 (m, 1H). MS: 503.7 [M+H].

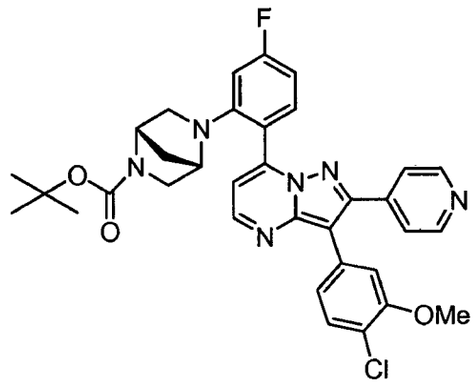
Example 47: 7-(4-Fluoro-2-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-3-(1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine



Following the procedure of Example 30, 7-(2-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-4-fluorophenyl)-3-(1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine provided 7-(4-fluoro-2-((1S,4S)-5-methyl-2,5-

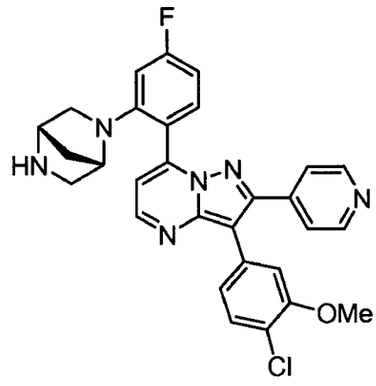
diazabicyclo[2.2.1]heptan-2-yl)phenyl)-3-(1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine as a hydrochloride salt. MS: 517.7 [M+H].

Example 48: (1S,4S)-tert-Butyl 5-(2-(3-(4-chloro-3-methoxyphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-5-fluorophenyl)-2,5-diazabicyclo[2.2.1]-heptane-2-carboxylate



Following the procedure of Example 44, Steps 1-2, starting from 1-(2,4-difluorophenyl)ethanone, followed by the procedure of Example 7, Step 4, using 4-(4-chloro-3-methoxyphenyl)-3-(pyridin-4-yl)-1H-pyrazol-5-amine provided (1S,4S)-tert-butyl 5-(2-(3-(4-chloro-3-methoxyphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-5-fluorophenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate as a trifluoroacetate salt. MS: 627.3 [M+H].

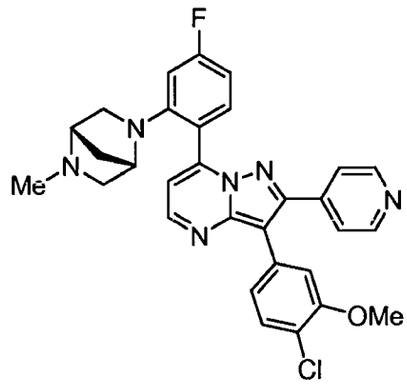
Example 49: 7-(2-((1S,4S)-2,5-Diazabicyclo[2.2.1]heptan-2-yl)-4-fluorophenyl)-3-(4-chloro-3-methoxyphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine



Following the procedure of Example 44, Step 9, (1S,4S)-tert-butyl 5-(2-(3-(4-chloro-3-methoxyphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-5-fluorophenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate gave 7-(2-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-

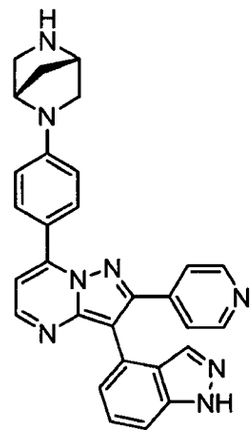
2-yl)-4-fluorophenyl)-3-(4-chloro-3-methoxyphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine as a trifluoroacetate salt. MS: 527.1 [M+H].

Example 50: 3-(4-Chloro-3-methoxyphenyl)-7-(4-fluoro-2-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine



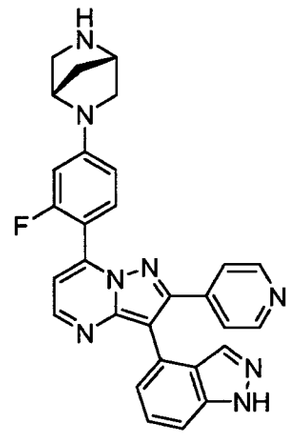
Following the procedure of Example 30, reductive alkylation of 7-(2-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-4-fluorophenyl)-3-(4-chloro-3-methoxyphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine provided 3-(4-chloro-3-methoxyphenyl)-7-(4-fluoro-2-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine as a trifluoroacetate salt. MS: 541.1 [M+H].

Example 51: 7-(4-((1S,4S)-2,5-Diazabicyclo[2.2.1]heptan-2-yl)phenyl)-3-(1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine



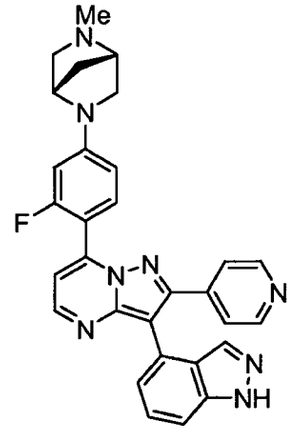
Following the procedure of Example 44, starting from 1-(4-fluorophenyl)ethanone, 7-(4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-3-(1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine was obtained as a hydrochloride salt. MS: 485.7 [M+H].

Example 52: 7-(4-((1S,4S)-2,5-Diazabicyclo[2.2.1]heptan-2-yl)-2-fluorophenyl)-3-(1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine



Following the procedure of Example 44, starting from 1-(2,4-difluorophenyl)ethanone, 7-(4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-2-fluorophenyl)-3-(1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine was obtained as a hydrochloride salt. MS: 503.1 [M+H].

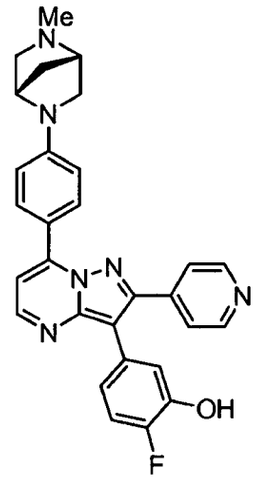
Example 53: 7-(2-Fluoro-4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-3-(1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine



Following the procedure of Example 30, reductive alkylation of 7-(4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-2-fluorophenyl)-3-(1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine provided 7-(2-fluoro-4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-3-(1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine, isolated as a hydrochloride salt. ^{1}H NMR (400 MHz, CD_3OD) δ 8.72–8.68 (m, 2H), 8.62 (d, J = 4.4 Hz, 1H), 8.2–8.16 (m, 2H), 8.05–7.96 (m, 1H), 7.79 (d, J = 0.8 Hz, 1H), 7.75–7.70 (m, 1H), 7.61 (dd, J = 6.8, 8.4 Hz, 1H), 7.35 (dd, J = 0.8, 7.2 Hz, 1H), 7.30 (dd, J =

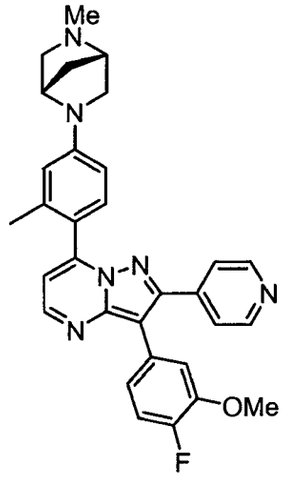
1.2, 4.0 Hz, 1H), 6.82–6.70 (m, 2H), 4.50 (s, 1H), 3.92–3.80 (m, 2H), 3.63 (d, J = 11.2Hz, 1H), 3.04 (s, 3H), 2.55–2.48 (m, 1H), 2.40–2.33 (m, 1H). MS: 517.1 [M+H].

Example 54: 5-(7-(4-((1S,4S)-2,5-Diazabicyclo[2.2.1]heptan-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-fluorophenol



Following the procedure of Example 8, 3-(4-fluoro-3-methoxyphenyl)-7-(4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine and boron tribromide afforded 2-fluoro-5-(7-(4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)phenol, isolated as a hydrochloride salt. ^{1}H NMR (400 MHz, CD_3OD) δ 8.84–8.79 (m, 2H), 8.58 (d, J = 4.8 Hz, 1H), 8.38–8.32 (m, 4H), 7.35 (d, J = 4.8 Hz, 1H), 7.20 (dd, J = 8.0, 10.8 Hz, 1H), 7.13 (dd, J = 2, 8.4 Hz, 1H), 6.98–6.90 (m, 3H), 4.49 (s, 1H), 3.91–3.78 (m, 3H), 3.63 (d, J = 11.2 Hz, 1H), 3.03 (s, 3H), 2.54–2.44 (m, 1H), 2.39–2.28 (m, 1H). MS: 493.2 [M+H].

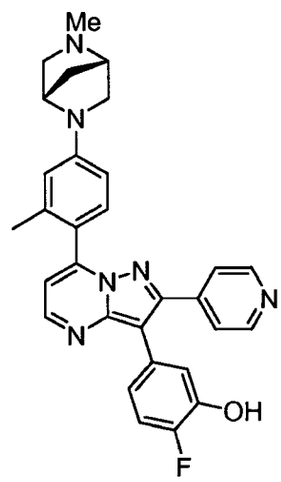
Example 55: 3-(4-Fluoro-3-methoxyphenyl)-7-(2-methyl-4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine



Step 1: Following the procedure of Example 7, Step 4, (1S,4S)-tert-butyl 5-(4-((E)-3-(dimethylamino)acryloyl)-3-methylphenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (41 mg, 0.11 mmol) and 4-(4-fluoro-3-methoxyphenyl)-3-(pyridin-4-yl)-1H-pyrazol-5-amine, afforded 7-(4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-2-methylphenyl)-3-(4-fluoro-3-methoxyphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine. MS: 507.2 [M+H].

Step 5: Following the procedure of Example 30, reductive alkylation of 7-(4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-2-methylphenyl)-3-(4-fluoro-3-methoxyphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine gave 3-(4-fluoro-3-methoxyphenyl)-7-(2-methyl-4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine, isolated as a trifluoroacetate salt. MS: 521.3 [M+H].

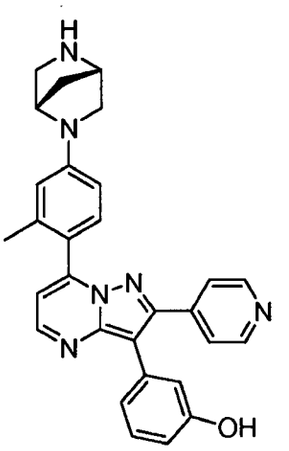
Example 56: 2-Fluoro-5-(7-(2-methyl-4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)phenol



Following the procedure of Example 8, 3-(4-fluoro-3-methoxyphenyl)-7-(2-methyl-4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-

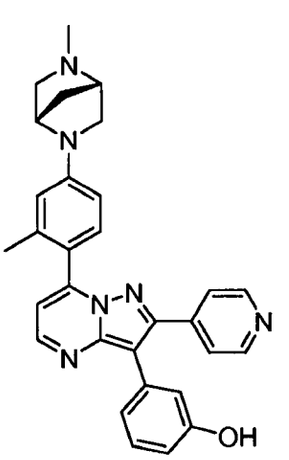
a]pyrimidine and boron tribromide gave 2-fluoro-5-(7-(2-methyl-4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)phenol, isolated as a trifluoroacetate salt. MS: 507.3 [M+H].

Example 57: 3-(7-(4-((1S,4S)-2,5-Diazabicyclo[2.2.1]heptan-2-yl)-2-methylphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)phenol



Following the procedure of Example 7, Step 4, 3-(3-amino-5-pyridin-4-yl-1H-pyrazol-4-yl)phenol and (1S,4S)-tert-butyl 5-(4-((E)-3-(dimethylamino)acryloyl)-3-methylphenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate afforded 3-(7-(4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-2-methylphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)phenol, isolated as a trifluoroacetate salt. MS: 475.3 [M+H].

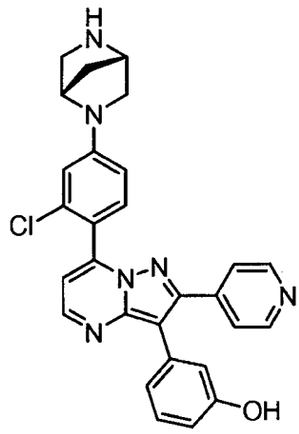
Example 58: 3-(7-(2-Methyl-4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)phenol



Following the procedure of Example 30, reductive alkylation of 3-(7-(4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-2-methylphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-

3-yl)phenol afforded 3-(7-(2-methyl-4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)phenol, isolated as a trifluoroacetate salt. MS: 489.3 [M+H].

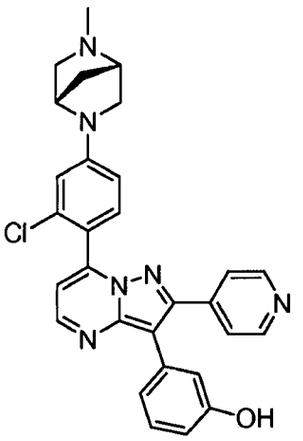
Example 59: 3-(7-(4-((1S,4S)-2,5-Diazabicyclo[2.2.1]heptan-2-yl)-2-chlorophenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)phenol



Step 1: Following the procedure of Example 44, Steps 1-2, (1S,4S)-tert-butyl 5-(3-chloro-4-((E)-3-(dimethylamino)acryloyl)phenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate was prepared starting from 1-(2-chloro-4-fluorophenyl)ethanone.

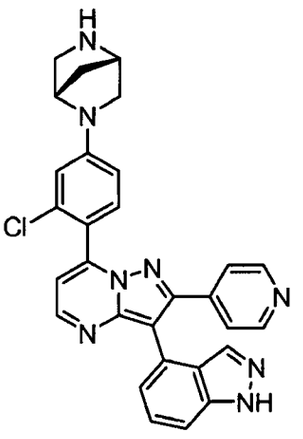
Step 2: Following the procedure of Example 7, Step 4, (1S,4S)-tert-butyl 5-(3-chloro-4-((E)-3-(dimethylamino)acryloyl)phenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate and 3-(3-amino-5-pyridin-4-yl-1H-pyrazol-4-yl)phenol afforded 3-(7-(4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-2-chlorophenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)phenol as a trifluoroacetate salt. MS: 495.3 [M+H].

Example 60: 3-(7-(2-Chloro-4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)phenol



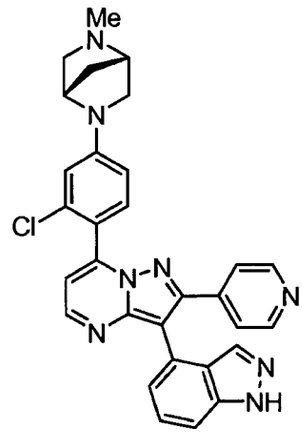
Following the procedure of Example 30, reductive alkylation of 3-(7-(4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-2-chlorophenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)phenol afforded 3-(7-(2-chloro-4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)phenol, isolated as a trifluoroacetate salt. MS: 509.3 [M+H].

Example 61: 7-(4-((1S,4S)-2,5-Diazabicyclo[2.2.1]heptan-2-yl)-2-chlorophenyl)-3-(1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine



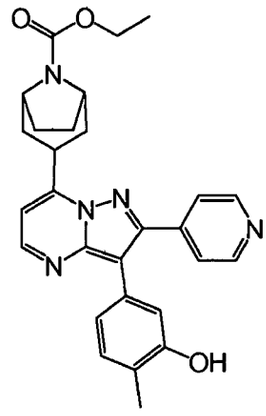
Following the procedure of Example 44, Step 8, (1S,4S)-tert-butyl 5-(3-chloro-4-((E)-3-(dimethylamino)acryloyl)phenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate and 4-(1H-indazol-4-yl)-3-(pyridin-4-yl)-1H-pyrazol-5-amine (34mg, 0.12 mmol) provided 7-(4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-2-chlorophenyl)-3-(1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine as a trifluoroacetate salt after deprotection with trifluoroacetic acid. MS: 519.2 [M+H].

Example 62: 7-(2-Chloro-4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-3-(1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine



Following the procedure of Example 30, reductive alkylation of 7-(4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-2-chlorophenyl)-3-(1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine gave 7-(2-chloro-4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-3-(1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine, isolated as a trifluoroacetate salt. MS: 533.3 [M+H].

Example 63: Ethyl 3-[3-(3-hydroxy-4-methylphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate trifluoroacetate salt



[0002] Step 1: According to the procedure of Example 7, Step 4, (E)-ethyl 3-(3-(dimethylamino)acryloyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (0.37 g, 1.3 mmol) and 3-(pyridin-4-yl)-1H-pyrazol-5-amine provided ethyl 3-(2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate.

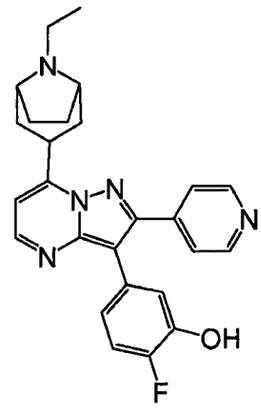
Step 2: To a solution of ethyl 3-(2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (0.8 g, 2.1 mmol) in dichloromethane (75 mL) was added N-iodosuccinimide (5.7 g, 25 mmol) in four portions over a 3 hour period and the reaction was then stirred for an additional 16 hours. The reaction mixture was washed with saturated sodium thiosulfate (2 x 200 mL) and the organic layer was dried over anhydrous

sodium sulfate, filtered and then concentrated *in-vacuo* to give 0.8 g of ethyl 3-(3-iodo-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate as a yellow solid. This product was used in the next step without further purification. MS: 504.3 [M+H].

Step 3: To a suspension of ethyl 3-(3-iodo-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.20 mmol) in 1.5 mL of dimethoxyethane was added 2M sodium carbonate (0.5 mL), 3-methoxy-4-methylboronic acid (40 mg, 0.24 mmol) and a catalytic amount of (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium(II) dichloromethane complex (16 mg, 0.02 mmol). The mixture was heated to 100° C for 60 minutes in a microwave reactor. Additional portions of 3-methoxy-4-methylboronic acid (20 mg, 0.12 mmol) and (1,1'-bis(diphenylphosphino)ferrocene) dichloropalladium(II) dichloromethane complex (10 mg, 0.012 mmol) were added, and the mixture was reacted at 100° C for an additional 40 minutes in the microwave reactor. The crude product was purified by silica gel chromatography eluting with a gradient of 99:1 to 97:3 dichloromethane/methanol to provide 67 mg (68% yield) of 3-[3-(3-methoxy-4-methyl-phenyl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidin-7-yl]-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid ethyl ester as an orange oil. MS: 498.4 [M+H].

Step 4: Following the procedure of Example 8, 3-[3-(3-methoxy-4-methyl-phenyl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidin-7-yl]-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid ethyl ester was reacted with boron tribromide in dichloromethane to provide ethyl 3-[3-(3-hydroxy-4-methylphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate trifluoroacetate salt, as a white solid (15% yield) after purification by preparative HPLC (H_2O/acetonitrile/trifluoroacetic acid). MS: 484.0 [M+H].

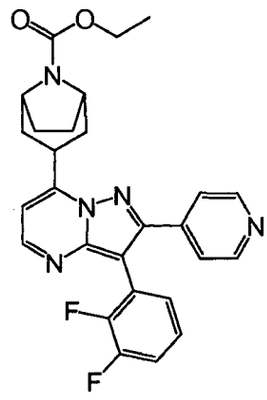
Example 64: 5-(7-(8-Ethyl-8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-fluorophenol



Step 1: Following the procedure of Example 20, Step 7, 7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-3-iodo-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine (150 mg, 0.326 mmol) reacted with 4-fluoro-3-methoxyphenylboronic acid (167 mg, 0.983 mmol) to yield 7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-3-(4-fluoro-3-methoxyphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine as a yellow solid. MS 458.1 [M+H].

Step 2: Following the procedure of Example 8, 7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-3-(4-fluoro-3-methoxyphenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine was reacted with boron tribromide and then purified using preparative TLC using a 5-10% methanol/dichloromethane gradient to provide 4.8 mg (3.3% yield) 5-(7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-fluorophenol as a yellow solid. MS 444.3 [M+H].

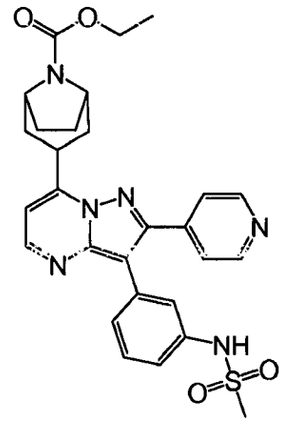
Example 65: Ethyl 3-(3-(2,3-difluorophenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate



Following the procedure of Example 20, Step 7, ethyl 3-(3-iodo-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.199 mmol) was reacted with 2,3-difluorophenylboronic acid (141 mg, 0.89 mmol) to yield 47.1 mg (48.5%) of ethyl 3-(3-(2,3-difluorophenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-

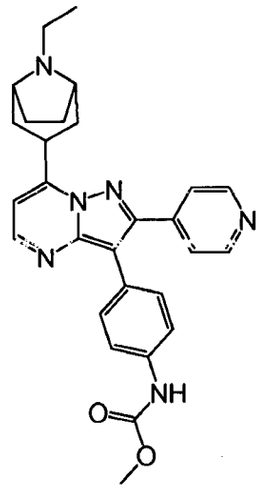
azabicyclo[3.2.1]octane-8-carboxylate as a yellow solid after preparative TLC eluting with 4% methanol in dichloromethane. MS 490.3 [M+H].

xample 66: Ethyl 3-(3-(3-(methylsulfonamido)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate



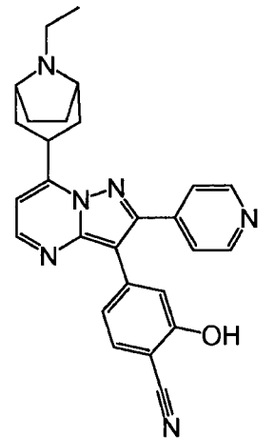
Following the procedure of Example 20, Step 7, ethyl 3-(3-iodo-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.199 mmol) was reacted with 3-(methylsulfonamido)phenylboronic acid (192 mg, 0.89 mmol) to yield 76.3 mg (70.3%) of ethyl 3-(3-(3-(methylsulfonamido)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate as a yellow solid after preparative TLC eluting with 4% methanol in dichloromethane. MS 547.3 [M+H].

Example 67: Methyl 4-(7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)phenylcarbamate



A mixture of 4-(7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)aniline (65 mg, 0.15 mmol) and triethylamine (62 □L, 0.45 mmol) in dichloromethane (3 mL) was added to a solution of triphosgene (23 mg, 0.075 mmol) in dichloromethane (0.5 mL) and the resulting mixture was stirred for 10 minutes. Methanol (2 mL) was then added to the reaction and the resulting mixture was stirred for an additional 30 minutes. The reaction was diluted with dichloromethane (5 mL) and washed with saturated sodium bicarbonate (2 x 5 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in-vacuo* to give a solid. The crude solid was purified by silica gel flash chromatography, eluting with 15% methanol in dichloromethane, to give 48 mg (66% yield) of methyl 4-(7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)phenylcarbamate as a yellow solid. MS 483.3 [M+H].

Example 68: 4-(7-(8-Ethyl-8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-hydroxybenzonitrile



Step 1: To a solution of 4-bromo-2-fluorobenzonitrile (5 g, 25 mmol) in tetrahydrofuran was added sodium methoxide (125 mmol) in methanol (20 mL) and the reaction was stirred at 40° C for 3 hours. The reaction was then cooled to room temperature and Amberlyst™ 15 was added and the mixture was stirred for 2 hours. The reaction was filtered and the organics were concentrated *in-vacuo* to give 4-bromo-2-methoxybenzonitrile as a white solid that was used directly in the next reaction. MS 212.1 [M+H].

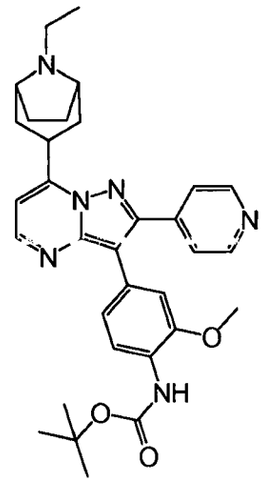
Step 2: According to the procedure of Example 40, Step 4, 4-bromo-2-methoxybenzonitrile was converted into 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile which was used directly in the next reaction.

Step 3: The reaction of 7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-3-iodo-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine with 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-

yl)benzonitrile, according to the procedure of Example 20, Step 7, provided 4-(7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-methoxybenzonitrile as a brown solid that was used directly in the next reaction.

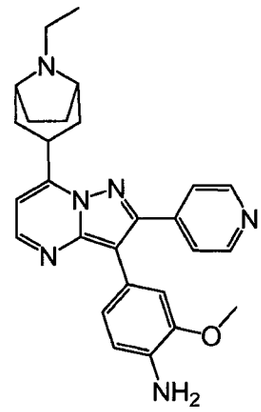
Step 4: Following the procedure of Example 8, 4-(7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-methoxybenzonitrile (0.066 g, 0.14 mmol) was reacted with a 1 M solution of boron tribromide in dichloromethane (4.6 mL) to provide 0.019 g (30% yield) of 4-(7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-hydroxybenzonitrile as a yellow solid. MS 451.3 [M+H].

Example 69: tert-Butyl 4-(7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-methoxyphenylcarbamate



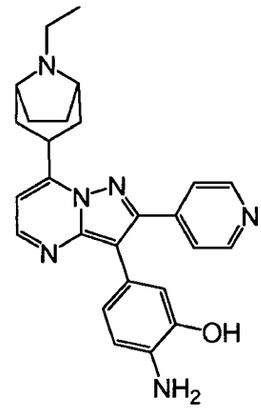
According to the procedure of Example 20, Step 7, the reaction of 7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-3-iodo-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine with tert-butyl 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate, provided 0.28 g (39% yield) of tert-butyl 4-(7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-methoxyphenylcarbamate as a yellow solid. MS 555.5 [M+ H].

Example 70: 4-(7-(8-Ethyl-8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-methoxyaniline



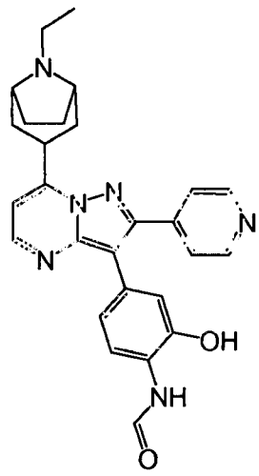
To a solution of tert-butyl 4-(7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-methoxyphenylcarbamate (281 mg, 0.51 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (0.5 mL). The reaction was stirred for 5 hours and then concentrated *in-vacuo*. The crude solid was suspended in saturated sodium bicarbonate (100 mL) and extracted with 5% methanol in dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give 0.22 g (94% yield) of 4-(7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-methoxyaniline as a yellow solid. MS 455.4 [M+ H].

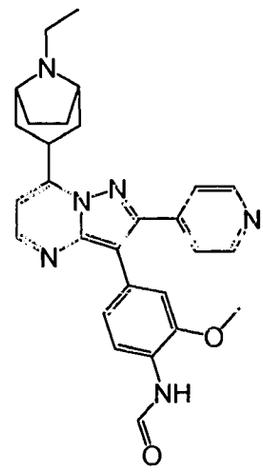
Example 71: 2-Amino-5-(7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)phenol



According to the procedure of Example 8, 4-(7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-methoxyaniline (0.21 g, 0.46 mmol) was reacted with a 1 M solution of boron tribromide in dichloromethane (4.6 mL) to provide 0.068 g (34% yield) of 2-amino-5-(7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)phenol as a yellow solid. MS 441.3 [M+H].

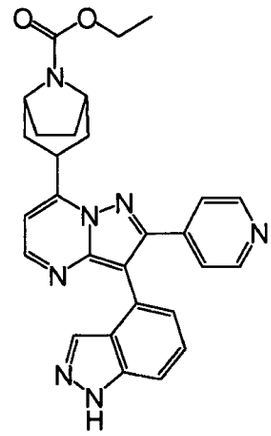
Examples 72a & 72b: N-(4-(7-(8-Ethyl-8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-hydroxyphenyl)formamide (WYE-126925), N-(4-(7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-methoxyphenyl)formamide





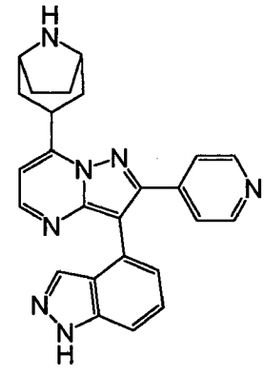
A mixture of formic acid (19 mg, 0.42 mmol) and acetic anhydride (34.5 mg, 0.34 mmol) was stirred at 60° C for 2 hours and then cooled to room temperature and added to a solution of a mixture of 2-amino-5-(7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)phenol and 4-(7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-methoxyaniline (1:1, 58 mg, 0.13 mmol) in 1 mL of THF at 0° C. The reaction was stirred for 2 hours and then quenched with saturated potassium carbonate. The mixture was extracted with 5% methanol in dichloromethane and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and then concentrated *in-vacuo*. The crude product was purified by preparatory TLC eluting with 10% methanol in dichloromethane to give 4.1 mg of Example 72a N-(4-(7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-hydroxyphenyl)formamide as an orange solid (MS 469.4 [M+H]) and 6.4 mg of Example 72b N-(4-(7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-methoxyphenyl)formamide as a orange solid (MS 483.3 [M+H]).

Example 73: Ethyl 3-[3-(1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate



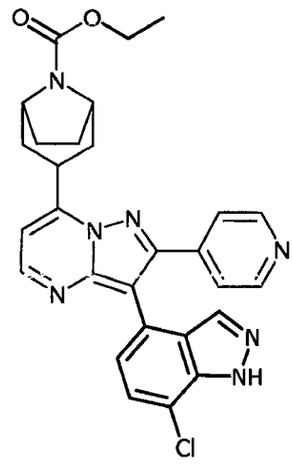
According to the procedure of Example 63, Step 3, 6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-and 3-(3-iodo-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidin-7-yl)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid ethyl ester provided ethyl 3-[3-(1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate in 40% yield after purification by RP-HPLC. MS 494.3 [M+H].

Example 74: 7-(8-Azabicyclo[3.2.1]oct-3-yl)-3-(1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5- a]pyrimidine



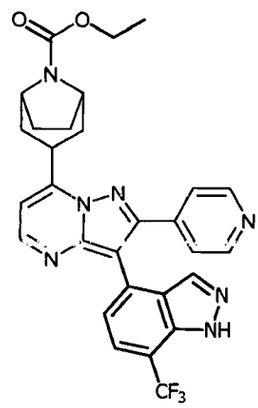
Following the procedure of Example 9, ethyl 3-[3-(1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate was reacted with iodotrimethylsilane in refluxing chloroform to provide 7-(8-azabicyclo[3.2.1]oct-3-yl)-3-(1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine as a yellow solid in 90% yield after silica gel chromatography, eluting with a gradient of 95:5 to 4:1 dichloromethane/methanol followed by 80:20:1 dichloromethane/methanol/aqueous ammonium hydroxide. MS: 422.2 [M+H].

Example 75: Ethyl 3-[3-(7-chloro-1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate



According to the procedure of Example 63, Step 3, 3-(3-iodo-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidin-7-yl)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid ethyl ester and 7-chloro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-indazole gave ethyl 3-[3-(7-chloro-1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate in 42% yield following purification by RP-HPLC. MS 528.0 [M+H].

Example 76: Ethyl 3-{2-pyridin-4-yl-3-[7-(trifluoromethyl)-1H-indazol-4-yl]pyrazolo[1,5- a]pyrimidin-7-yl}-8-azabicyclo[3.2.1]octane-8-carboxylate



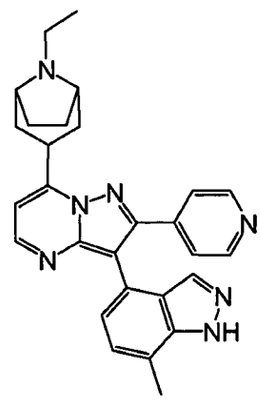
Step 1: To a solution of 2,2,6,6-tetramethylpiperidine (725 mg, 5.18 mmol) in THF (10 mL) at -78°C was added a solution of 2.5M butyllithium in hexanes (2.07 mL, 5.18 mmol) and 4-bromo-2-fluoro-1-trifluoromethyl-benzene (1.2 g, 4.9 mmol). The mixture warmed to –20° C for 2 hours, and then the reaction was quenched with water (100 mL), neutralized with 1M HCl and extracted with ether (3 x 30 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography to provide 6-bromo-2-fluoro-3-trifluoromethyl-benzaldehyde in 82% yield. MS: 270.0 [M+H].

Step 2: To a solution of 6-bromo-2-fluoro-3-trifluoromethyl-benzaldehyde (1.0 g, 3.7 mmol) in dmethoxyethane, DME (5 mL) was added hydrazine hydrate (5 mL). The mixture was refluxed for 3 hours, and then cooled to room temperature. The solvent was evaporated, water (100 mL) was added and the reaction mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over sodium sulfate, filtered, and then concentrated *in-vacuo*. The residue was purified by silica gel chromatography to afford 4-bromo-7-(trifluoromethyl)-1H-indazole in 42% yield. MS 264.9 [M+H].

Step 3: To a solution of 4-bromo-7-(trifluoromethyl)-1H-indazole (500 mg, 1.89 mmol) in DMSO (5 mL) was added potassium acetate (610 g, 6.23 mmol), 1,1'-bis(diphenyl phosphino)ferrocene palladium chloride (77 mg, 0.09 mmol) and bis(pinacolato)diboron (576 g, 2.27 mmol). The mixture was degassed and heated in oil bath overnight at 100°C. The reaction was filtered through a pad of Celite™, water (60 mL) was added to the filtrate, and the mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were dried over sodium sulfate, filtered, and then concentrated *in-vacuo* to provide 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-7-trifluoromethyl-1H-indazole which was used in the next step without further purification.

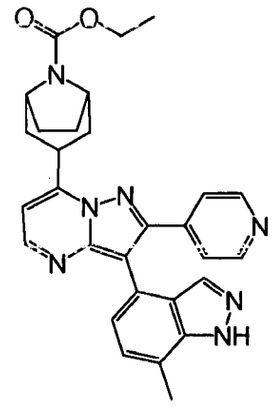
Step 4: According to the procedure of Example 63, Step 3, 3-(3-iodo-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidin-7-yl)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid ethyl ester and 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-7-trifluoromethyl-1H-indazole gave ethyl 3-{2-pyridin-4-yl-3-[7-(trifluoromethyl)-1H-indazol-4-yl]pyrazolo[1,5-a]pyrimidin-7-yl}-8-azabicyclo[3.2.1]octane-8-carboxylate (32 mg, 37% yield) after purification by RP-HPLC. MS: 562.3 [M+H].

Example 77: 7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-3-(7-methyl-1H-indazol-4-yl)-2-pyridin- 4-ylpyrazolo[1,5-a]pyrimidine, trifluoroacetate salt



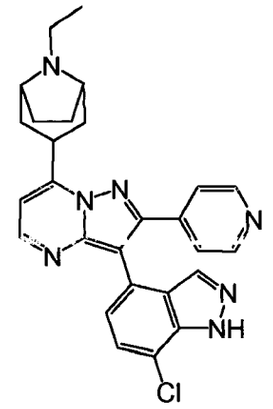
According to the procedure for Example 63, Step 3, 7-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-indazole and 7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-3-iodo-2-pyridin-4-ylpyrazolo[1,5- a]pyrimidine provided 7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-3-(7-methyl-1H-indazol-4-yl)-2-pyridin- 4-ylpyrazolo[1,5-a]pyrimidine, trifluoro acetate salt, as a yellow solid in 18% yield following purification by RP-HPLC. MS: 464.3 [M+H].

Example 78: Ethyl 3-[3-(7-Methyl-1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7- yl]-8-azabicyclo[3.2.1]octane-8-carboxylate, trifuoroacetate salt



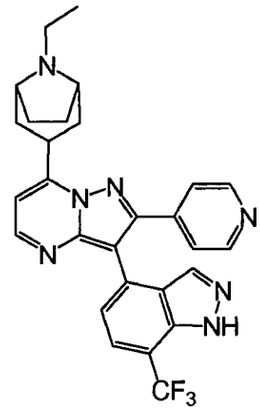
According to the procedure of Example 63, Step 3, 7-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-indazole and 3-(3-iodo-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidin-7-yl)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid ethyl ester provided ethyl 3-[3-(7-methyl-1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate, trifluoro acetate salt, as a yellow solid in 8% yield following purification by RP-HPLC. MS: 508.3 [M+H].

Example 79: 3-(7-Chloro-1H-indazol-4-yl)-7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin- 4-ylpyrazolo[1,5-a]pyrimidin, trifluoroacetate salt



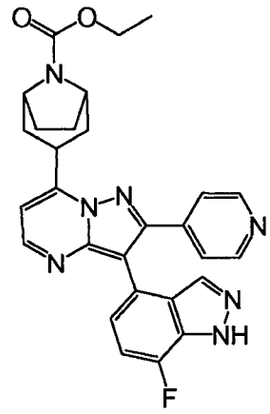
According to the procedure of Example 63, Step 3, 7-chloro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-indazole and 7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-3-iodo-2-pyridin-4-ylpyrazolo[1,5- a]pyrimidine provided 3-(7-chloro-1H-indazol-4-yl)-7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin, trifluoro acetate salt, as a yellow solid in 35% yield following purification by RP-HPLC. MS: 484.1 [M+H].

Example 80: 7-(8-Ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-yl-3-[7-(trifluoromethyl)- 1H-indazol-4-yl]pyrazolo[1,5-a]pyrimidine, trifluoroacetate salt



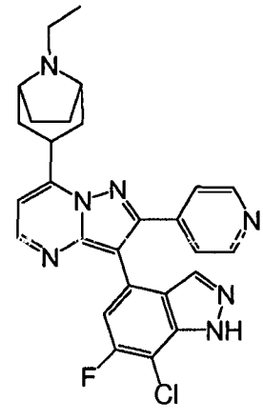
According to the procedure of Example 63, Step 3, 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-7-trifluoromethyl-1H-indazole and 7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-3-iodo-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine provided 7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-yl-3-[7-(trifluoromethyl)-1H-indazol-4-yl]pyrazolo[1,5-a]pyrimidine, trifluoro acetate salt, as a yellow solid in 8% yield following purification by RP-HPLC. MS: 518.3 [M+H].

Example 81: Ethyl 3-[3-(7-fluoro-1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate, trifluoroacetate salt



[0003] According to the procedure of Example 63, Step 3, 7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole and 3-(3-iodo-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidin-7-yl)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid ethyl ester gave ethyl 3-[3-(7-fluoro-1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylat, trifluoroacetate salt, as a yellow solid in 19% yield following purification by RP-HPLC. MS: 512.3 [M+H].

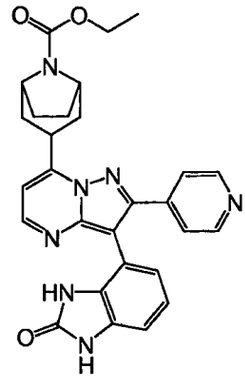
Example 82: 3-(7-Chloro-6-fluoro-1H-indazol-4-yl)-7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, trifluoro acetate salt



Step 1: According to the procedure of Example 41, Steps 1-3, 5-bromo-2-chloro-1,3-difluorobenzne afforded 7-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole as a white solid. MS: 297.1 [M+H].

Step 2: According to the procedure of Example 63, Step 3, 7-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole and 7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-3-iodo-2-pyridin-4-ylpyrazolo[1,5- a]pyrimidine provided 3-(7-chloro-6-fluoro-1H-indazol-4-yl)-7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2- pyridin-4-ylpyrazolo[1,5a]pyrimidine, trifluoro acetate salt, as a yellow solid in 7% yield following purification by RP-HPLC. MS: 502.1 [M+H].

[0004] Example 83: Ethyl 3-[3-(2-oxo-2,3-dihydro-1H-benzimidazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate



Step 1: To a solution of 4-bromo-benzo[1,2,5]thiadiazole (1.15g, 5.35 mmol) in methanol (10 mL) was added sodium borohydride (203 mg, 5.35 mmol) and cobalt(II) chloride hexahydrate (120 mg, 0.533 mmol). The mixture was refluxed for 3 hours, then cooled to room temperature and filtered to remove the black solid. The solvent was evaporated, water (100 mL) was added and the mixture was extracted with ether (3 x 30 mL). The combined organic extracts were dried over sodium sulfate, filtered, and then concentrated *in-vacuo*, to provide 3-bromo-benzene-1,2-diamine (810 mg, 81% yield). MS: 187.0 [M+H].

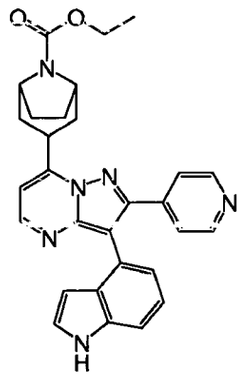
Step 2: To a solution of 3-bromo-benzene-1,2-diamine (810 mg, 4.33 mmol) in THF (10 mL) was added triphosgene (2.57 g, 8.66 mmol) and triethylamine (1.15 mL, 13 mmol), and the resulting reaction was heated at 50°C overnight. The solvent was then evaporated, water (60 mL) was added, and the mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were dried over sodium sulfate, filtered, and then concentrated *in-vacuo*. The residue was purified by silica gel chromatography to give 4-bromo-1,3-dihydro-benzoimidazol-2-one (701 mg) in 76% yield. MS: 211.0 [M-H].

Step 3: To a solution of 4-bromo-1,3-dihydro-benzoimidazol-2-one (701 mg, 3.29 mmol) in DMSO (2 mL) was added potassium acetate (803 g, 10.9 mmol), 1,1'-bis(diphenyl phosphino)ferrocene palladium chloride (134 mg, 0.16 mmol) and bis(pinacolato)diboron (1.67 g, 6.58 mmol), and the reaction was degassed and heated in a microwave reactor for 30 minutes at 150° C. The reaction mixture was then filtered through a pad of Celite™, water (60 mL) was added, and the mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were dried over sodium sulfate, filtered, and then concentrated *in-vacuo* to give 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,3-dihydro-benzoimidazol-2-one, which was used in the next step without further purification.

Step 4: According to the procedure of Example 63, Step 3, 3-(3-iodo-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidin-7-yl)-8-aza-bicyclo [3.2.1]octane-8-carboxylic acid ethyl ester and

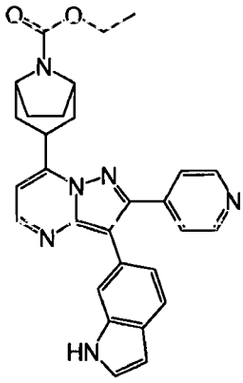
4-(4,4,5,5-tetramethyl-[1,3,2 dioxaborolan-2-yl)-1,3-dihydro-benzoimidazol-2-one afforded 3-[3-(2-oxo-2,3-dihydro-1H-benzoimidazol-4-yl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidin-7-yl]-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid ethyl ester (47 mg, 45%) after purification by RP-HPLC. MS: 510.4 [M+H].

Example 84: Ethyl 3-[3-(1H-indol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8- azabicyclo[3.2.1]octane-8-carboxylate



According to the procedure of Example 63, Step 3, 3-(3-iodo-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidin-7-yl)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid ethyl ester and 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-indole provided to give ethyl 3-[3-(1H-indol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate in 51% yield following purification by RP-HPLC. MS: 493.4 [M+H].

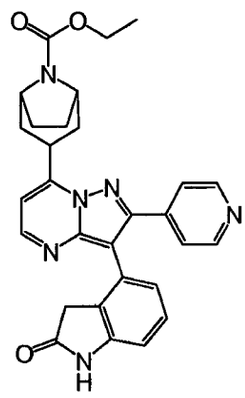
Example 85: Ethyl 3-[3-(1H-indol-6-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate



According to the procedure of Example 63, Step 3, 3-(3-iodo-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidin-7-yl)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid ethyl ester and 6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-indole provided ethyl 3-[3-(1H-indol-6-yl)-2-

pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate in 47% yield following purification by RP-HPLC. MS: 493.3 [M+H].

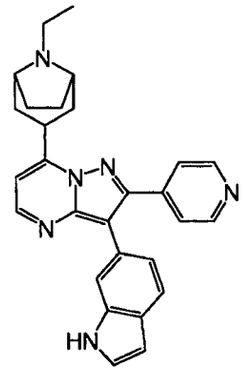
Example 86: Ethyl 3-[3-(2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-yl)-2-pyridin-4- ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate



Step 1: According to the procedure of Example 40, Step 4, 4-bromooxindole provided 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,3-dihydro-indol-2-one, which was used in the next step without purification.

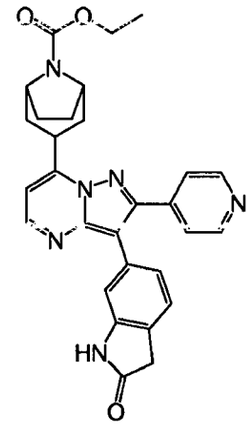
Step 2: According to the procedure of Example 63, Step 3, 3-(3-iodo-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidin-7-yl)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid ethyl ester and 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,3-dihydro-indol-2-one provided ethyl 3-[3-(2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-yl)-2-pyridin-4- ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate in 41% yield following purification by RP-HPLC. MS: 511.2 [M+H].

Example 87: 7-(8-Ethyl-8-azabicyclo[3.2.1]oct-3-yl)-3-(1H-indol-6-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine



Following the procedure of Example 63, Step 3, 7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-3-iodo-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine and 6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-indole gave 7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-3-(1H-indol-6-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine in 31% yield following purification by RP-HPLC. MS: 449.3 [M+H].

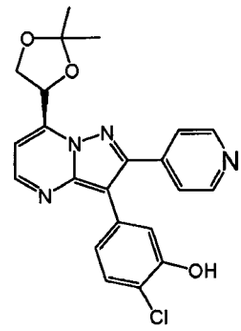
Example 88: Ethyl 3-[3-(2-oxo-2,3-dihydro-1H-indol-6-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate



Step 1: According to the procedure of Example 40, Step 4, 6-bromooxindole provided 6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,3-dihydro-indol-2-one, which was used in the next step without purification.

Step 2: Following the procedure of Example 63, Step 3, 3-(3-iodo-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidin-7-yl)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid ethyl ester and 6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,3-dihydro-indol-2-one afforded ethyl 3-[3-(2-oxo-2,3-dihydro-1H-indol-6-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate in 42% yield following purification by RP-HPLC. MS: 509.3 [M+H].

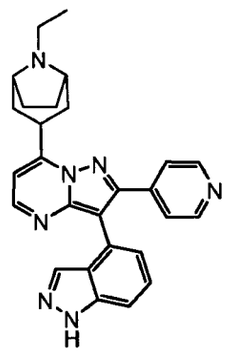
Example 89: 2-Chloro-5-[7-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-pyridin-4-ylpyrazolo[1,5- a]pyrimidin-3-yl]phenol



Step 1: A solution of 4 g (27.74 mmol) of 1-[(4*R*)-2,2-dimethyl-1, 3-dioxolan-4-yl] ethanone, (prepared according to the procedure of Synthetic Communications, 16(12), 1517-22, 1986) in DMF-DMA (40 mL) was heated to 100°C for 19 hours. The solvent was then removed under reduced pressure to give a brown, viscous oil. The crude oil was purified by Biotage™ chromatography (cartridge 40s), eluting with a gradient of ethyl acetate/hexanes (1:2) and 100% ethyl acetate to afford (2*E*)-3-(dimethylamino)-1-[(4*R*)-2,2-dimethyl-1, 3-dioxolan-4-yl] prop-2-en-1-one as a light brown oil (1.4 g, 25.3 %). MS: 200.2 [M+H].

Step 2: A solution of (2*E*)-3-(dimethylamino)-1-[(4*R*)-2,2-dimethyl-1, 3-dioxolan-4-yl] prop-2-en-1-one (0.100 g, 0.5 mmol) and 3-(5-amino-3-pyridin-4-yl-1H-pyrazol-4-yl)-phenol (0.173 g, 0.606 mmol) in acetic acid (5 mL) was heated at 100°C for 19hours. The solvent was then removed *in-vacuo*. The resulting crude oil (0.194 g) was diluted with dichloromethane (20 mL) and the organics were washed with saturated aqueous sodium bicarbonate (2x5 mL) and brine (5 mL). The organics were dried over magnesium sulfate, filtered, and concentrated *in-vacuo*. The residue was purified by Biotage™ chromatography (cartridge 40s), eluting with ethyl acetate to afford 2-chloro-5-{7-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-pyridin-4-ylpyrazolo [1,5-*a*] pyrimidin-3-yl}phenol as a yellow crystalline solid (0.048 g, 4.7 %). MS: 423 [M+H].

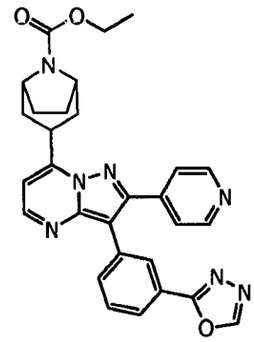
Example 90: 7-(8-Ethyl-8-azabicyclo[3.2.1]octan-3-yl)-3-(1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine



Step 1: Using the procedure of Example 76, Step 3, 4-bromo-1H-indazole was converted into 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole which was used in the next reaction without further purification.

Step 2: The reaction of 7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-3-iodo-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine with 24-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole, using the procedure of Example 20, Step 7, provided 6.3 mg (4% yield) of 7-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-3-(1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine as a yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.57 (d, *J*=4.4 Hz, 1H), 8.51 (m, 2H), 7.71 (d, *J*=5.2 Hz, 2H), 7.65 (d, *J*=8.4 Hz, 1H), 7.52 (m, 2H), 7.24 (d, *J*=7.2 Hz, 1H), 7.13 (d, *J*=4.4 Hz, 1H), 4.42 (m, 1H), 3.22 (q, *J*=7.2, 2H), 2.68 (m, 2H), 2.30-2.49 (m, 8H), 1.46 (t, *J*=7.2 Hz, 3H). MS: 450.3 [M+H].

Example 91: Ethyl 3-(3-(3-(1,3,4-oxadiazol-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate



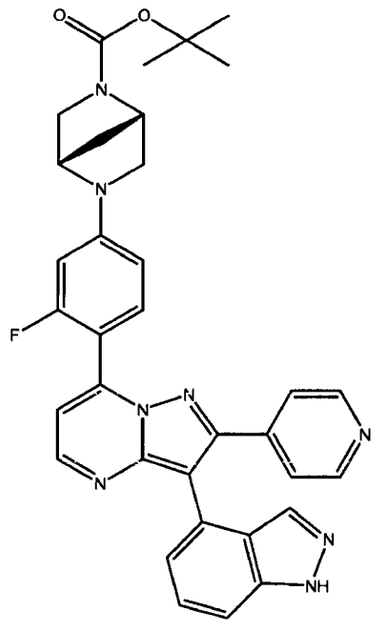
Step 1: A suspension of 3-bromobenzohydrazide (6.01 g, 27.9 mmol) in triethyl orthoformate (40 ml, 240 mmol) was brought to reflux under a nitrogen atmosphere and stirred vigorously overnight. After cooling to room temperature, the solvent was removed *in-vacuo* to give a pale, yellow syrup that crystallized on standing. Recrystallization from ethyl acetate/hexanes gave 2-(3-bromophenyl)-1,3,4-oxadiazole (4.86 g; 77 %). MS: 223/225 [M+H].

Step 2: To a mixture of 2-(3-bromophenyl)-1,3,4-oxadiazole (1.06 g, 4.71 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.40 g, 5.51 mmol), and potassium acetate (1.32 g, 13.45 mmol) was added DMSO (30 mL) and ([1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(ii) (0.0993 g, 0.136 mmol). The vessel was capped and placed under a nitrogen atmosphere, heated to 80° C and stirred vigorously for about 4.5 hours. The reaction was cooled to room temperature overnight and then poured into water and ethyl acetate and the resulting mixture was filtered through a pad of

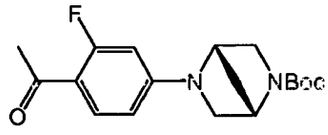
Celite™. The layers were separated and the aqueous phase was washed with a second portion of ethyl acetate. The combined organics were dried over magnesium sulfate, then filtered, and concentrated *in-vacuo* to yield a brown syrup that solidified on standing. The crude solid was dissolved in a mixture of dichloromethane and ethyl acetate, adsorbed onto silica, and purified on a 40 g silica column to give the desired boronate ester, 2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1,3,4-oxadiazole (0.28 g; 21.8 %) as an off-white solid. MS: 273.2 [M+H].

Step 3: A small vial was charged with ethyl 3-(3-iodo-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (0.1006 g, 0.200 mmol), 2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1,3,4-oxadiazole (0.0779 g, 0.286 mmol), [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (0.0102 g, 0.012 mmol), and DME (2 mL). To this mixture was added 2M aqueous sodium carbonate (0.3 mL, 0.600 mmol) and the resulting heterogeneous orange mixture was rigorously degassed, placed under a nitrogen atmosphere, and heated to 80° C. After 3 hours, the reaction was cooled to room temperature and stirred overnight. The crude reaction was diluted with acetonitrile and filtered through a pad of magnesium sulfate and Celite™. After removing the solvent *in-vacuo*, the resulting dark brown syrup was purified by semi-preparative RP HPLC to afford ethyl 3-(3-(3-(1,3,4-oxadiazol-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate as a bright yellow solid (0.0408 g; 39 %). MS: 522.1 [M+H].

Example 92: *tert*-Butyl (1S,4S)-5-{3-fluoro-4-[3-(1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2- carboxylate

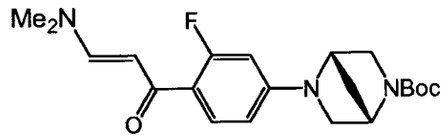


Step 1: *tert*-Butyl (1S,4S)-5-(4-acetyl-3-fluorophenyl)-2,5-diazabicyclo[2.2.1]heptane-2- carboxylate



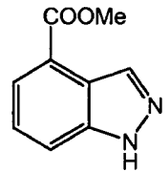
To a solution of (1S,4S)-tert-butyl 2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (0.2 g, 1 mmol) in 4 mL of HMPA, 1-(2,4-difluorophenyl)ethanone (0.151 mL, 1.2 mmol) and potassium carbonate (0.552 g, 4 mmol) were added. This solution was heated at 70° C for 36 hours in an oil bath. The mixture was then cooled to room temperature, and diluted with 100mL of ether, and washed with water three times. The aqueous layer was then washed with ether, and the organic layers combined. The combined ether layers were dried over sodium sulfate and concentrated to yield a residue which was purified by silica gel chromatography (12:88, ^{i}PrOH:Hexanes) to give 0.290 g (87%) of *tert*-butyl (1S,4S)-5-(4-acetyl-3-fluorophenyl)-2,5-diazabicyclo[2.2.1]heptane-2- carboxylate as a white solid. MS: 335.2 [M+H].

Step 2: *tert*-butyl (1S,4S)-5-{4-[(2E)-3-(dimethylamino)prop-2-enoyl]-3-fluorophenyl}- 2,5-diazabicyclo[2.2.1]heptane-2-carboxylate



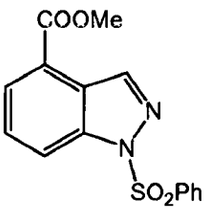
A solution of *tert*-butyl (1S,4S)-5-(4-acetyl-3-fluorophenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (0.42 g, 1.26 mmol) and *tert*-butoxybis(dimethylamino)methane (0.8 mL, 3.8 mmol) in 3 mL THF was heated at 100° C overnight in a sealed tube. The reaction mixture was concentrated and then diluted with 1mL water to precipitate the desired product. The aqueous layer was decanted and the residue was washed with water. The residue was dissolved in EtOAc, washed with water, dried over $NaSO_4$, and filtered. The filtrate was evaporated to give 0.455 g (93%) of *tert*-butyl (1S,4S)-5-{4-[(2E)-3-(dimethylamino)prop-2-enoyl]-3-fluorophenyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate as a yellow solid. MS: 390.2 [M+H].

Step 3: methyl 1H-indazole-4-carboxylate



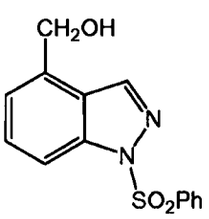
To a cold (0°-5° C) solution of methyl-3-amino-2-methyl benzoate (16.6 mL, 19.0 g, 0.12 mol) in chloroform (200 mL) was added dropwise acetic anhydride (24.8 mL, 0.26 mol) followed by stirring for 5 minutes. The resulting mixture was allowed to warm to room temperature and stirred for 1 hour and then was added potassium acetate (3.35g, 0.034 mol) and isoamyl nitrite (33.0 mL, 0.25 mol) and heated under reflux for 20 hours. The mixture was cooled to room temperature and solvent was evaporated to yield a brown solid. Water was added to the solid, followed by evaporation to yield a solid residue. The residue was treated with concentrated hydrochloric acid and the resulting mixture was heated at 50°C for 2 hours. After cooling with an ice bath, the solution was basified to pH 14 with a 50% potassium hydroxide solution. The resulting solid was collected by filtration, washed with water and dried to yield 17.8 g of methyl 1H-indazole-4-carboxylate as a beige solid. MS: 177.0 [M+H].

Step 4: methyl 1-(phenylsulfonyl)-1H-indazole-4-carboxylate



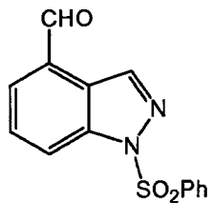
To a cold (0°-5°C) suspension of sodium hydride (0.6 g, 15.0 mmol) in DMF (20 mL) was added methyl 1H-indazole-4-carboxylate (2.4 g, 13.62 mmol) [D.Batt, et al. J. Med. Chem., 2000, 43, 41-58] in portions over a period of 5 minutes and the resulting mixture was stirred at 5° C for 15 minutes. A solution of benzenesulfonyl chloride (1.9 mL, 15.0 mmol) was then added dropwise and the resulting mixture was stirred at 5° C for 30 minutes and then at room temperature for 3 hours. The mixture was poured on to ice and the solid was collected by filtration, washed with water and dried to yield 3.91 g (91%) of methyl 1-(phenylsulfonyl)-1H-indazole-4-carboxylate as a beige solid. MS: 317.0 [M+H].

Step 5: [1-(phenylsulfonyl)-1H-indazol-4-yl]methanol



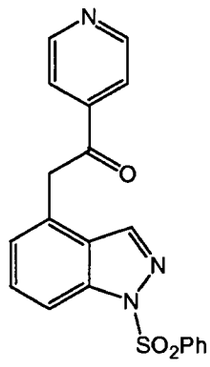
To a suspension of methyl 1-(phenylsulfonyl)-1H-indazole-4-carboxylate (3.11g, 9.83 mmol) in a mixture of THF (30 mL) and toluene (15 mL) was added lithium borohydride as a 2.0M solution in THF (2.7 mL, 5.5 mmol), and the resulting mixture was stirred and heated at 70°C for 30 minutes. Additional 2.0 M lithium borohydride solution (2.0 mL. 4.0 mmol) was added in portions over a period of 2.5 hours until all of the starting ester was consumed. The mixture was then cooled and poured on to ice water and the resulting two layers were separated. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The crude oil was purified by silica gel chromatography (3:1 hexane/ethyl acetate, then 3:2 hexane/ethyl acetate) to yield 2.0 g (71%) of [1-(phenylsulfonyl)-1H-indazol-4-yl]methanol as a white solid. MS: 289.1 [M+H].

Step 6: 1-(phenylsulfonyl)-1H-indazole-4-carbaldehyde



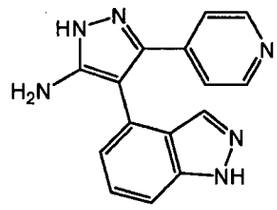
A mixture of [1-(phenylsulfonyl)-1H-indazol-4-yl]methanol (13.0 g, 45.08 mmol) and Dess-Martin periodinane (22.9 g, 54.0 mmol) in dichloromethane (420 mL) was stirred at room temperature for 1 hour. The reaction was quenched by stirring for 20 minutes with a saturated sodium thiosulfate solution (100 mL) and a saturated solution of sodium bicarbonate (75 mL). The two layers were separated and the aqueous layer was extracted with methylene chloride. The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The resulting crude solid was dissolved in methylene chloride and run through a silica gel plug to yield 12.65 g (98%) of 1-(phenylsulfonyl)-1H-indazole-4-carbaldehyde as a white solid. MS: 287.1 [M+H].

Step 7: 2-[1-(phenylsulfonyl)-1H-indazol-4-yl]-1-pyridin-4-ylethanone



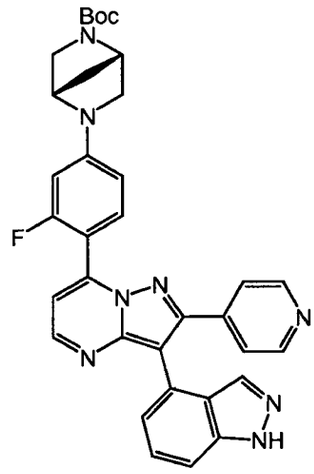
A mixture of 1-(phenylsulfonyl)-1H-indazole-4-carboxaldehyde (12.33 g, 43.07 mmol), diphenyl (phenylamino)(pyridin-4-yl)methylphosphonate (17.6 g, 42.27 mmol, prepared according to the procedure of Tet. Letters 39, 1717-1720, 1988), cesium carbonate (16.44 g, 50.46 mmol), tetrahydrofuran (246 mL) and isopropyl alcohol (82 mL) was heated at 45° C for 3.5 hours. The yellow mixture was cooled to room temperature and poured in to ice-cold solution of 3N HCl (250 mL) and stirred at room temperature for 18 hours. The yellow solution was extracted with ether (2X200 mL) and ether extract was re-extracted with 10% HCl (2X100 mL). The combined HCl extracts were cooled to 0°-5° C and neutralized to pH 7-8 using 2.5 N NaOH. The solid was collected by filtration, washed with ice cold water and dried to yield 15.5 g (97%) of 2-(1-(phenylsulfonyl)-1H-indazol-4-yl)-1-(pyridin-4-yl)ethanone as a beige solid. MS: 378.0 [M+H].

Step 8: 4-(1H-indazol-4-yl)-3-pyridin-4-yl-1H-pyrazol-5-amine



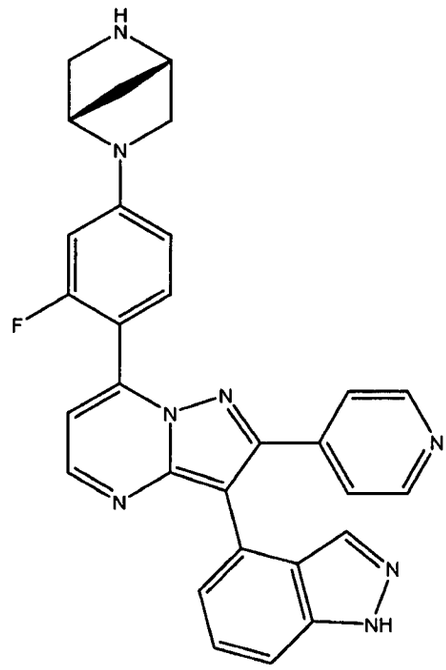
To a cold (0°-5° C) solution dimethylformamide (13.0 mL, 254.3 mmol)) was added dropwise a solution of phosphorus oxychloride (9.9 mL, 106.2 mmol), and the resulting mixture was stirred for 20 min. To this mixture was added dropwise solution of 2-(1-(phenylsulfonyl)-1H-indazol-4-yl)-1-(pyridin-4-yl)ethanone (8.0g, 21.2 mmol) in chloroform (80 mL), heated to 80° C and stirred for 18 hours. The reaction was cooled to room temperature and quenched with ice-cold saturated solution of sodium bicarbonate (500 mL). After extraction with 5% methanol in dichloromethane (4X150 mL), the organic layer was dried over anhydrous sodium sulfate, filtered, and the filtrate was evaporated to yield semi-solid. The crude mixture was dissolved in dimethylformamide 26 mL) followed by the addition of hydroxylamine hydrochloride (1.77g, 25.45 mmol) and stirred at room temperature for 2.5 hours. After cooling to 0° C, phosphorus oxychloride (3.0 mL, 32.2 mmol) was added and the mixture stirred overnight at room temperature. The reaction was quenched with ice-cold saturated solution of sodium bicarbonate. The solid was collected by filtration, washed with small amount of ice-cold water and dried. The crude solid 3-chloro-2-(1H-indazol-4-yl)-3-(pyridin-4-yl)acrylonitrile was dissolved in ethanol (80 mL) followed by the addition of hydrazine monohydrate (3.0 mL, 95.6 mmol) and heated under reflux for 2.5 h. After cooling to room temperature, the solvent was removed by evaporation. The crude product was purified by silica gel flash chromatography, eluting with methanol in dichloromethane (2-12% gradient), to give 4.7 g (80% yield) of 4-(1H-indazol-4-yl)-3-(pyridin-4-yl)-1H-pyrazol-5-amine as a beige solid. MS: 277.1 [M+H].

Step 9: *tert*-butyl (1S,4S)-5-{3-fluoro-4-[3-(1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2- carboxylate



A mixture of *tert*-butyl (1S,4S)-5-{4-[(2E)-3-(dimethylamino)prop-2-enoyl]-3-fluorophenyl}- 2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (2.3g, 5.9 mmol), 4-(1H-indazol-4-yl)-3-(pyridin-4-yl)-1H-pyrazol-5-amine (1.59 g, 5.75 mmol) and trifluoroacetic acid (4.4 mL, 57.5 mmol) in 25 ml of ethanol was stirred at room temperature overnight. The reaction mixture was evaporated, cooled and stirred with saturated solution of sodium bicarbonate. The solid was collected by filtration, washed with water and dried. The crude solid was purified by silica gel chromatography (3-6% ^{i}PrOH/CH_2Cl_2). Further purification was achieved by recrystallization from hot EtOH or EtOH/hexane to yield 2.43g (70%) of *tert*-butyl (1S,4S)-5-{3-fluoro-4-[3-(1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2- carboxylate as a yellow solid. MS: 603.2 [M+H].

Example 93: 7-{4-[(1S,4S)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-fluorophenyl}-3-(1H-indazol-4- yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine



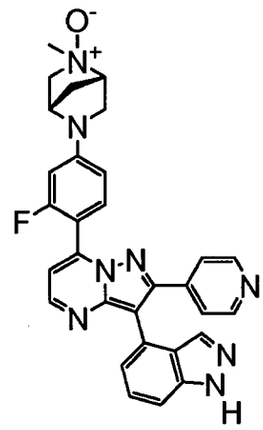
tert-Butyl (1S,4S)-5-{3-fluoro-4-[3-(1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (2.43 g, 4.0 mmol) was dissolved in 60 mL of methanol and then 30 mL of concentrated hydrochloric acid was added and the resulting mixture was stirred at room temperature for 3 hours. The precipitated solid was collected by filtration, then washed with a small amount of methanol. The filtrate was evaporated to dryness, and the residue was taken up in a minimal amount of methanol. The resulting solid was collected by filtration, washed with a minimal quantity of methanol and the solids combined. An ice-cooled saturated solution of sodium bicarbonate was added to the crude material. After filtration, the crude solid was purified by a short silica gel column (80:18:2, methylene chloride:methanol:ammonium hydroxide) to give 1.9 g (95%) of 7-{4-[(1S,4S)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-fluorophenyl}-3-(1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine as a yellow solid. MS: 503.3 [M+H].

Example 94: 7-{2-Fluoro-4-[(1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine

A mixture of 7-{4-[(1S,4S)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-fluorophenyl}-3-(1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine (1.9 g, 3.78 mmol), 37% HCHO (1.0 mL, 13.3 mmol), $NaBH(OAc)_3$ (2.12 g,10.04 mmol) and 6 drops of acetic acid in 35 mL of DMF was stirred at room temperature for 3 hours. The DMF was evaporated to dryness and 80 mL 7N ammonia methanol solution was added to the residue, stirred for 2 hours and the solvent was evaporated to dryness. A saturated solution of sodium bicarbonate was stirred into the resulting residue. The solid was collected by filtration, washed with water and dried. The crude solid was purified by flash chromatography (80:20, CH_2Cl_2/methanol) to give 1.7g

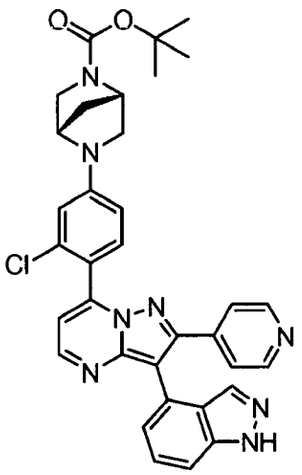
(87%) of a yellow solid. This solid was re-crystallized from hot ethanol to yield 1.4 g (72%) of 7-{2-fluoro-4-[(1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine as a yellow solid. MS: 279.6 [M+ACN+2H].

Example 95: 7-{2-fluoro-4-[(1S,4S)-5-methyl-5-oxido-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine

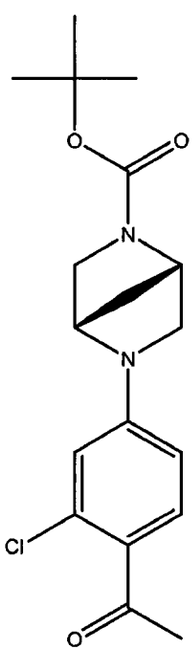


A mixture of 7-{2-fluoro-4-[(1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1H- indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine (0.23 g, 0.45 mmol) and 3-chloroperbenzoic acid (0.09g, 0.40 mmol) in methylene chloride was stirred at room temperature for 3 hours. The solvent was evaporated and the residue was stirred with a saturated solution of sodium bicarbonate. The resulting solid was collected by filtration, washed with water and dried. The crude solid was purified by silica gel chromatography, eluting with 20% methanol in methylene chloride, then with mixture of 10% methanol and 1% ammonium hydroxide in methylene chloride to yield 0.121g (51%) of 7-{2-fluoro-4-[(1S,4S)-5-methyl-5-oxido-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine as a yellow solid. MS: 287.7 [M+ACN+2H].

Example 96: (1S,4S)-5-{3-Chloro-4-[3-(1H-indazol-4-yl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester

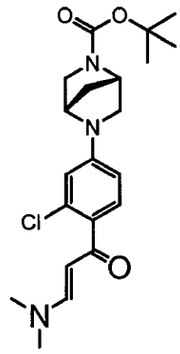


Step 1: *tert*-butyl(1S,4S)-5-(4-acetyl-3-chlorophenyl)-2,5-diazabicyclo[2.2.1]heptane-2- carboxylate



To a solution of (1S,4S)-tert-butyl 2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (4.13 g, 20.86 mmol) in 20 mL of DMF, 2'-chloro-4'-fluoroacetophenone (3.0 g, 17.4 mmol) and potassium carbonate (7.2 g, 52.14 mmol) were added. This mixture was heated at 100° C for 16 hours, cooled to room temperature and diluted with 200 mL of methylene chloride. The organic layer was dried and concentrated to yield a residue which was purified by silica gel chromatography (eluting with a gradient of 15:85 to 30:70 EtOAc/hexane), to yield 4.02g (66%) *tert*-butyl(1S,4S)-5-(4-acetyl-3-chlorophenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate as a beige solid. MS 351.1 [M+H].

Step 2: (1S,4S)-tert-butyl 5-(4-((E)-3-(dimethylamino)acryloyl)-3-chlorophenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

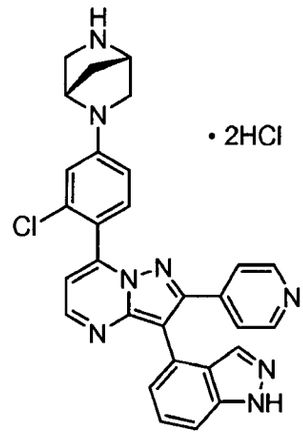


A mixture of (1S,4S)-tert-butyl 5-(4-acetyl-3-chlorophenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (2.457g, 7.00 mmol) and 5.00 mL of C-tert-butoxy-N,N,N',N'-tetramethylmethanediamine was heated to 100° C for 3 hours. The mixture was then concentrated *in vacuo* and the gummy residue was digested with 75 mL of diethyl ether. The solution was washed with 75 mL of water and 75 mL of saturated NaCl solution, dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo* to give 2.679g (97%) of (1S,4S)-tert-butyl 5-(4-((E)-3-(dimethylamino)acryloyl)-3-chlorophenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate as a light yellow foam used without purification. MS: 406.3 [M+H].

Step 3: (1S,4S)-5-{3-Chloro-4-[3-(1H-indazol-4-yl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester

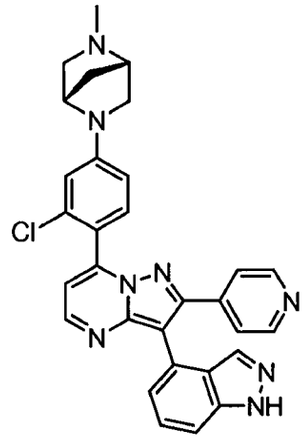
To a solution of (1S,4S)-*tert*-butyl 5-(4-((E)-3-(dimethylamino)acryloyl)-3-chlorophenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (2.638g, 6.50 mmol) and 4-(1H-indazol-4-yl)-3-(pyridin-4-yl)-1H-pyrazol-5-amine (1.877g, 6.79 mmol) in 30 mL of methanol was added 5 mL of trifluoroacetic acid and the resulting solution was stirred at room temperature under a nitrogen atmosphere for 108 hours. The mixture was partitioned between 200 mL of dichloromethane and 200 mL of saturated sodium bicarbonate solution. The organic phase was separated and the aqueous phase was extracted with an additional 100 mL of dichloromethane. The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and the solvent was removed *in vacuo*. The resulting yellow/brown foam was purified by silica gel chromatography to provide 3.374g (84%) of (1S,4S)-5-{3-chloro-4-[3-(1H-indazol-4-yl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester, as a yellow foam. MS: 619.3 [M+H].

Example 97: 7-[2-Chloro-4-((1S,4S)-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-phenyl]-3-(1H-indazol-4-yl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine bis-hydrochloride salt



To a solution of (1S,4S)-5-{3-chloro-4-[3-(1H-indazol-4-yl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester (3.370g, 5.44 mmol) in 50 mL of methanol was added 25 mL of concentrated hydrochloric acid solution over 2-3 minutes. The resulting dark red solution was stirred at room temperature for 30 minutes. The solvents were removed *in vacuo* and the residue was digested with 50 mL of methanol. The resulting crystals were filtered and rinsed with fresh methanol. The damp product was quickly transferred to a desiccator and dried under high vacuum overnight to provide 2.638g (82%) of 7-[2-chloro-4-((1S,4S)-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-phenyl]-3-(1H-indazol-4-yl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine bis-hydrochloride salt as yellow/orange crystals. MS: 260.6 [M+CH_3CN+2H].

Example 98: 7-[2-Chloro-4-((1S,4S)-5-methyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-phenyl]-3-(1H-indazol-4-yl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine

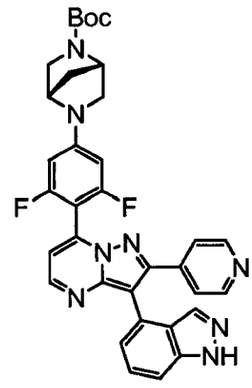


Step 1: 7-[2-Chloro-4-((1S,4S)-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-phenyl]-3-(1H-indazol-4-yl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine bis-hydrochloride salt (2.800 g, 4.73 mmol) was digested with 50 mL of half-saturated sodium bicarbonate solution taking care to avoid uncontrolled foaming. The resulting solid was filtered, washed with several portions of water and vacuum dried to give 2.287g (93%) of 7-[2-chloro-4-((1S,4S)-2,5-diaza-

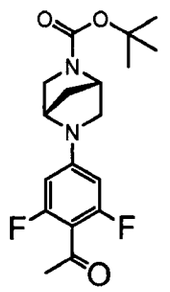
bicyclo[2.2.1]hept-2-yl)-phenyl]-3-(1H-indazol-4-yl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine free base as a yellow solid.

Step 2: To a solution of 7-[2-Chloro-4-((1S,4S)-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-phenyl]-3-(1H-indazol-4-yl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine (2.283g, 4.40 mmol) in 20 mL of dimethylformamide was added 37% aqueous formaldehyde solution (1.10 mL, 14.77 mmol) followed by 3 drops of acetic acid and sodium borohydride (2.797g, 13.15 mmol). The mixture was warmed slightly with a heat gun and diluted with an additional 20 mL of dimethylformamide to aid dissolution. After the removal of some insoluble material the mixture was stirred 2.5 hours at room temperature. It was then concentrated to dryness by rotary evaporation and the residue was digested with 20 mL of 7N methanolic ammonia solution. The resulting mixture was stirred 15 hours at room temperature. It was then filtered to remove small amounts of insoluble material and the filtrate was concentrated *in vacuo*. The residue was digested with 50 mL of dichloromethane and filtered. The solid was washed with several additional portions of dichloromethane. The combined filtrate and washings were concentrated *in vacuo* to give a yellow solid that was purified by silica gel chromatography to give 1.756g of yellow powder. This material was partitioned between 150 mL of dichloromethane and 150 mL of half-saturated sodium bicarbonate solution. The organic phase was separated and the aqueous phase extracted with 50 mL of dichloromethane. The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to give 1.746g of 7-[2-chloro-4-((1S,4S)-5-methyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-phenyl]-3-(1H-indazol-4-yl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine as a yellow powder. MS: 533.1 [M+H].

Example 99: *tert*-butyl (1S,4S)-5-{3,5-difluoro-4-[3-(1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2- carboxylate

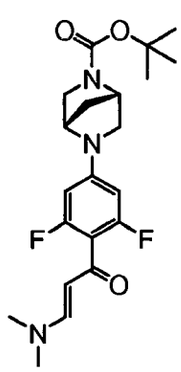


Step 1: (1S,4S)-*tert*-Butyl 5-(4-acetyl-3,5-difluorophenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate



To a solution of 1-(2,4,6-trifluorophenyl)ethanone in 30 mL of hexamethylphosphoramide, (3.9 g, 22.5 mmol) (1S,4S)-tert-butyl 2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (3.0 g, 15 mmol) and potassium carbonate (6.2 g, 45 mmol) were added. This solution was stirred at room temperature for 4 days. The mixture was diluted with 200 mL of diethyl ether and was washed with 200 mL water. The aqueous solution was extracted twice with diethyl ether twice. The combined organic layer was washed with water three times, then dried, and concentrated. The residue was purified by silica gel chromatography (isopropanol, hexanes) to give 3.3 g (62% yield) of (1S,4S)-*tert*-butyl 5-(4-acetyl-3,5-difluorophenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate. MS: 353.1 [M+H].

Step 2: (1S,4S)-tert-butyl 5-(4-((E)-3-(dimethylamino)acryloyl)-3,5-difluorophenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

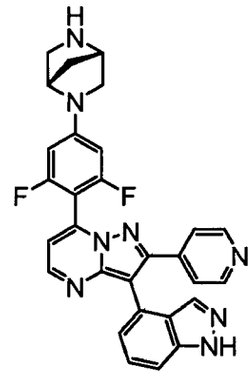


A mixture of (1S,4S)-*tert*-butyl 5-(4-acetyl-3,5-difluorophenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (3.3 g, 9.4 mmol) and 30 mL of 1,1-dimethoxy-N,N-dimethylmethanamine were refluxed for 35 hours. The reaction mixture was concentrated and the residue was purified by silica gel chromatography (isopropanol, dichloromethane) to give 3.8 (99%) of (1S,4S)-*tert*-butyl 5-(4-((E)-3-(dimethylamino)acryloyl)-3,5-difluorophenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate. MS: 408.3 [M+H].

Step 3: *tert*-Butyl (1S,4S)-5-{3,5-difluoro-4-[3-(1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2- carboxylate

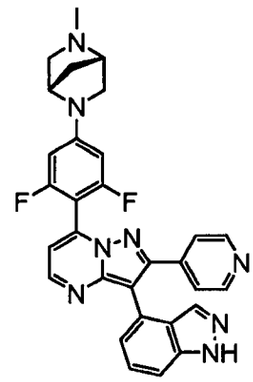
To a solution of 2,2,2-trifluoroacetic acid (0.54 mL) in 18 mL of methanol, (1S,4S)-tert-butyl 5-(4-((E)-3-(dimethylamino)acryloyl)-3,5-difluorophenyl)-2,5-diazabicyclo-[2.2.1]heptane-2-carboxylate (1.1 g, 2.6 mmol) and 4-(1H-indazol-4-yl)-3-(pyridin-4-yl)-1H-pyrazol-5-amine (0.72 g, 2.6 mmol) were added. This solution was stirred at room temperature for 3 days. The mixture was basified with methanolic ammonia, adsorbed onto silica gel, and purified by silica gel chromatography (isopropanol, dichloromethane) to give 1.4g (87% yield) of *tert*-butyl (1S,4S)-5-{3,5-difluoro-4-[3-(1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2- carboxylate. MS: 621.3 [M+H].

Example 100: 7-(4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-2,6-difluorophenyl)-3-(1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine



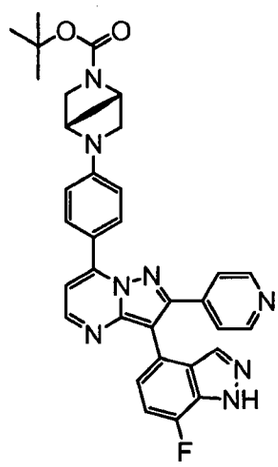
A solution of (1S,4S)-*tert*-butyl 5-(4-(3-(1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-3,5-difluorophenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (1.4 g, 2.3 mmol) in 6N HCl/methanol (19 mL concentrated HCl and 19 mL methanol) was stirred for 1 hour. The mixture was concentrated, basified with methanolic ammonia, adsorbed onto silica gel, and purified with silica gel chromatography (ammonia, methanol, dichloromethane) to give 1.1 g (93% yield) of 7-(4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-2,6-difluorophenyl)-3-(1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine. MS: 521.3 [M+H].

Example 101: 7-{2,6-difluoro-4-[(1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3- (1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine

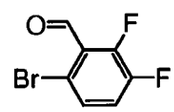


To a solution of 7-(4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-2,6-difluorophenyl)-3-(1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine (1.1 g, 2.1 mmol) in 30 mL of DMF, formaldehyde (0.47 mL, 6.3 mmol) and sodium triacetoxyhydroborate (1.3 g, 6.3 mmol) were added. This solution was stirred at room temperature for 2 hours, then concentrated. The residue was stirred with 15 mL of 7 N methanolic ammonia overnight. The solution was concentrated and purified with silica gel chromatography (methanol, dichloromethane) to give 0.95 g (84% yield) of 7-(2,6-difluoro-4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-3-(1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine. MS: 535.4 [M+H].

Example 102: *tert*-Butyl (1S,4S)-5-{4-[3-(7-fluoro-1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2- carboxylate

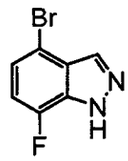


Step 1: 6-Bromo-2,3-difluoro-benzaldehyde



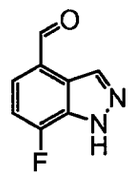
To a dry flask, under nitrogen, was added 9.24 mL of 2,2,6,6-tetramethylpiperidine (0.054 mol, 1.05 equiv) and 103.5 mL of tetrahydrofuran (THF), which was then cooled to –78 °C. 21.7 mL of n-butyllithium (0.054 mol, 1.05 equiv) was added dropwise, followed by 5.86 mL of 1-bromo-3,4-difluorobenzene (0.052 mol, 1.0 equiv) in 6 mL of THF. The resulting mixture was stirred at –78 °C for 2 hours and 4.21 ml of N,N-dimethylformamide (DMF) (0.054 mol, 1.05 equiv) was added. The mixture was allowed to warm up to –20 °C, then quenched with 44 ml of 1N HCl in a dropwise addition. This solution was then extracted with diethyl ether and the organic layer was washed with 1N HCl three times, followed by a brine wash. After drying the organic layer over magnesium sulfate ($MgSO_4$), it was concentrated *in-vacuo* to yield 11.12 g of 6-bromo-2,3-difluoro-benzaldehyde as a brown oil which was used without purification in the next reaction.

Step 2: 4-Bromo-7-fluoro-1H-indazole



A 11.2 g portion of 6-bromo-2,3-difluoro-benzaldehyde was dissolved in 51 mL of dimethoxyethane. To this was added 51 mL of anhydrous hydrazine, followed by refluxing for 2.5 hours; reaction monitored by thin layer chromatography (TLC). Dimethoxyethane was evaporated off and the remaining residue cooled in an ice bath. Ice was added and the resulting white solid filtered off, and washed with cold water. The solid was then warmed in dichloromethane and filtered. The filtrate was evaporated to dryness and warmed up in dichloromethane and filtered again. In total, 6.19 g of 4-bromo-7-fluoro-1H-indazole was recovered as a white solid in 32% yield. MS: 215.0, 217.0 [M+H].

Step 3: 7-Fluoro-1H-indazole-4-carbaldehyde



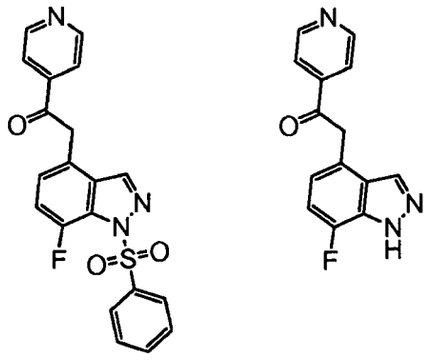
To 0.614g of sodium hydride (0.015 mol, 1.1 equiv) in a dry flask, under nitrogen, was added 46 mL of THF. The mixture was cooled to 0 °C in an ice bath. To this mixture was added 3 g of 4-bromo-7-fluoro-1H-indazole (0.014 mol, 1.0 equiv), followed by stirring at

0 °C for 5 minutes. The resulting pink mixture was warmed to room temperature and stirred for another 15 minutes, after which the reaction turned brown. It was then cooled to –78 °C and 23 mL of 1.7M t-butyllithium in pentane was added slowly (0.039 mol, 2.8 equiv) while stirring at –78 °C for 10 minutes. To this mixture was added 2.16 mL of dimethylformamide in 7.5 mL of tetrahydrofuran dropwise. The mixture was stirred for 5 minutes at –78 °C. then warmed to room temperature. After stirring for another 30 minutes, the product mixture was quenched with 2M hydrochloric acid (HCl) and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and evaporated to dryness. A quantitative yield (2.51 g) of 7-fluoro-1H-indazole-4-carbaldehyde was obtained as a pink solid containing a small quantity of DMF. MS: 165.2 [M+H].

Step 4: 1-Benzenesulfonyl-7-fluoro-1H-indazole-4-carbaldehyde

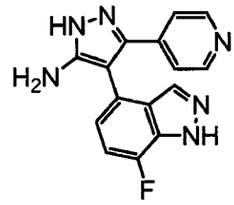
A 2.29 g portion of 7-fluoro-1H-indazole-4-carbaldehyde (0.014 mol, 1.0 equiv) was dissolved in 100 mL of THF. To this was added 0.614 g of NaH (0.015 mol, 1.1 equiv), followed by 20 minutes of stirring. To the reaction mixture, 3.6 mL of benzenesulfonylchloride (0.028 mol, 2.0 equiv) were added, and the reaction was stirred for another hour. The reaction was quenched with H_2O and extracted with dichloromethane. The organic layer was dried over $MgSO_4$ and evaporated to dryness to yield a wet orange solid, which was then washed with diethyl ether to produce 3.54 g of 1-benzenesulfonyl-7-fluoro-1H-indazole-4-carbaldehyde as a light orange solid in 83% yield. MS: 305.2 [M+H]. The procedures for the following 3 steps are based on examples disclosed in a copending application, U. S. Provisional Application No. 61/067,843.

Step 5: 2-(1-benzenesulfonyl-7-fluoro-1H-indazol-4-yl)-1-pyridin-4-yl-ethanone (CAT1788145) and 2-(7-fluoro-1H-indazol-4-yl)-1-pyridin-4-yl-ethanone



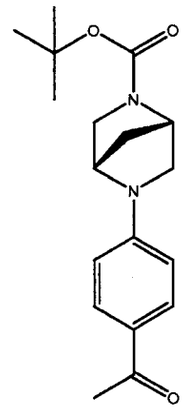
By the procedure of Example 44, step 6, 1-benzenesulfonyl-7-fluoro-1H-indazole-4-carbaldehyde was reacted with diphenyl(phenylamino)(pyridin-4-yl)methylphosphonate to provide a 4:1 mixture of 2-(1-benzenesulfonyl-7-fluoro-1H-indazol-4-yl)-1-pyridin-4-yl-ethanone and 2-(7-fluoro-1H-indazol-4-yl)-1-pyridin-4-yl-ethanone. This mixture was subsequently used without purification. Products: 2-(1-benzenesulfonyl-7-fluoro-1H-indazol-4-yl)-1-pyridin-4-yl-ethanone MS: 396.1 [M+H] and 2-(7-fluoro-1H-indazol-4-yl)-1-pyridin-4-yl-ethanone 256.3 [M+H].

Step 6: 4-(7-Fluoro-1H-indazol-4-yl)-5-pyridin-4-yl-2H-pyrazol-3-ylamine



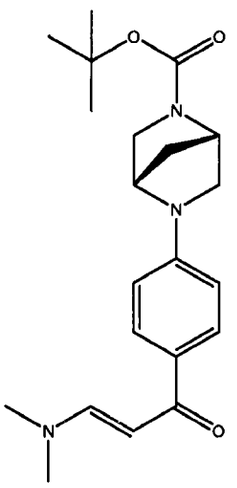
Following the procedure of Example 44, step 7, the mixture of 4:1 2-(1-benzenesulfonyl-7-fluoro-1H-indazol-4-yl)-1-pyridin-4-yl-ethanone and 2-(7-fluoro-1H-indazol-4-yl)-1-pyridin-4-yl-ethanone was converted to 4-(7-fluoro-1H-indazol-4-yl)-5-pyridin-4-yl-2H-pyrazol-3-ylamine. MS: 295.2 [M+H].

Step 7: *tert*-butyl (1S,4S)-5-(4-acetylphenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate



Following the procedure of Example 44, Step 1, (1S,4S)-*tert*-butyl 2,5-diazabicyclo[2.2.1]heptane-2-carboxylate was reacted with 1-(4-fluorophenyl)ethanone to provide *tert*-butyl (1S,4S)-5-(4-acetylphenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate as an off-white solid. MS: 317.2 [M+H].

Step 8: 5-[4-(3-Dimethylamino-acryloyl)-phenyl]-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester

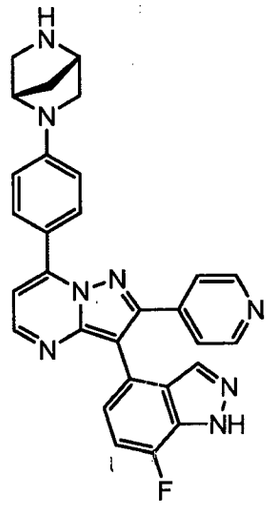


Following the procedure of Example 92, Step 2, *tert*-butyl (1S,4S)-5-(4-acetylphenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate was reacted with *tert*-butoxybis(dimethylamino)methane to provide 5-[4-(3-dimethylamino-acryloyl)-phenyl]-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester as a pale yellow solid. MS: 372.3 [M+H]. The procedure for the following step is bsed on an example disclosed in a copending application, U. S. Provisional Application No. 61/067,843.

Step 9: *tert*-Butyl (1S,4S)-5-{4-[3-(7-fluoro-1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2- carboxylate

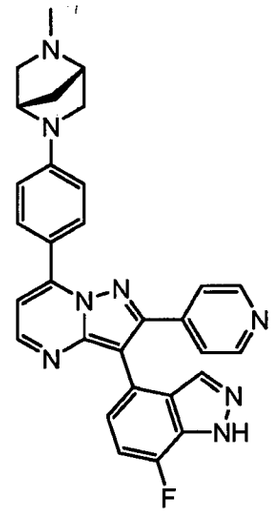
Following the procedure of Example 98, Step 4, 4-(7-fluoro-1H-indazol-4-yl)-5-pyridin-4-yl-2H-pyrazol-3-ylamine (0.38 g, 1.3 mmol) and 5-[4-(3-dimethylamino-acryloyl)-phenyl]-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester (0.53 g, 1.4 mmol) provided a mixture of 3.7:1 of the regioisomers 5-{4-[3-(7-fluoro-1H-indazol-4-yl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2,5-diaza-bicyclo[2.2.1]-heptane-2-carboxylic acid tert-butyl ester and 5-{4-[3-(7-fluoro-1H-indazol-4-yl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidin-5-yl]-phenyl}-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester. These isomers were separated by flash chromatography using a gradient of 1% to 3% MeOH/CH_2Cl_2, providing *tert*-butyl (1S,4S)-5-{4-[3-(7-fluoro-1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate as a yellow solid. MS: 603.3 [M+H].

Example 103: 7-[4-(2,5-Diaza-bicyclo[2.2.1]hept-2-yl)-phenyl]-3-(7-fluoro-1H-indazol-4-yl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine



A portion of *tert*-butyl (1S,4S)-5-{4-[3-(7-fluoro-1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (0.32 g, 5.2 mmol) was dissolved in 10.8 mL of 4N HCl (concentrated HCl diluted with methanol) and followed by mass spectrometry until completion of the reaction. The mixture was concentrated *in vacuo* and purified by flash chromatography using 9:1:0.1 MeOH/CH_2Cl_2/ammonium hydroxide to provide 0.24 g of 7-[4-(2,5-diaza-bicyclo[2.2.1]hept-2-yl)-phenyl]-3-(7-fluoro-1H-indazol-4-yl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine as a yellow solid (92% yield). MS: 503.3 [M+H].

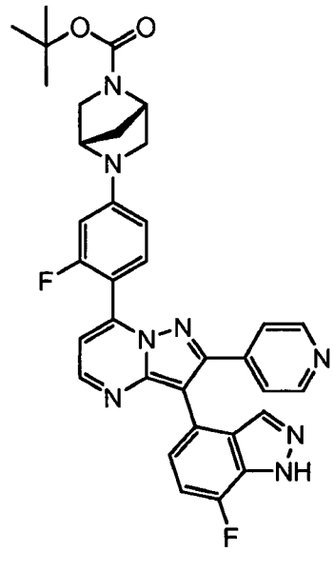
Example 104: 3-(7-fluoro-1H-indazol-4-yl)-7-{4-[(1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine hydrochloride



A 0.22 g portion of 7-[4-(2,5-diaza-bicyclo[2.2.1]hept-2-yl)-phenyl]-3-(7-fluoro-1H-indazol-4-yl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine was dissolved in 7.8 mL of DMF, and

0.16 mL of 37% formaldehyde in H_2O solution was added (2.2 mmol, 5.0 equiv), followed by 0.05 mL of acetic acid (0.9 mmol, 2.0 equiv). This mixture was stirred for 15 minutes, then 0.46 g of sodium triacetoxyborohydride ($Na(OAc)_3BH$) (2.2 mmol, 5.0 equiv) was added and the reaction stirred for one hour. The product mixture was quenched with 5 mL of 7N ammonia in methanol and stirred for another 30 minutes. The reaction was then concentrated *in vacuo* and purified by flash chromatography using 9:1:0.1 $MeOH/CH_2Cl_2$/ammonium hydroxide. The yellow solid was then dissolved in dichloromethane and washed with saturated sodium bicarbonate, dried over $MgSO_4$ and evaporated to dryness to produce 0.22 g of a yellow solid. This solid was then dissolved in 5 mL of methanol and cooled in an ice bath. To this was added 0.34 mL of 3N methanolic HCl and the mixture was stirred at 0 °C for 15 minutes. The product mixture was concentrated *in vacuo* to yield 0.2 g of 3-(7-fluoro-1H-indazol-4-yl)-7-[4-(5-methyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-phenyl]-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine hydrochloric salt as an orange-red solid (83% yield). MS: 517.3 [M+H].

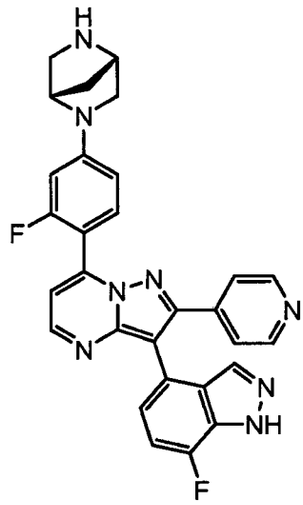
Example 105: *tert*-Butyl (1S,4S)-5-{3-fluoro-4-[3-(7-fluoro-1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate



A 2.31 g portion of 5-[4-(3-dimethylamino-acryloyl)-3-fluoro-phenyl]-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (1.1 equiv, 5.9 mmol) was dissolved in 37 mL of methanol. To this was added 1.59 g of 4-(7-fluoro-1H-indazol-4-yl)-5-pyridin-4-yl-2H-pyrazol-3-ylamine (1.0 equiv, 5.4 mmol), followed by 1.1 mL of trifluoroacetic acid and the reaction was stirred at room temperature for 16 hours. The reaction was concentrated *in vacuo*, neutralized with saturated aqueous sodium bicarbonate ($NaHCO_3$) and filtered. The

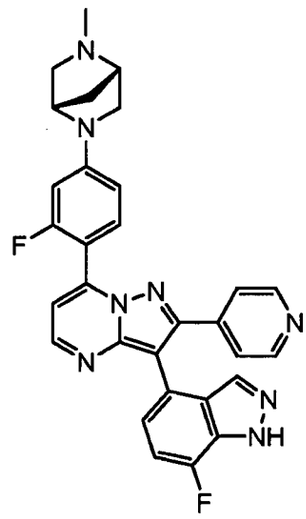
solid was washed with water and dried *in vacuo*. Purification was carried out by silica flash chromatography, eluting with 5%-10% methanol/ethyl acetate to yield 2.37g of 5-{3-fluoro-4-[3-(7-fluoro-1H-indazol-4-yl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester as a yellow solid (70.7% yield). MS: 621.3 [M+H].

Example 106: 7-{4-[(1S,4S)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-fluorophenyl}-3-(7-fluoro-1H- indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine



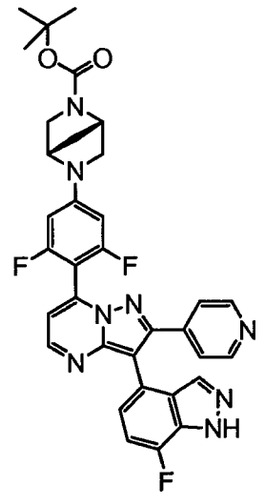
Following the procedure of Example 103, 5-{3-fluoro-4-[3-(7-fluoro-1H-indazol-4-yl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester provided 7-[4-(2,5-diaza-bicyclo[2.2.1]hept-2-yl)-2-fluoro-phenyl]-3-(7-fluoro-1H-indazol-4-yl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine. MS: 521.2 [M+H]; 261.2 [M+2H].

Example 107: 3-(7-fluoro-1H-indazol-4-yl)-7-{2-fluoro-4-[(1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine



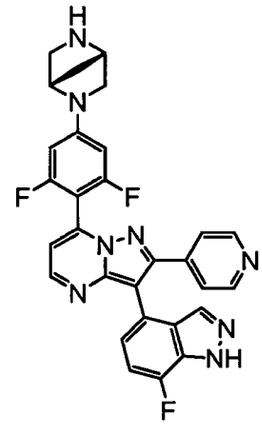
A 1.44 g portion of 7-[4-(2,5-diaza-bicyclo[2.2.1]hept-2-yl)-2-fluoro-phenyl]-3-(7-fluoro-1H-indazol-4-yl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine (2.8 mmol, 1.0 equiv) was dissolved in 50 mL of DMF, and 1 mL of a 37% aqueous formaldehyde (13.8 mmol, 5.0 equiv) solution was added. To this mixture was added 0.32 mL of acetic acid (5.5 mmol, 2.0 equiv)) and the solution was stirred for 15 minutes. A 2.93 g portion of $Na(OAc)_3BH$ (13.8 mmol, 5.0 equiv) was added, and the reaction stirred for one hour. The product mixture was quenched with 30 mL of 7N ammonia in MeOH and stirred for another 30 minutes. The reaction was then partitioned between water and ethyl acetate and the aqueous layer was extracted with ethyl actate again. The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow oil. Upon the addition of water to this oil, a solid precipitated out. The resulting solid was filtered and dried to provide 1.3 g of 3-(7-fluoro-1H-indazol-4-yl)-7-[2-fluoro-4-(5-methyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-phenyl]-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine as a yellow solid (88% yield). MS: 535.2 [M+H].

Example 108: *tert*-Butyl (1S,4S)-5-{3,5-difluoro-4-[3-(7-fluoro-1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate



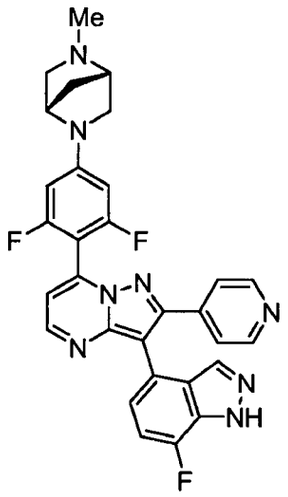
Following the procedure of Example 100, Step 3, (1S,4S)-tert-butyl 5-(3,5-difluoro-4-(3-(7-fluoro-1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)phenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate was prepared from 4-(7-fluoro-1H-indazol-4-yl)-3-(pyridin-4-yl)-1H-pyrazol-5-amine and (1S,4S)-tert-butyl 5-(4-((E)-3-(dimethylamino)acryloyl)-3,5-difluorophenyl)-2,5-diazabicyclo[2.2.1]-heptane-2-carboxylate. MS: 639.2 [M+H].

Example 109: 7-{4-[(1S,4S)-2,5-Diazabicyclo[2.2.1]hept-2-yl]-2,6-difluorophenyl}-3-(7-fluoro- 1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine



Following the procedure of Example 102, 7-(4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-2,6-difluorophenyl)-3-(7-fluoro-1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine was prepared from (1S,4S)-*tert*-butyl 5-(3,5-difluoro-4-(3-(7-fluoro-1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)phenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate. MS: 539.3 [M+H].

Example 110: 7-{2,6-Difluoro-4-[(1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3- (7-fluoro-1H-indazol-4-yl)-2-yridin-4-ylpyrazolo[1,5-a]pyrimidine



Following the procedure of Example 101, 7-(2,6-difluoro-4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-3-(7-fluoro-1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine was prepared from 7-(4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-2,6-difluorophenyl)-3-(7-fluoro-1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine, MS: 553.2 [M+H].

Examples 111-210 are summarized in Table 1.

Example	Compound Name	MS, ESI (m/z)
111	ethyl 3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-5-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate	494
112	2-{3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]oct-8-yl}ethanol	466.3
113	3-(1*H*-indazol-4-yl)-7-(8-isopropyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	464.3
114	3-(1*H*-indazol-4-yl)-7-[8-(methylsulfonyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	500.3
115	3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxamide	465.2
116	2-{3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]oct-8-yl}-*N*,*N*-dimethyl-2-oxoethanamine	507.3
117	{3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]oct-8-yl}acetonitrile	461.2
118	*N*-ethyl-3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxamide	493.2
119	7-(8-acetyl-8-azabicyclo[3.2.1]oct-3-yl)-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	464.2
120	3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-*N*,*N*-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxamide	493.2
121	*tert*-butyl (1*S*,4*S*)-5-{[3-(4-chloro-3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]methyl}-2,5-	547.2;

Example	Compound Name	MS, ESI (m/z)
	diazabicyclo[2.2.1]heptane-2-carboxylate	
122	*tert*-butyl (1*S*,4*S*)-5-{4-[3-(7-fluoro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-5-yl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate	603.2
123	*tert*-butyl (1*S*,4*S*)-5-{3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate	585.3
124	7-{3-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	485.2
125	*tert*-butyl (1*S*,4*S*)-5-{4-[3-(7-chloro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate	619.2
126	3-(1*H*-indazol-4-yl)-7-{3-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	499.2
127	3-(7-chloro-1*H*-indazol-4-yl)-7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	519.3
128	*tert*-butyl (2*S*)-2-({3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]oct-8-yl}carbonyl)pyrrolidine-1-carboxylate	619.3;
129	3-(1*H*-indazol-4-yl)-7-(8-L-prolyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	519.3
130	1-{3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]oct-8-yl}propan-2-one	478.2
131	ethyl 3-[3-(7-fluoro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-5-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate	512.3
132	7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-fluorophenyl}-3-(3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	493.2
133	3-(7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-fluorophenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol	479.2
134	3-(7-{2-fluoro-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol	493.2
135	7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-methylphenyl}-3-(7-fluoro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	517.2
136	3-(7-fluoro-1*H*-indazol-4-yl)-7-{2-methyl-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	531.2
137	7-(8-azabicyclo[3.2.1]oct-3-yl)-3-(7-fluoro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	440.2
138	{3-[3-(7-fluoro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]oct-8-yl}acetonitrile	479.1
139	3-(7-chloro-1*H*-indazol-4-yl)-5-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	519.0
140	3-(1*H*-indazol-4-yl)-7-[6-(8-methyl-3,8-diazabicyclo[3.2.1]oct-3-yl)pyridin-3-yl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	514.3
141	3-(7-chloro-1*H*-indazol-4-yl)-7-{4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	533.3;
142	7-(1,4-dioxaspiro[4.5]dec-8-yl)-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	453.3;
143	3-(1*H*-indazol-4-yl)-7-{4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.2]oct-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	513.2
144	7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.2]oct-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	499.2
145	7-{2-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-4,6-difluorophenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	521.7

Example	Compound Name	MS, ESI (m/z)
146	5-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-*N*,*N*-dimethylaniline	528.3
147	7-{2,4-difluoro-6-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	535.2
148	2-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-*N*,*N*-dimethyl-5-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]aniline	542.3
149	7-{*cis*-4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]cyclohexyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	491.5
150	3-(1*H*-indazol-4-yl)-7-[*cis*-4-(3-oxa-8-azabicyclo[3.2.1]oct-8-yl)cyclohexyl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	506.5
151	3-(1*H*-indazol-4-yl)-7-[*trans*-4-(3-oxa-8-azabicyclo[3.2.1]oct-8-yl)cyclohexyl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	506.5
152	3-(1*H*-indazol-4-yl)-7-[*cis*-4-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)cyclohexyl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	506.2
153	3-(1*H*-indazol-4-yl)-7-[*trans*-4-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)cyclohexyl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	506.2
154	3-(1*H*-indazol-4-yl)-7-{*cis*-4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl]cyclohexyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	492.5
155	3-(1*H*-indazol-4-yl)-7-{*trans*-4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl]cyclohexyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	492.4
156	7-{*trans*-4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]cyclohexyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	491.5
157	7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-3-(trifluoromethyl)phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	553.2
158	7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-1-naphthyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	535.2
159	3-(1*H*-indazol-4-yl)-7-{4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]-3-(trifluoromethyl)phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	567.2
160	3-(1*H*-indazol-4-yl)-7-{4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]-1-naphthyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	549.2
161	7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-3,5-difluorophenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	521.2
162	7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2,3-difluorophenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	521.2
163	7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2,5-difluorophenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	521.5
164	7-{3,5-difluoro-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	535.2
165	7-{2,3-difluoro-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	535.2
166	7-{2,5-difluoro-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	535.2
167	7-{4-[(1*S*,4*S*)-5-ethyl-2,5-diazabicyclo[2.2.1]hept-2-yl]-2,6-difluorophenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	549.3
168	7-{2,6-difluoro-4-[(1*S*,4*S*)-5-isobutyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	577.3
169	7-{2,6-difluoro-4-[(1*S*,4*S*)-5-isopropyl-2,5-diazabicyclo[2.2.1]hept-	563.2

Example	Compound Name	MS, ESI (m/z)
	2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	
170	7-{4-[(1*S*,4*S*)-5-cyclobutyl-2,5-diazabicyclo[2.2.1]hept-2-yl]-2,6-difluorophenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	575.2
171	7-(1,4-dioxaspiro[4.5]dec-8-yl)-3-(7-fluoro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	471.2
172	7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.2]oct-2-yl]-2-fluorophenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	517.2
173	7-{2-fluoro-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.2]oct-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	531.2
174	3-(1*H*-indazol-4-yl)-2-pyridin-4-yl-7-{2,3,5,6-tetrafluoro-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}pyrazolo[1,5-a]pyrimidine	571.2
175	*tert*-butyl (1*S*,4*S*)-5-{3-chloro-4-[3-(7-fluoro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate	637.3
176	7-{*cis*-4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]cyclohexyl}-3-(7-fluoro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	509.2
177	3-(7-fluoro-1*H*-indazol-4-yl)-7-{*cis*-4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl]cyclohexyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	510.3
178	3-(7-fluoro-1*H*-indazol-4-yl)-7-{*trans*-4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl]cyclohexyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	510.3
179	3-(7-fluoro-1*H*-indazol-4-yl)-7-[*cis*-4-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)cyclohexyl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	524.3
180	3-(7-fluoro-1*H*-indazol-4-yl)-7-[*trans*-4-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)cyclohexyl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	524.3
181	3-(7-fluoro-1*H*-indazol-4-yl)-7-[*cis*-4-(3-oxa-8-azabicyclo[3.2.1]oct-8-yl)cyclohexyl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	524.3
182	3-(7-fluoro-1*H*-indazol-4-yl)-7-[*trans*-4-(3-oxa-8-azabicyclo[3.2.1]oct-8-yl)cyclohexyl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	524.3
183	7-{*trans*-4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]cyclohexyl}-3-(7-fluoro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	509.2
184	7-{2-chloro-4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(7-fluoro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	289.6
185	7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-3-fluorophenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	503.2
186	7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-(trifluoromethyl)phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	553.2
187	7-{2-bromo-4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	563.1
188	7-{3-fluoro-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	517.2
189	3-(1*H*-indazol-4-yl)-7-{4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-(trifluoromethyl)phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	567.2
190	7-{2-bromo-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	577.1
191	7-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	451.2
192	7-{2,6-difluoro-4-[(1*S*,4*S*)-5-methyl-5-oxido-2,5-	551.3

Example	Compound Name	MS, ESI (m/z)
	diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	
193	3-(1*H*-indazol-4-yl)-7-{5-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-ylmethyl]furan-3-yl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	490.1
194	*tert*-butyl (1*S*,4*S*)-5-({4-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]furan-2-yl}methyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate	589.1
195	7-{5-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]furan-3-yl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	489.2
196	*tert*-butyl (1*S*,4*S*)-5-({5-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]thiophen-2-yl}methyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate	605.2
197	3-(1*H*-indazol-4-yl)-7-{5-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-ylmethyl]thiophen-2-yl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	506.1
198	7-{5-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]thiophen-2-yl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	505.1
199	ethyl (3-endo)-3-[3-(1*H*-indazol-4-yl)-6-methyl-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate	508.2
200	3-(1*H*-indazol-4-yl)-7-[6-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)pyridin-3-yl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	501.2
201	3-(1*H*-indazol-4-yl)-7-{6-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl]pyridin-3-yl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	487.2
202	*tert*-butyl (1*S*,4*S*)-5-{3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]benzyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate	599.3
203	*tert*-butyl (1*S*,4*S*)-5-{4-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]benzyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate	599.3
204	3-(1*H*-indazol-4-yl)-7-{4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-ylmethyl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	500.2
205	7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-2-fluorophenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	517.2
206	7-{2-fluoro-4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-ylmethyl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	518.2
207	7-{2-fluoro-4-[(1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]hept-5-ylmethyl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	518.2
208	7-{3-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	499.2
209	7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine	499.3
210	9-{3-fluoro-4-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]benzyl}-3,7-dioxa-9-azabicyclo[3.3.1]nonane	548.3

STANDARD BIOLOGICAL AND PHARMALOGICAL TEST PROCEDURES

Evaluation of representative compounds of this invention in standard pharmacological test procedures indicated that the compounds of this invention possess significant anticancer activity and are inhibitors of Raf kinase. Based on the activity shown in the standard pharmacological test procedures, the compounds of this invention are therefore

useful as antineoplastic agents. In particular, these compounds are useful in treating, inhibiting the growth of, or eradicating neoplasms such as those of the breast, kidney, bladder, thyroid, mouth, larynx, esophagus, stomach, colon, ovary, lung, pancreas, liver, prostate and skin. Compounds of the invention are useful as anti-inflammation agents and possess activity against inflammation associated with Raf kinases.

TESTING FOR RAF KINASE INHIBITORS

Compounds of formula A were tested as Raf Kinase inhibitors for B-Raf kinase, mutant B-Raf kinase and C-Raf kinase, which are associated with inhibiting growth of tumor cells containing oncogenic forms of Receptor Tyrosine Kinases, K-Ras and Raf kinases.

B-RAF KINASE:

Reagents: Flag/GST-tagged recombinant human B-Raf produced in Sf9 insect cells, human non-active Mek-1-GST (recombinant protein produced in *E. coli*); and a phospho-MEK1 specific poly-clonal Ab from Cell Signaling Technology (Cat. #9121).

TESTING FOR B-RAF KINASE INHIBITORS

B-Raf1 Kinase Assay Procedure: B-Raf-1 is used to phosphorylate GST-MEK1. MEK1 phosphorylation is measured by a phospho-specific antibody (from Cell Signaling Technology, Cat. #9121) that detects phosphorylation of two serine residues at positions 217 and 221 on MEK1.

The following Kinase Assay Protocol was employed in accordance with the invention:

B-Raf Assay Stock Solutions

1. Assay Dilution Buffer (ADB): 20 mM MOPS, pH 7.2, 25 mM ß-glycerol phosphate, 5mM EGTA, 1 mM sodium orthovanadate, 1mM dithiothreitol, 0.01% Triton X-100.

2. Magnesium/ATP Cocktail: ADB solution (minus Triton X-100) plus 200 µM cold ATP and 40 mM magnesium chloride.

4. Active Kinase: Active B-Raf: Used at 0.2 nM per assay point.

5. Non-active GST-MEK1: Used at 2.8 nM final concentration).

6. TBST - Tris (50 mM, pH 7.5), NaCl (150 mM), Tween-20 (0.05 %)

7. Anti-GST Ab (GE)

8. Anti pMEK Ab (Upstate)

9. Anti-rabbit Ab / Europium conjugate (Wallac).

B-RAF ASSAY PROCEDURE:

1. Added 25 µL of ADB containing B-Raf and Mek per assay (i.e. per well of a 96 well plate)

2. Added 25 µL of 0.2 mM ATP and 40 mM magnesium chloride in Magnesuium/ATP Cocktail.

3. Incubated for 45 minutes at RT with occasional shaking.

4.Transfered this mixture to an anti-GST Ab coated 96 well plate (Nunc Immunosorb plates coated o/n with a-GST. Plate freshly washed 3 x with TBS-T before use.

5. Incubated o/n at 30°C in cold room.

6. Washed 3 x with TBST, ed Anti-Phospho MEK1 (1:1000, dilution depended upon lot)

7. Incubated for 60 minutes at RT in a shaking incubator

8. Washed 3 x with TBST, add Anti-rabbit Ab / Europium conjugate (Wallac) (1:500, dilution depended upon lot)

9. Incubated for 60 minutes at RT on a platform shaker.

10. Washed plate 3 x with TBS-T

11. Added 100 μL of Wallac Delfia Enhancement Solution and agitated for 10 minutes.

12. Read plates in Wallac Victor model Plate Reader.

13. Collected data and analyzed for single point and IC_{50} determinations as described by Mallon R., et al. (2001) Anal. Biochem. 294:48.

TESTING FOR C-RAF KINASE INHIBITORS

Assayed in a Raf-MEK-MAP kinase cascade assay as described previously (Mallon R, et al (2001) Anal. Biochem. 294:48.), except that C-Raf kinase was purchased from Upstate, Lake Placid, NY and used at a concentration of 0.215 nM per assay point.

TESTING FOR MUTANTS OF B-RAF KINASE INHIBITORS

Assayed in a Raf-MEK-MAP kinase cascade assay as described previously (Mallon R, et al (2001) Anal. Biochem. 294:48.), except that B-Raf kinase mutants (V600 E) were used.

ANALYSIS OF RESULTS

B-Raf IC_{50} determinations were performed on compounds of formula A from single point assays with > 80 % inhibition. Single point assay: % inhibition at 10 mg/mL (% inhibition = 1 – sample treated with compound of Formula A/ untreated control sample). The % inhibition was determined for each compound concentration. IC_{50} determinations –Typically the B-Raf assay was run at compound concentrations from 1μM to 3 nM or 0.1 μM to 300 pm in half log dilutions.

Selected compounds of formula A exhibited Raf kinase IC_{50} values rangng from 1μM to 0.1 nM, indicating that the compounds are effective inhibitors of Raf kinases, including B-Raf kinase, mutant B-Raf kinase and C-Raf kinase. The data is summarized in Table 2.

Table 2. B-Raf IC_{50} Data for compounds of Formula A

Example Mean IC_{50} (μM)

Example	Mean IC_{50} (uM)
1	0.002
2	0.002
3	0.001
4	>1
5	0.006
6	0.057
7	0.087
8	0.001
9	0.004
10	0.054
11	0.002
12	0.0004
13	0.0003
14	0.002
15	0.01
16	0.009
17	0.044
18	0.0006
19	0.071
20	0.835
21	>1
22	>1
23	>1
24	NT
25	0.001
26	0.01
27	<0.0003
28	0.016
29	0.0005
30	<0.003
31	0.0018
32	0.0087
33	<0.0003
34	0.0023
35	0.0015
36	0.0082
37	0.021
38	0.0005
39	0.0005
40	0.0007
41	<0.0003
42	0.0004
43	0.134
44	0.0006
45	<0.0003
46	0.0032
47	0.0008
48	>1.0
49	0.255
50	>1.0
51	0.0008
52	<0.0003
53	<0.0003
54	0.15
55	NT
56	<0.0003
57	<0.0003

Example	Mean IC_{50} (uM)
58	<0.0003
59	<0.0003
60	<0.0003
61	<0.0003
62	<0.0003
63	<0.0003
64	0.003
65	0.302
66	0.329
67	>1.0
68	0.058
69	NT
70	NT
71	NT
72a	0.566
72b	0.417
73	0.002
74	NT
75	0.0003
76	0.004
77	0.017
78	0.0007
79	0.004
80	0.048
81	0.0004
82	0.002
83	>1.0
84	>1.0
85	0.036
86	0.27
87	0.032
88	>1.0
89	NT
90	0.046
91	0.162
92	NT
93	<0.0003
94	0.0001
95	0.00059
96	NT
97	<0.0003
98	<0.0003
99	0.0016
100	<0.0002
101	<0.0001
102	0.00204
103	<0.0003
104	0.00024
105	NT
106	<0.0003
107	<0.0003
108	NT
109	<0.0003
110	<0.0001
111	Not Tested
112	0.0228
113	0.067

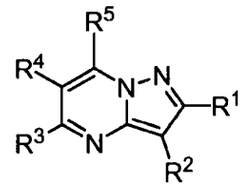
Example	Mean IC_{50} (uM)
114	0.0049
115	0.0091
116	0.0618
117	0.0028
118	0.0067
119	0.0091
120	0.0064
121	>0.1
122	0.0191
123	Not Tested
124	0.0376
125	0.0449
126	0.0612
127	0.0313
128	0.0394
129	0.0021
130	0.0759
131	0.0010
132	0.0004
133	<0.0003
134	<0.0003
135	<0.0003
136	<0.0003
137	0.0038
138	0.0004
139	0.0012
140	0.0012
141	0.0023
142	0.0022
143	0.0007
144	0.0006
145	0.0744
146	0.0063
147	>0.1
148	0.0073
149	0.0032
150	0.0399
151	0.0064
152	0.0064
153	0.0037
154	0.0114
155	0.0035
156	0.0006
157	0.0012
158	0.0209
159	0.002
160	0.0253
161	0.0027
162	0.0005
163	<0.0003
164	0.0096
165	0.0006
166	0.0004
167	<0.0003
168	<0.0003
169	<0.0003
170	<0.0003

Example	Mean IC_{50} (uM)
171	Not Tested
172	0.0003
173	0.0004
174	0.0004
175	0.001
176	0.001
177	0.004
178	0.0067
179	0.0086
180	0.0018
181	0.0021
182	0.0013
183	<0.0003
184	<0.0003
185	0.0017
186	0.0011
187	<0.0003
188	0.0019
189	0.0014
190	<0.0003
191	0.0561
192	0.0004
193	0.0188
194	0.0091
195	0.013
196	0.0115
197	0.0057
198	0.0036
199	0.0055
200	0.0058
201	0.0084
202	>0.1
203	0.012
204	0.010
205	0.00035
206	0.0015
207	0.0005
208	0.042
209	0.0006
210	0.0007

NT= Not tested

WHAT IS CLAIMED IS:

1. A compound of formula A:



A

and pharmaceutically acceptable salts thereof;

wherein

R^1 is a 5-7 membered heterocyclic ring or heteroaryl ring, said ring comprising 1-3 heteroatoms selected from N, O or S, and said ring optionally substituted with one to four substituents selected from -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^9OR^7$, $-R^9NR^7R^7$, $-R^9S(O)_mR^7$, $-R^9C(O)R^7$, $-R^9C(O)OR^7$, $-R^9C(O)NR^7R^7$, $-R^9OC(O)R^7$, $-R^9OC(O)OR^7$, $-R^9OC(O)NR^7R^7$, $-R^9NR^7C(O)R^7$, $-R^9NR^7C(O)OR^7$, $-R^9NR^7C(O)NR^7R^7$, $-YR^9R^{10}$, $-YR^9NR^7R^7$ and $-YR^{10}$;

R^2 is selected from an aryl ring, a 9-14 membered bicyclic aryl ring, a 5-7 membered heteroaryl ring and a 9-14 membered bicyclic heteroaryl ring, said heteroaryl ring comprising 1-3 heteroatoms selected from N, O and S, said ring optionally substituted with one to four substituents selected from -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_2$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^9OR^7$, $-R^9NR^7R^7$, $-R^9S(O)_mR^7$, $-R^9C(O)R^7$, $-R^9C(O)OR^7$, $-R^9C(O)NR^7R^7$, $-R^9OC(O)R^7$, $-R^9OC(O)OR^7$, $-R^9OC(O)NR^7R^7$, $-R^9NR^7C(O)R^7$, $-R^9NR^7C(O)OR^7$, $-R^9NR^7C(O)NR^7R^7$, $-OPO(OR^7)_2$, $-YR^9R^{10}$, $-YR^9NR^7R^7$ and $-YR^{10}$;

R^3, R^4 and R^5 are each independently selected from carbon-linked R^6, $-X-W-R^6$, H, J, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-NR^7C(O)R^7$, -CN, alkyl of 1-6 carbon atoms, branched alkyl of 1-8 carbon atoms, cycloalkyl ring of 3-10 carbons, aryl ring, 5-7 membered heterocyclic ring, and 5-10 membered heteroaryl ring, said heterocyclic ring or heteroaryl ring comprising 1-3

heteroatoms selected from N, O and S, said alkyl of 1-6 carbon atoms, branched alkyl of 1-8 carbon atoms, aryl ring, 5-7 membered heterocyclic ring, and 5-10 membered heteroaryl ring is optionally substituted with one to four substituents selected from -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$ $-R^8NR^7C(O)NR^7R^7$ and YR^{10}, wherein at least one of R^3, R^4 and R^5 comprises R^6;

R^6 is a 6-14 membered bridged, bicyclic heterocyclic ring or bicyclic spiro heterocyclic ring, said ring optionally substituted with one or more substituents selected from -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$or $-R^8NR^7C(O)NR^7R^7$ and YR^{10};

R^7 is H or is independently selected from alkyl of 1-6 carbon atoms, branched alkyl of 1-8 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, aryl ring and a 5-10 membered heteroaryl ring, optionally substituted with one to four substituents selected from -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, -R, -OR, $-S(O)_mR$, -NRR, $-NRS(O)_mR$, $-OR^9OR$, $-OR^9NRR$, $-N(R)R^9OR$, $-N(R)R^9NRR$, -NRC(O)R, -C(O)R, -C(O)OR, -C(O)NRR, -OC(O)R, -OC(O)OR, -OC(O)NRR, NRC(O)R, -NRC(O)OR, -NRC(O)NRR, $-R^8OR$, $-R^8NRR$, $-R^8S(O)_mR$, $-R^8C(O)R$, $-R^8C(O)OR$, $-R^8C(O)NRR$, $-R^8OC(O)R$, $-R^8OC(O)OR$, $-R^8OC(O)NRR$, $-R^8NRC(O)R$, $-R^8NRC(O)OR$, $-R^8NRC(O)NRR$ and ZR^{10}, wherein R is selected from alkyl of 1-6 carbon atoms, branched alkyl of 1-8 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-10 carbon atoms, aryl of 6-10 carbon atoms and heteroaryl of 6-10 atoms, the heteroaryl comprising 1-3 heteroatoms selected from N, O and S;

R^8 is a divalent group independently selected from alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, aryl, heteroaryl, cycloalkyl, and cycloheteroalkyl;

R^9 is independently a divalent alkyl group of 2-6 carbon atoms;

R^{10} is independently selected from cycloalkyl ring of 3-10 carbons, bicycloalkyl ring of 3-10 carbons, aryl ring, heterocyclic ring, heteroaryl ring and a heteroaryl ring fused to one to three aryl or heteroaryl rings, each heterocyclic ring or heteroaryl ring comprising 1-3 heteroatoms selected from N, O and S, each optionally substituted with one to four substituents selected from –H, -aryl, $-CH_2$-aryl, -NH-aryl, -O-aryl, $-S(O)_m$-aryl, -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$-, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $-NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$, and $-R^8NR^7C(O)NR^7R^7$;

J is fluoro, chloro, bromo, or iodo;

m is an integer of 0-2;

Y is a divalent group independently selected from a bond, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, O, and $-NR^7$;

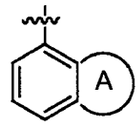
X is selected from a divalent alkyl group of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl ring of 3-10 carbons, bicycloalkyl ring of 3-10 carbons, aryl ring, heterocyclic ring and a heteroaryl ring, each heterocyclic ring or heteroaryl ring comprising 1-3 heteroatoms selected from N, O or S; optionally substituted with one to four substituents selected from –H, -aryl, $-CH_2$-aryl, -NH-aryl, -O-aryl, $-S(O)_m$-aryl, -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$-, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $-NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$, and $-R^8NR^7C(O)NR^7R^7$;

W is selected from a bond, Z, -OZ-, -ZO- $-S(O)_mZ$-, $-S(O)_2NR^7Z$-, $-NR^7S(O)_mZ$ -, $-NR^7Z$-, $-ZNR^7$-, -C(O)Z-; -C(O)OZ-, $-C(O)NR^7Z$-, $-NR^7C(O)Z$-, $-NR^7C(O)NR^7Z$-, -OC(O)Z-, $-NR^7C(O)OZ$-, and -OC(O) NR^7Z-; and

Z is a bond or a divalent alkyl of 1-6 carbon atoms.

2. The compound of claim 1, wherein R^1 is 4-pyridinyl or 4-morpholinyl, optionally substituted with one to four substituents selected from -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$, $-R^8NR^7C(O)NR^7R^7$, $-OPO(OR^7)_2$, $-YR^8R^{10}$, $-YR^8NR^7R^7$ and $-YR^{10}$.

3. The compound of claim 2, wherein R^2 is an aryl ring or a bicyclic ring of formula

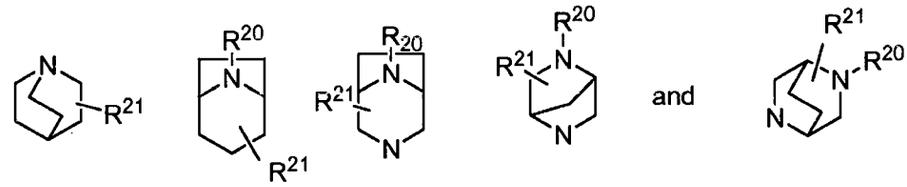


wherein  refers to a 5-7 membered heteroaryl ring comprising 1-3 heteroatoms selected from N, O and S, said ring optionally substituted with one to four substituents selected from -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$, $-R^8NR^7C(O)NR^7R^7$, $-YR^8R^{10}$, $-YR^8NR^7R^7$ and $-YR^{10}$.

4. The compound of claim 2, wherein R^2 is a phenyl ring or an indazolyl ring, optionally substituted with one to four substituents selected from -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$, $-R^8NR^7C(O)NR^7R^7$, $-YR^8R^{10}$, $-YR^8NR^7R^7$ and $-YR^{10}$.

5. The compound of claim 2, wherein R^2 is selected from halogen substituted phenyl, C_1-C_6 alkylsulfonamido substituted phenyl, carbamate substituted phenyl, C_1-C_6 alkoxy substituted phenylcarbamate, benzonitrile, hydroxyl substituted benzonitrile, C_1-C_6 alkoxy substituted benzonitrile, hydroxyphenyl, C_1-C_6 alkyl substituted hydroxyphenyl, halogen substituted hydroxyphenyl, C_1-C_6 alkoxyphenyl, halogen substituted C_1-C_6 alkoxyphenyl, hydroxypyridinyl, C_1-C_6 alkoxypyridinyl, amino phenyl, halogen substituted amino phenyl, hydroxyl substituted amino phenyl, formamide substituted phenyl, hydroxyl substituted phenylformamide, C_1-C_6 alkoxy substituted phenylformamide, C_1-C_6 alkoxy substituted amino phenyl, urea substituted phenyl, benzamido, C_1-C_6 alkyl substituted benzamido, halogen substituted benzamido, indazolyl, C_1-C_6 alkyl substituted indazolyl, halogen substituted indazolyl, halo C_1-C_6 alkyl substituted indazolyl, perfluoro C_1-C_6 alkyl substituted indazolyl, benzamidazolyl, halogen substituted benzamidazolyl, dihydro-pyrrolodinyl, substituted dihydro-pyrrolodinyl, dihydro-indolyl, substituted dihydro-indolyl and oxadiazolyl substituted phenyl.

6. The compound of claim 2, wherein R^6 is a bridged, bicyclic heterocyclic ring selected from:



optionally substituted on nitrogen with R^{20} and optionally substituted on one or more carbons of the bridged, bicyclic heterocyclic ring with R^{21}, wherein

R^{20} is selected from H, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-C(O)R^7$, $-S(O)_mR^7$, alkyl of 1-6 carbon atoms, branched alkyl of 1-8 carbon atoms, cycloalkyl ring of 3-10 carbons, aryl ring, 5-7 membered heterocyclic ring and 5-10 membered heteroaryl ring, each heterocyclic ring or heteroaryl ring comprising 1-3 heteroatoms selected from N, O or S, each of the alkyl of 1-6 carbon atoms, branched alkyl of 1-8 carbon atoms, aryl ring, heterocyclic ring and heteroaryl ring optionally substituted with one to four substituents selected from -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$ or $-R^8NR^7C(O)NR^7R^7$ and YR^{10}; and

R^{21} is selected from H, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$or $-R^8NR^7C(O)NR^7R^7$ and YR^{10}.

7. The compound of claim 4, wherein R^5 is R^6.

8. The compound of claim 4, wherein R^5 is X-W-R^6, X is aryl or heteroaryl and W is a bond.

9. The compound of claim 4, wherein R^5 is X-W-R^6, X is aryl or heteroaryl and W is ZN R^7 or NR^7Z.

10. A compound of claim 4 wherein R^5 is a bicyclic spiro heterocyclic ring comprising 1-3 heteroatoms selected from N, O and S, optionally substituted with one to four substituents selected from -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$, $-R^8NR^7C(O)NR^7R^7$ and YR^{10}.

11. A compound selected from 3-(7-{6-[(1-azabicyclo[2.2.2]oct-4-ylmethyl)amino]pyridin-3-yl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol, 3-(7-{6-[(3*S*)-1-azabicyclo[2.2.2]oct-3-ylamino]pyridin-3-yl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol, 3-(7-{6-[(3*R*)-1-azabicyclo[2.2.2]oct-3-ylamino]pyridin-3-yl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol, (3*R*)-*N*-{4-[3-(3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]pyridin-2-yl}quinuclidin-3-amine, (3*R*)-*N*-{5-[3-(4-chloro-3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]pyridin-2-yl}quinuclidin-3-amine, 3-{7-[(1-azabicyclo[2.2.2]oct-4-ylmethyl)amino]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl}phenol, ethyl 3-[3-(3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate, ethyl 3-[3-(3-hydroxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]-octane-8-carboxylate, 3-[7-(8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]phenol, ethyl 3-[3-(4-chloro-3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate, ethyl 3-[3-(4-chloro-3-hydroxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate, 5-[7-(8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]-2-chlorophenol, 5-[7-(8-acetyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]-2-chlorophenol, 2-chloro-5-{7-[8-(methylsulfonyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl}phenol, 5-[7-(8-acetyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]-2-chlorophenyl acetate, 7-(8-azabicyclo[3.2.1]oct-3-yl)-3-(4-chloro-3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(4-chloro-3-methoxyphenyl)-7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 2-chloro-5-[7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]phenol, 7-(8-azabicyclo[3.2.1]oct-3-yl)-3-(3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-3-(2-methoxypyridin-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 4-[7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]pyridin-2-ol, 4-[7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]aniline, 1-{4-[7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]phenyl}urea, 3-(3-methoxyphenyl)-7-[4-(8-methyl-3,8-diazabicyclo[3.2.1]oct-3-yl)phenyl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-{7-[4-(8-methyl-3,8-diazabicyclo[3.2.1]oct-3-yl)phenyl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl}phenol, 3-(4-chloro-3-methoxyphenyl)-7-[4-(8-methyl-3,8-diazabicyclo[3.2.1]oct-3-yl)phenyl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 2-chloro-5-{7-[4-(8-methyl-3,8-diazabicyclo[3.2.1]oct-3-yl)phenyl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl}phenol, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol, 3-(7-{4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol, 3-(4-chloro-3-methoxyphenyl)-7-{4-[(1*S*,4*S*)-2,5-

diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(4-fluoro-3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 5-(7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)-2-fluorophenol, 3-(1*H*-indazol-4-yl)-7-{6-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]pyridin-3-yl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-7-{4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(3-methoxyphenyl)-7-{4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]-hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(4-fluoro-3-methoxyphenyl)-7-{4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 5-(7-{4-[(1*S*,4*S*)-5-ethyl-2,5-diazabicyclo[2.2.1]-hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)-2-fluorophenol, 5-(7-{4-[(1*S*,4*S*)-5-acetyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)-2-fluorophenol, 7-{6-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]pyridin-3-yl}-3-(7-methyl-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(7-chloro-1*H*-indazol-4-yl)-7-{6-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]pyridin-3-yl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(7-fluoro-1*H*-indazol-4-yl)-7-{6-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]pyridin-3-yl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(7-{6-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]pyridin-3-yl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)benzamide, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-methylphenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-7-{2-methyl-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-4-fluorophenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-fluoro-2-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, *tert*-butyl (1*S*,4*S*)-5-{2-[3-(4-chloro-3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-5-fluorophenyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate, 3-(4-chloro-3-methoxyphenyl)-7-{2-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-4-fluorophenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(4-chloro-3-methoxyphenyl)-7-{4-fluoro-2-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo-[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-fluorophenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2-fluoro-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 2-fluoro-5-(7-{4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol, 3-(4-fluoro-3-methoxyphenyl)-7-{2-methyl-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 2-fluoro-5-(7-{2-methyl-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol, 3-(7-{4-[(1*S*,4*S*)-2,5-

diazabicyclo[2.2.1]hept-2-yl]-2-methylphenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol, 3-(7-{2-methyl-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol, 3-(7-{2-chloro-4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol, 3-(7-{2-chloro-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol, 7-{2-chloro-4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2-chloro-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, ethyl 3-[3-(3-hydroxy-4-methylphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate, 5-[7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]-2-fluorophenol, ethyl 3-[3-(2,3-difluorophenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate, ethyl 3-(3-{3-[(methylsulfonyl)amino]-phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate, methyl {4-[7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]phenyl}carbamate, 4-[7-(8-ethyl-8-azabicyclo[3.2.1]-oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]-2-hydroxybenzonitrile, tert-butyl {4-[7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]-2-methoxyphenyl}carbamate, 4-[7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]-2-methoxyaniline, 2-amino-5-[7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]phenol, *N*-{4-[7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]-2-hydroxyphenyl}formamide, *N*-{4-[7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]-2-methoxyphenyl}formamide, ethyl 3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate, 7-(8-azabicyclo[3.2.1]oct-3-yl)-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo-[1,5-a]pyrimidine, ethyl 3-[3-(7-chloro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate, ethyl 3-{2-pyridin-4-yl-3-[7-(trifluoromethyl)-1*H*-indazol-4-yl]pyrazolo[1,5-a]pyrimidin-7-yl}-8-azabicyclo[3.2.1]-octane-8-carboxylate, 7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-3-(7-methyl-1H-indazol-4-yl)-2-pyridin- 4-ylpyrazolo[1,5-a]pyrimidine, ethyl 3-[3-(7-methyl-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate, 3-(7-chloro-1*H*-indazol-4-yl)-7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-yl-3-[7-(trifluoromethyl)-1*H*-indazol-4-yl]pyrazolo[1,5-a]pyrimidine, ethyl 3-[3-(7-fluoro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate, 3-(7-chloro-6-fluoro-1*H*-indazol-4-yl)-7-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, ethyl 3-[3-(2-oxo-2,3-dihydro-1*H*-benzimidazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]-octane-8-carboxylate, ethyl 3-[3-(1*H*-indol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-

a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate, ethyl 3-[3-(1*H*-indol-6-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate, ethyl 3-[3-(2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-b]pyridin-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate, 7-(8-ethyl-8-azabicyclo-[3.2.1]oct-3-yl)-3-(1*H*-indol-6-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, ethyl 3-[3-(2-oxo-2,3-dihydro-1*H*-indol-6-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate, 2-chloro-5-[7-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl]phenol, 7-(8-Ethyl-8-azabicyclo[3.2.1]-octan-3-yl)-3-(1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine, Ethyl 3-(3-(3-(1,3,4-oxadiazol-2-yl)phenyl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate, *tert*-Butyl (1S,4S)-5-{3-fluoro-4-[3-(1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl}-2,5-diazabicyclo-[2.2.1]heptane-2- carboxylate, 7-{4-[(1S,4S)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-fluorophenyl}-3-(1H-indazol-4- yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2-Fluoro-4-[(1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2-fluoro-4-[(1S,4S)-5-methyl-5-oxido-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo-[1,5-a]pyrimidine, (1S,4S)-5-{3-Chloro-4-[3-(1H-indazol-4-yl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester, 7-[2-Chloro-4-((1S,4S)-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-phenyl]-3-(1H-indazol-4-yl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine bis-hydrochloride salt, 7-[2-Chloro-4-((1S,4S)-5-methyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-phenyl]-3-(1H-indazol-4-yl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine, *tert*-butyl (1S,4S)-5-{3,5-difluoro-4-[3-(1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2- carboxylate, 7-(4-((1S,4S)-2,5-diazabicyclo[2.2.1]-heptan-2-yl)-2,6-difluorophenyl)-3-(1H-indazol-4-yl)-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine, 7-{2,6-difluoro-4-[(1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3- (1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, *tert*-Butyl (1S,4S)-5-{4-[3-(7-fluoro-1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate, 7-[4-(2,5-Diaza-bicyclo[2.2.1]hept-2-yl)-phenyl]-3-(7-fluoro-1H-indazol-4-yl)-2-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine, 3-(7-fluoro-1H-indazol-4-yl)-7-{4-[(1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine hydrochloride, *tert*-Butyl (1S,4S)-5-{3-fluoro-4-[3-(7-fluoro-1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2- carboxylate, 7-{4-[(1S,4S)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-fluorophenyl}-3-(7-fluoro-1H- indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(7-fluoro-1H-indazol-4-yl)-7-{2-fluoro-4-[(1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, *tert*-Butyl (1S,4S)-5-{3,5-difluoro-4-[3-(7-fluoro-1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2- carboxylate, 7-{4-[(1S,4S)-2,5-Diazabicyclo[2.2.1]hept-2-yl]-2,6-difluorophenyl}-3-(7-fluoro-1H-indazol-4-yl)-2-pyridin-4-

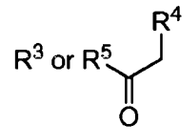
ylpyrazolo[1,5-a]pyrimidine, 7-{2,6-Difluoro-4-[(1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3- (7-fluoro-1H-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, ethyl 3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-5-yl]-8-azabicyclo[3.2.1]-octane-8-carboxylate, 2-{3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]oct-8-yl}ethanol, 3-(1*H*-indazol-4-yl)-7-(8-isopropyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-7-[8-(methylsulfonyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxamide, 2-{3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]oct-8-yl}-*N*,*N*-dimethyl-2-oxoethanamine, {3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]oct-8-yl}acetonitrile, *N*-ethyl-3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxamide, 7-(8-acetyl-8-azabicyclo[3.2.1]oct-3-yl)-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-*N*,*N*-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxamide, *tert*-butyl (1*S*,4*S*)-5-{[3-(4-chloro-3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]methyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate, *tert*-butyl (1*S*,4*S*)-5-{4-[3-(7-fluoro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-5-yl]phenyl}-2,5-diazabicyclo-[2.2.1]heptane-2-carboxylate, *tert*-butyl (1*S*,4*S*)-5-{3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate, 7-{3-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, *tert*-butyl (1*S*,4*S*)-5-{4-[3-(7-chloro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate, 3-(1*H*-indazol-4-yl)-7-{3-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(7-chloro-1*H*-indazol-4-yl)-7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, *tert*-butyl (2*S*)-2-({3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]oct-8-yl}carbonyl)pyrrolidine-1-carboxylate, 3-(1*H*-indazol-4-yl)-7-(8-L-prolyl-8-azabicyclo[3.2.1]oct-3-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 1-{3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]oct-8-yl}propan-2-one, ethyl 3-[3-(7-fluoro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-5-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-fluorophenyl}-3-(3-methoxyphenyl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-fluorophenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol, 3-(7-{2-fluoro-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-3-yl)phenol, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-methylphenyl}-3-(7-fluoro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(7-fluoro-1*H*-indazol-4-yl)-7-{2-methyl-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo-[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-(8-azabicyclo[3.2.1]oct-3-yl)-3-(7-fluoro-

1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, {3-[3-(7-fluoro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]oct-8-yl}acetonitrile, 3-(7-chloro-1*H*-indazol-4-yl)-5-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-7-[6-(8-methyl-3,8-diazabicyclo[3.2.1]oct-3-yl)pyridin-3-yl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(7-chloro-1*H*-indazol-4-yl)-7-{4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-(1,4-dioxaspiro[4.5]dec-8-yl)-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-7-{4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.2]oct-2-yl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo-[2.2.2]oct-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-4,6-difluorophenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 5-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-*N*,*N*-dimethylaniline, 7-{2,4-difluoro-6-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 2-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-*N*,*N*-dimethyl-5-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]aniline, 7-{*cis*-4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]cyclohexyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-7-[*cis*-4-(3-oxa-8-azabicyclo[3.2.1]oct-8-yl)cyclohexyl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-7-[*trans*-4-(3-oxa-8-azabicyclo[3.2.1]-oct-8-yl)cyclohexyl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-7-[*cis*-4-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)cyclohexyl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-7-[*trans*-4-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)cyclohexyl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-7-{*cis*-4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl]cyclohexyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-7-{*trans*-4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl]cyclohexyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{*trans*-4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]cyclohexyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-3-(trifluoromethyl)phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-1-naphthyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-7-{4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]-3-(trifluoromethyl)phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-7-{4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]-1-naphthyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-3,5-difluorophenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2,3-difluorophenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2,5-difluorophenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{3,5-difluoro-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-

ylpyrazolo[1,5-a]pyrimidine, 7-{2,3-difluoro-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2,5-difluoro-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-[(1*S*,4*S*)-5-ethyl-2,5-diazabicyclo[2.2.1]-hept-2-yl]-2,6-difluorophenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2,6-difluoro-4-[(1*S*,4*S*)-5-isobutyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2,6-difluoro-4-[(1*S*,4*S*)-5-isopropyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-[(1*S*,4*S*)-5-cyclobutyl-2,5-diazabicyclo[2.2.1]hept-2-yl]-2,6-difluorophenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-(1,4-dioxaspiro[4.5]dec-8-yl)-3-(7-fluoro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.2]oct-2-yl]-2-fluorophenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2-fluoro-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.2]oct-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-2-pyridin-4-yl-7-{2,3,5,6-tetrafluoro-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}pyrazolo[1,5-a]pyrimidine, *tert*-butyl (1*S*,4*S*)-5-{3-chloro-4-[3-(7-fluoro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate, 7-{*cis*-4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]cyclohexyl}-3-(7-fluoro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(7-fluoro-1*H*-indazol-4-yl)-7-{*cis*-4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl]cyclohexyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(7-fluoro-1*H*-indazol-4-yl)-7-{*trans*-4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl]cyclohexyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(7-fluoro-1*H*-indazol-4-yl)-7-[*cis*-4-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)cyclohexyl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(7-fluoro-1*H*-indazol-4-yl)-7-[*trans*-4-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)cyclohexyl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(7-fluoro-1*H*-indazol-4-yl)-7-[*cis*-4-(3-oxa-8-azabicyclo[3.2.1]oct-8-yl)cyclohexyl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(7-fluoro-1*H*-indazol-4-yl)-7-[*trans*-4-(3-oxa-8-azabicyclo[3.2.1]oct-8-yl)cyclohexyl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{*trans*-4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]cyclohexyl}-3-(7-fluoro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2-chloro-4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]-hept-2-yl]phenyl}-3-(7-fluoro-1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-3-fluorophenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-(trifluoromethyl)phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2-bromo-4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{3-fluoro-4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-7-{4-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-(trifluoromethyl)phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2-bromo-4-[(1*S*,4*S*)-5-

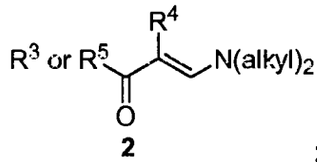
methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2,6-difluoro-4-[(1*S*,4*S*)-5-methyl-5-oxido-2,5-diazabicyclo[2.2.1]hept-2-yl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-7-{5-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-ylmethyl]furan-3-yl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, *tert*-butyl (1*S*,4*S*)-5-({4-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]furan-2-yl}methyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate, 7-{5-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]furan-3-yl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, *tert*-butyl (1*S*,4*S*)-5-({5-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]thiophen-2-yl}methyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate, 3-(1*H*-indazol-4-yl)-7-{5-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-ylmethyl]thiophen-2-yl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{5-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]thiophen-2-yl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, ethyl (3-endo)-3-[3-(1*H*-indazol-4-yl)-6-methyl-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate, 3-(1*H*-indazol-4-yl)-7-[6-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)pyridin-3-yl]-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 3-(1*H*-indazol-4-yl)-7-{6-[(1*S*,4*S*)-2-oxa-5-azabicyclo-[2.2.1]hept-5-yl]pyridin-3-yl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, *tert*-butyl (1*S*,4*S*)-5-{3-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]benzyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate, *tert*-butyl (1*S*,4*S*)-5-{4-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]benzyl}-2,5-diazabicyclo[2.2.1]-heptane-2-carboxylate, 3-(1*H*-indazol-4-yl)-7-{4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]-hept-5-ylmethyl]phenyl}-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-2-fluorophenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2-fluoro-4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-ylmethyl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{2-fluoro-4-[(1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]hept-5-ylmethyl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{3-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 7-{4-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]phenyl}-3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidine, 9-{3-fluoro-4-[3-(1*H*-indazol-4-yl)-2-pyridin-4-ylpyrazolo[1,5-a]pyrimidin-7-yl]benzyl}-3,7-dioxa-9-azabicyclo[3.3.1]nonane and pharmaceutically acceptable salts thereof.

12. A method for making a compound of claim 1, comprising the steps of: (a) reacting a substituted ketone of formula 1



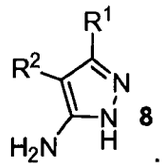
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with an acetal of N,Ndialkylformamide or an acetal of N,N-dialkylacetamide, to provide an enaminone compound of formula 2



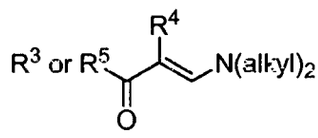
2 ; and

(b) reacting the enaminone compound of formula 2 with a substituted 3-aminopyrazole of formula 8



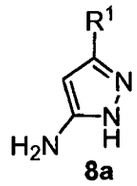
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13. A method a method for making a compound of claim 1, comprising the steps of: (a) reacting an enaminone compound of formula 2



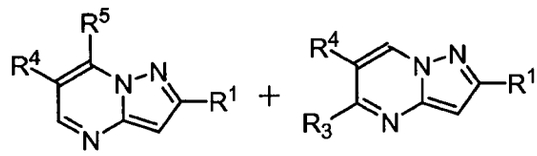
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with an aminopyrazole of formula 8a



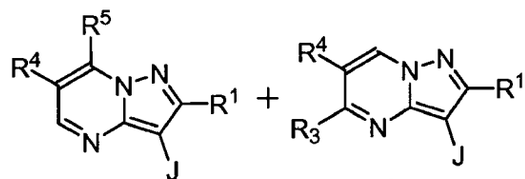
8a

to provide compounds of formula 3c and 3d



3c 3d ;

(b) halogenating one or both of the compounds of formula 3c and 3d to provide one or both of compounds of formula 3e and 3f



3e 3f ; and

(c) subjecting one or both of the compounds of formula 3e and 3f to a palladium catalyzed, Suzuki coupling using aryl or heteroaryl boronic acids or corresponding boronate esters.

14. The method according to claim 13, comprising an additional step of separating compounds of formula 3c and 3d prior to step (b).

15. The method according to claim 13, comprising an additional step of separating compounds of formula 3e and 3f prior to step (c).

16. The method according to claim 13, comprising an additional step of separating compounds after step (c).

17. A pharmaceutical composition comprising a compound according to any of claims 1-10 and a pharmaceutically acceptable carrier.

18. A pharmaceutical composition comprising a compound according to any of claims 1-10 in combination with other kinase-inhibiting pharmaceutical compositions or chemotherapeutic agents, and a pharmaceutically acceptable carrier.

19. A pharmaceutical composition according to claims 16 or 17, that is capable of inhibiting Raf kinase activity.

20. A method of treating a disease associated with inhibiting Raf kinase activity in a mammal comprising administering to the mammal a pharmaceutically effective amount of a compound according to any one of claims 1-10.

21. The method of claim 20, wherein the disease is associated with a B-Raf kinase dependent condition, a mutant B-Raf kinase condition, or a C-Raf kinase dependent condition.

22. The method of claim 20, wherein the disease comprises inflammation or cancer.

23. The method of claim 22, wherein the cancer is selected from breast, kidney, bladder, thyroid, mouth, larynx, esophagus, stomach, colon, ovary, lung, pancreas, skin, liver, prostate and brain cancer.

24. A method of treating a B-Raf kinase-dependent cancer by administering to a patient a compound any one of claims 1-10.

25. The method of claim 24, wherein the cancer is selected from the group consisting of: breast, kidney, bladder, thyroid, mouth, larynx, esophagus, stomach, colon, ovary, lung, pancreas, skin, liver, prostate and brain cancer.

International application No
PCT/US2009/035422

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D491/20 A61K31/519 A61P35/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/109093 A (WYETH CORP [US]; GOPALSAMY ARIAMALA [US]; CISZEWSKI GREGORY M [US]; SH) 27 September 2007 (2007-09-27) paragraphs [0116] - [0143]; claim 1	1-25
X	WO 2004/052315 A (MERCK & CO INC [US]; FRALEY MARK E [US]) 24 June 2004 (2004-06-24) cited in the application claim 1	1-25
A	US 2004/157838 A1 (GRIFFITH DAVID A [US]) 12 August 2004 (2004-08-12)	1-25

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
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"O" document referring to an oral disclosure, use, exhibition or other means
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"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
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 April 2009	08/05/2009

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, Fax: (+31-70) 340-3016	Seelmann, Ingo

Information on patent family members

International application No
PCT/US2009/035422

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007109093 A	27-09-2007	AU 2007227557 A1	27-09-2007
		CA 2643968 A1	27-09-2007
		CN 101405289 A	08-04-2009
		EP 1996594 A2	03-12-2008
WO 2004052315 A	24-06-2004	AU 2003299651 A1	30-06-2004
US 2004157838 A1	12-08-2004	NONE	

DERIVADOS BICÍCLICOS HETEROCÍCLICOS O ESPIROBICÍCLICOS HETEROCÍCLICOS ENLAZADOS, DE PIRAZOLO[1,5-A]PIRIMIDINAS, PROCEDIMIENTOS PARA SU PREPARACIÓN Y USOS DE LOS MISMOS

CAMPO DE LA INVENCIÓN

La presente invención se refiere a nuevas composiciones de pirazolo[1,5-a]pirimidina que son útiles para inhibir el crecimiento anormal de determinados tipos de células. La invención se refiere a determinados derivados bicíclicos heterocíclicos o espirobicíclicos heterocíclicos enlazados de pirazolo[1,5-a]pirimidinas, a sus sales farmacéuticamente aceptables correspondientes y procedimientos para su preparación y uso. Los derivados bicíclicos heterocíclicos o espirobicíclicos heterocíclicos enlazados de pirazolo[1,5-a]pirimidinas inhiben el crecimiento de células tumorales, que contienen formas oncogénicas de Receptores de Tirosina Quinasas, K-Ras y Raf quinasas.

ANTECEDENTES DE LA INVENCIÓN

Raf es una familia multigénica que expresa oncoproteinas quinasas: A-Raf, B-Raf y C-Raf (también conocida como Raf-1) como se describe en las publicaciones de McCubrey y col., en Leukemia, 12(I2), 1903-1929 (1998); en Ikawa y col., en Mol. and Cell. Biol. 8(6), 2651-2654 (1988); en Sithanandarn y col., en Oncogene 5, 1775-1780 (1990); en Konishi y col., en Biochem. and Biophys. Res. Comm. 216(2), 526-534 (1995). Estas tres Raf quinasas están funcionalmente presentes en determinadas células hematopoyéticas humanas y su expresión aberrante puede dar como resultado la anulación de la dependencia de citocina. Sus mecanismos reguladores difieren en que C-Raf y

A-Raf parecen necesitar fosforilación adicional de serina y tirosina dentro de la región N del dominio quinasa para la actividad completa, como describen Mason y col., en EMBO J. 18, 2137-2148 (1999). Además, la B-Raf quinasa parece tener una mayor actividad quinasa basal que cualquiera de las quinasas A-Raf o C-Raf. Estas tres Raf quinasas desempeñan funciones críticas en la transmisión de señales mitógenas y anti-apoptoticas. La B-Raf quinasa está frecuentemente mutada en diversos cánceres humanos, como describen Wan y col., en Cell 116, 855-867 (2004), indicando que las Raf quinasas específicas están asociadas con el cáncer. Las B-Raf quinasas serina/treonina quinasa citoplásmicas y los receptores de tirosina quinasas de la familia del receptor del factor de crecimiento derivado de plaquetas (PDGFR) frecuentemente se encuentran activadas en cáncer por mutaciones de un aminoácido equivalente. Estudios estructurales han proporcionado información importante sobre por qué estas quinasas tan diferentes comparten similares puntos calientes oncogénicos y por qué la región yuxtamembrana de PDGFR es también una diana oncogénica frecuente, como describe Dibb en Nature Reviews, Cancer 4(9), 718-27 (2004).

La B-Raf codifica una quinasa regulada por Ras que media en el crecimiento celular y la activación de la ruta de transformación maligna que controla el crecimiento y la supervivencia de la célula. La activación de una ruta Ras/Raf/MEK da como resultado una cascada de eventos desde la superficie celular hacia el núcleo celular, incidiendo finalmente en la proliferación, apoptosis, diferenciación y transformación celular. La activación de las mutaciones B-Raf se han encontrado en el 66 % de los melanomas malignos y en una menor fracción de otros cánceres incluyendo los colorrectales, según

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notifican Davies H., y col. (2002) *Nature* 417:906 y Rajagopalan H., y col. (2002) Nature 418, 934. Recientemente, se ha observado que B-Raf muta frecuentemente en diversos cánceres humanos, como describen Wan y col. (2004) Cell 116, 855-867. Las mutaciones de B-Raf también explican la activación de la ruta MAP quinasa común en carcinomas pulmonares no microcíticos (CPNM). Determinadas mutaciones B-Raf notificadas hasta ahora en CPNM no son V600 (89 %; $P < 10^{-7}$), sugiriendo fuertemente que las mutaciones de B-Raf en CPNM son cualitativamente diferentes de las de los melanomas. Por lo tanto, puede haber diferencias terapéuticas entre los cánceres de pulmón y los melanomas en respuesta a inhibidores de Raf quinasa, como describen Karasarides y col., en Oncogene 23(37), 6292-6298 (2004) y Bollag y col., en Current Opinion in Invest. Drugs, 4(12), 1436-1441 (2003). Sin embargo, mutaciones B-Raf no comunes en cánceres pulmonares humanos pueden identificar una subserie de tumores sensibles a la terapia diana, como describen Brose y col., en Cancer Research 62(23):6997-7000 (2002) y como se describe en la solicitud de Patente de Estados Unidos Publicación Nº 2005/267060.

Las Raf quinasas también son componentes clave de las rutas de transducción de señal por las que los estímulos extracelulares específicos provocan respuestas celulares exactas en células de mamíferos. Los receptores de la superficie celular activados activan las proteínas Ras/Rap en la cara interna de la membrana plasmática, que a su vez reclutan y activan a proteínas Raf. Las proteínas Raf activadas fosforilan y activan a las proteínas quinasas intracelulares MEK1 y MEK2. A su vez, las MEK activadas catalizan la fosforilación y la activación de la proteína quinasa activada por mitógeno

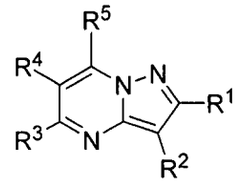
(MAPK) p42/p44. Una diversidad de sustratos citoplásmicos y nucleares de la MAPK activada se asocian directa o indirectamente con la respuesta celular frente al cambio del entorno celular. De hecho, se ha demostrado que las mutaciones B-Raf, predicen sensibilidad frente a la inhibición farmacológica de MEK por inhibidores de pequeña molécula limitando el crecimiento tumoral en xenoinjertos mutantes de B-Raf, como describen Solit y col., en Nature Letters to Editor, 6 de nov., 2005. Se han identificado tres genes distintos en mamíferos que codifican las proteínas Raf; A-Raf, B-Raf y C-Raf (también conocida con Raf-1) y se conocen variantes isofórmicas que se obtienen del corte y empalme diferencial del ARNm. Por lo tanto, es deseable identificar y caracterizar compuestos que inhiban el crecimiento de celular tumorales, que incluyan formas oncogénicas de Receptores de Tirosina Quinasas, K-Ras, A-Raf quinasa, B-Raf quinasa mutante, B-Raf quinasa y C-Raf quinasa.

La Publicación de Patente Internacional Nº WO 2004/052315 describe determinados inhibidores de tirosina quinasa, que incluyen determinadas pirazolo[1,5-a]pirimidinas bicíclicas sustituidas. Sin embargo, se han descrito pirazolo[1,5-a]pirimidinas bicíclicas no enlazadas y se sabe poco acerca de cómo otros sistemas anulares, incluyendo restos enlazados bicíclicos, se fusionan al armazón en anillo de pirazolo[1,5-a]pirimidina influenciando en la relación estructura-actividad (SAR) de las pirazolo[1,5-a]pirimidinas bicíclicas enlazadas. Existe una necesidad de nuevos compuestos que inhiban selectivamente la actividad Raf quinasa y que sean útiles para el tratamiento de trastornos mediados por cualquier Raf quinasa. Las composiciones pirazolo[1,5-a]pirimidinas bicíclicas enlazadas de la presente invención satisfacen esta necesidad insatisfecha y son útiles en el tratamiento de

enfermedades asociadas con Raf quinasas, incluyendo el cáncer y la inflamación en mamíferos.

SUMARIO DE LA INVENCIÓN

Por consiguiente, la invención proporciona un compuesto de fórmula A:



A

y sales farmacéuticamente aceptables del mismo;

en la que

R^1 es un anillo heterocíclico de 5-7 miembros o un anillo heteroarilo, comprendiendo dicho anillo 1-3 heteroátomos seleccionados entre N, O o S, y estando dicho anillo opcionalmente sustituido con uno a cuatro sustituyentes seleccionados entre -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$, $-R^8NR^7C(O)NR^7R^7$, $-YR^8R^{10}$, $-YR^8NR^7R^7$ y $-YR^{10}$;

R^2 se selecciona entre un anillo arilo, un anillo arilo bicíclico de 9-14 miembros, un anillo heteroarilo de 5-7 miembros y un anillo heteroarilo de 9-14 miembros, comprendiendo dicho anillo heteroarilo 1-3 heteroátomos seleccionados entre N, O y S, estando dicho anillo opcionalmente sustituido con uno a cuatro sustituyentes seleccionados entre -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, -

OR^7, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$, $-R^8NR^7C(O)NR^7R^7$, $-OPO(OR^7)_2$, $-YR^8R^{10}$, $-YR^8NR^7R^7$ y $-YR^{10}$;

cada uno de R^3, R^4 y R^5 se selecciona independientemente entre R^6 unido a carbono, –X-W-R^6, H, J, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-NR^7C(O)R^7$, -CN, alquilo de 1-6 átomos de carbono, alquilo ramificado de 1-8 átomos de carbono, anillo cicloalquilo de 3-10 carbonos, anillo arilo, anillo heterocíclico de 5-7 miembros y anillo heteroarilo de 5-10 miembros, comprendiendo dicho anillo heterocíclico o anillo heteroarilo 1-3 heteroátomos seleccionados entre N, O y S, estando dicho alquilo de 1-6 átomos de carbono, alquilo ramificado de 1-8 átomos de carbono, anillo arilo, anillo heterocíclico de 5-7 miembros y anillo heteroarilo de 5-10 miembros opcionalmente sustituidos con uno a cuatro sustituyentes seleccionados entre -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$ $-R^8NR^7C(O)NR^7R^7$ e YR^{10}, en los que al menos uno de R^3, R^4 y R^5 comprende R^6;

R^6 es un anillo heterocíclico, bicíclico, puenteado, o un anillo heterocíclico, espiro, bicíclico, de 6-14 miembros, estando dicho anillo opcionalmente

95

sustituido con uno o más sustituyentes seleccionados entre -J, -NO_2, -CN, -N_3, -CHO, -CF_3, -OCF_3, -R^7, -OR^7, -$S(O)_mR^7$, -NR^7R^7, -$NR^7S(O)_mR^7$, -OR^9OR^7, -$OR^9NR^7R^7$, -$N(R^7)R^9OR^7$, -$N(R^7)R^9NR^7R^7$, -$NR^7C(O)R^7$, -$C(O)R^7$, -$C(O)OR^7$, -$C(O)NR^7R^7$, -$OC(O)R^7$, -$OC(O)OR^7$, -$OC(O)NR^7R^7$, $NR^7C(O)R^7$, -$NR^7C(O)OR^7$, -$NR^7C(O)NR^7R^7$, -R^8OR^7, -$R^8NR^7R^7$, -$R^8S(O)_mR^7$, -$R^8C(O)R^7$, -$R^8C(O)OR^7$, -$R^8C(O)NR^7R^7$, -$R^8OC(O)R^7$, -$R^8OC(O)OR^7$, -$R^8OC(O)NR^7R^7$, -$R^8NR^7C(O)R^7$, -$R^8NR^7C(O)OR^7$ o -$R^8NR^7C(O)NR^7R^7$ e YR^{10};

R^7 es H o se selecciona independientemente entre alquilo de 1-6 átomos de carbono, alquilo ramificado de 1-8 átomos de carbono, alquenilo de 2-6 átomos de carbono, alquinilo de 2-6 átomos de carbono, anillo arilo y un anillo heteroarilo de 5-10 miembros, opcionalmente sustituido con uno a cuatro sustituyentes seleccionados entre -J, -NO_2, -CN, -N_3, -CHO, -CF_3, -OCF_3, -R, -OR, -$S(O)_mR$, -NRR, -$NRS(O)_mR$, -OR^9OR, -OR^9NRR, -$N(R)R^9OR$, -$N(R)R^9NRR$, -NRC(O)R, -C(O)R, -C(O)OR, -C(O)NRR, -OC(O)R, -OC(O)OR, -OC(O)NRR, NRC(O)R, -NRC(O)OR, -NRC(O)NRR, -R^8OR, -R^8NRR, -$R^8S(O)_mR$, -$R^8C(O)R$, -$R^8C(O)OR$, -$R^8C(O)NRR$, -$R^8OC(O)R$, -$R^8OC(O)OR$, -$R^8OC(O)NRR$, -$R^8NRC(O)R$, -$R^8NRC(O)OR$, -$R^8NRC(O)NRR$ y ZR^{10}, en los que R se selecciona entre alquilo de 1-6 átomos de carbono, alquilo ramificado de 1-8 átomos de carbono, alquenilo de 2-6 átomos de carbono, alquinilo de 2-6 átomos de carbono, cicloalquilo de 3-10 átomos de carbono, arilo de 6-10 átomos de carbono y heteroarilo de 6-10 átomos, comprendiendo el heteroarilo 1-3 heteroátomos seleccionados entre N, O y S;

R^8 es un grupo divalente seleccionado independientemente entre alquilo de 1-6 átomos de carbono, alquenilo de 2-6 átomos de carbono, alquinilo de 2-6 átomos de carbono, arilo, heteroarilo, cicloalquilo y cicloheteroalquilo;

R^9 es independientemente un grupo alquilo divalente de 2-6 átomos de carbono;

R^{10} se selecciona independientemente entre anillo cicloalquilo de 3-10 carbonos, anillo bicicloalquilo de 3-10 carbonos, anillo arilo, anillo heterocíclico, anillo heteroarilo y un anillo heteroarilo condensado con uno a tres anillos arilo o heteroarilo, comprendiendo cada anillo heterocíclico o anillo heteroarilo 1-3 heteroátomos seleccionados entre N, O y S, cada uno opcionalmente sustituido con uno a cuatro sustituyentes seleccionados entre –H, -arilo, $-CH_2$-arilo, -NH-arilo, -O-arilo, $-S(O)_m$-arilo, -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$-, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $-NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$ y $–R^8NR^7C(O)NR^7R^7$;

J es flúor, cloro, bromo o yodo;

m es un número entero de 0-2;

Y es un grupo divalente seleccionado independientemente entre un enlace, alquilo de 1-6 átomos de carbono, alquenilo de 2-6 átomos de carbono, alquinilo de 2-6 átomos de carbono, O y $-NR^7$;

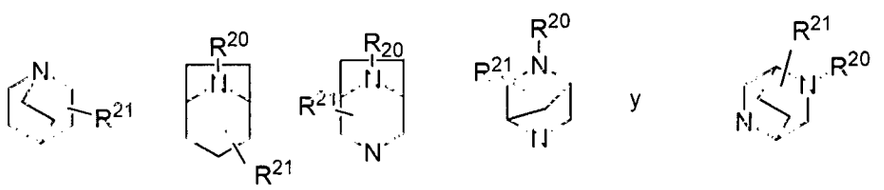
X se selecciona entre un grupo alquilo divalente de 1-6 átomos de carbono, alquenilo de 2-6 átomos de carbono, alquinilo de 2-6 átomos de carbono, anillo cicloalquilo de 3-10 carbonos, anillo bicicloalquilo de 3-10 carbonos, anillo arilo, anillo heterocíclico y un anillo heteroarilo, comprendiendo cada anillo heterocíclico o anillo heteroarilo 1-3 heteroátomos seleccionados entre N, O o

S; opcionalmente sustituido con uno a cuatro sustituyentes seleccionados entre –H, -arilo, -CH_2-arilo, -NH-arilo, -O-arilo, -$S(O)_m$-arilo, -J, -NO_2, -CN, -N_3, -CHO, -CF_3, -OCF_3, -R^7, -OR^7, -$S(O)_mR^7$, -NR^7R^7, -$NR^7S(O)_mR^7$, -OR^9OR^7, -$OR^9NR^7R^7$, -$N(R^7)R^9OR^7$, -$N(R^7)R^9NR^7R^7$, -$NR^7C(O)R^7$, -$C(O)R^7$, -$C(O)OR^7$, -$C(O)NR^7R^7$, -$OC(O)R^7$-, -$OC(O)OR^7$, -$OC(O)NR^7R^7$, -$NR^7C(O)R^7$, -$NR^7C(O)OR^7$, -$NR^7C(O)NR^7R^7$, -R^8OR^7, $R^8NR^7R^7$, -$R^8S(O)_mR^7$, -$R^8C(O)R^7$, -$R^8C(O)OR^7$, -$R^8C(O)NR^7R^7$, -$R^8C(O)R^7$, -$R^8C(O)OR^7$, -$R^8C(O)NR^7R^7$, -$R^8OC(O)R^7$, -$R^8OC(O)OR^7$, -$R^8OC(O)NR^7R^7$, -$R^8NR^7C(O)R^7$, -$R^8NR^7C(O)OR^7$ y –$R^8NR^7C(O)NR^7R^7$;

W se selecciona entre un enlace, Z, -OZ-, -ZO-, -$S(O)_mZ$-, -$S(O)_2NR^7Z$-, -$NR^7S(O)_mZ$ -, -NR^7Z-, -ZNR^7-, -C(O)Z-; -C(O)OZ-, -$C(O)NR^7Z$-, -$NR^7C(O)Z$-, -$NR^7C(O)NR^7Z$-, -OC(O)Z-, -$NR^7C(O)OZ$- y -OC(O) NR^7Z-; y

Z es un enlace o un alquilo divalente de 1-6 átomos de carbono.

La presente invención también proporciona un compuesto de fórmula A y sales farmacéuticamente aceptables del mismo; en la que el anillo heterocíclico, bicíclico, puenteado se selecciona entre:



opcionalmente sustituidos en el nitrógeno con R^{20} y opcionalmente sustituidos en uno o más carbonos con R^{21}, en los que

R^{20} se selecciona entre H, -C(O)OR^7, -C(O)NR^7R^7, -C(O)R^7, -$S(O)_mR^7$, alquilo de 1-6 átomos de carbono, alquilo ramificado de 1-8 átomos de carbono, anillo cicloalquilo de 3-10 carbonos, anillo arilo, anillo heterocíclico de 5-7 miembros y anillo heteroarilo de 5-10 miembros, comprendiendo cada anillo

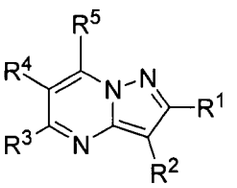
heterocíclico o anillo heteroarilo 1-3 heteroátomos seleccionados entre N, O o S, cada uno del alquilo de 1-6 átomos de carbono, alquilo ramificado de 1-8 átomos de carbono, anillo arilo, anillo heterocíclico y anillo heteroarilo opcionalmente sustituido con uno a cuatro sustituyentes seleccionados entre -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$ o $-R^8NR^7C(O)NR^7R^7$ e YR^{10}; y

R^{21} se selecciona entre H, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$ o $-R^8NR^7C(O)NR^7R^7$ e YR^{10}; en los que J, Y, m y R^{7-10} se han definido anteriormente.

La presente invención también proporciona una composición farmacéutica que comprende un compuesto de fórmula A o una sal farmacéuticamente aceptable del mismo y un vehículo farmacéuticamente aceptable. La presente invención también proporciona composiciones farmacéuticas que comprenden compuestos de fórmula A o una sal farmacéuticamente aceptable de los mismos junto con otros compuestos

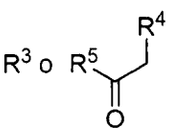
farmacéuticos o agentes quimoterapéuticos inhibidores de quinasas, y un vehículo farmacéuticamente aceptable.

La presente invención proporciona un procedimiento para preparar un compuesto de fórmula A:



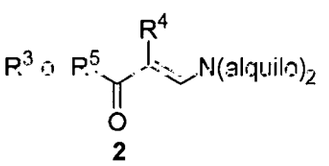
A

y sales farmacéuticamente aceptables del mismo; que comprende las etapas de: (a) hacer reaccionar una cetona sustituida de fórmula 1



1

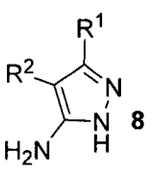
con un acetal de N,N-dialquilformamida o un acetal de N,N-dialquilacetamida, para proporcionar un compuesto de enaminona de fórmula 2



2

; y

(b) hacer reaccionar el compuesto de fórmula 2 con un 3-aminopirazol sustituido de fórmula 8,

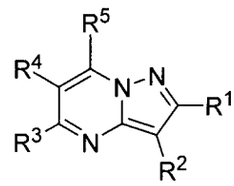


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para proporcionar un compuesto de fórmula A, en la que R^{1-10}, J, m, W, X, Y y

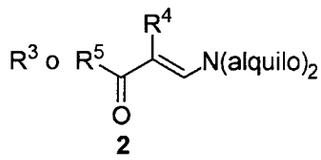
Z son como se han definido anteriormente.

La presente invención también proporciona un procedimiento para preparar un compuesto de fórmula A:



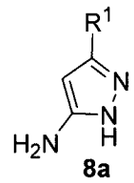
A

y sales farmacéuticamente aceptables del mismo; que comprende las etapas de: (a) hacer reaccionar un compuesto de enaminona de fórmula 2



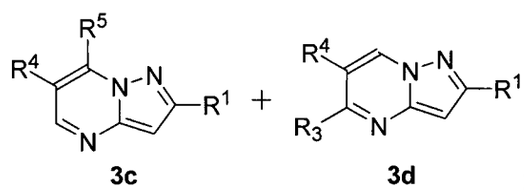
2

con un aminopirazol de fórmula 8a



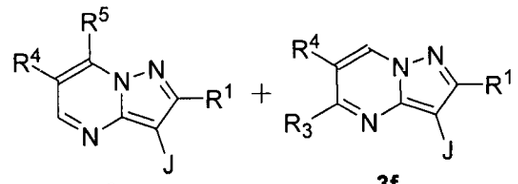
8a

para proporcionar compuestos de fórmula 3c y 3d



3c **3d** ;

(b) halogenar uno o los dos compuestos de fórmula 3c y 3d para proporcionar uno o los dos compuestos de fórmula 3e y 3f



3e **3f** ; y

(c) someter uno o los dos compuestos de fórmula 3e y 3f a un acoplamiento de Suzuki catalizado con paladio usando ácidos aril o heteroarilborónicos o ésteres boronato correspondientes para proporcionar uno o los dos compuestos de la invención.

La presente invención proporciona etapas independientes adicionales de separación de compuestos de fórmula 3c y 3d antes de la etapa de halogenación, separación de compuestos de fórmula 3e y 3f antes de la etapa de acoplamiento de Suzuki catalizado con paladio y separación de compuestos de fórmula A después de la etapa de acoplamiento de Suzuki catalizado con paladio, respectivamente.

La invención también proporciona procedimientos para inhibir la actividad Raf quinasa en una célula que comprenden poner en contacto una célula con un compuesto de fórmula A, por lo que el compuesto inhibe la actividad de una Raf quinasa seleccionada entre A-Raf quinasa, B-Raf quinasa, B-Raf quinasa mutante y C-Raf quinasa.

La presente invención también proporciona un procedimiento para tratar una afección dependiente de A-Raf quinasa, B-Raf quinasa, B-Raf quinasa mutante o C-Raf quinasa, comprendiendo dicha afección cáncer o inflamación, mediante la administración a un paciente de una cantidad farmacéuticamente eficaz de un compuesto de fórmula A.

La presente invención proporciona procedimientos de tratamiento de

enfermedades de mamíferos asociadas con una Raf quinasa seleccionada entre A-Raf quinasa, B-Raf quinasa, B-Raf quinasa mutante y C-Raf quinasa, mediante la administración a un paciente de un compuesto de fórmula A.

La presente invención proporciona procedimientos de tratamiento de un cáncer asociado con Raf quinasa en el que el cáncer se selecciona entre cáncer de mama, riñón, vejiga, tiroides, boca, laringe, esófago, estómago, colon, ovario, pulmón, páncreas, piel, hígado, próstata y cerebro.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Definiciones

Las siguientes definiciones se usan en relación a pirazolo[1,5-a]pirimidinas de la invención. El término "alquilo" se refiere a grupos alifáticos saturados de 1 a 8 átomos de carbono, incluyendo grupos alquilo de cadena lineal y grupos alquilo de cadena ramificada. En una realización, un alquilo de cadena lineal o de cadena ramificada tiene 6 o menos átomos de carbono en su cadena principal. El término "alquilo" puede usarse solo o como parte de un nombre químico, tal como "alquilamina". Los términos "alquenilo" y "alquinilo" se refieren a grupos alifáticos insaturados análogos en longitud y posible sustitución a los alquilos descritos anteriormente, pero que contienen al menos un doble o triple enlace carbono-carbono, respectivamente. El término "cicloalquilo" se refiere a anillos cicloalifáticos saturados o parcialmente insaturados de 3 a 10 átomos de carbono, incluyendo anillos cicloalquilo sin ramificar y anillos cicloalquilo ramificados. A menos que se defina otra cosa, el término "arilo", como se usa en el presente documento, se refiere a un resto carbocíclico aromático, por ejemplo, que tiene 6-20 átomos de carbono, incluyendo 6-10 átomos de carbono, que puede ser un solo anillo (monocíclico) o múltiples anillos

condensados juntos o enlazados covalentemente, en el que al menos uno de los anillos es aromático. Cualquier posición del anillo adecuada del resto arilo puede estar enlazada covalentemente a la estructura química definida. Los ejemplos de arilo incluyen fenilo y naftilo. El grupo arilo puede estar opcionalmente sustituido. Además de otros sustituyentes opcionales, el grupo arilo puede estar sustituido con un sustituyente oxo, lo que significa que uno de los átomos de carbono del anillo es parte de un grupo carbonilo.

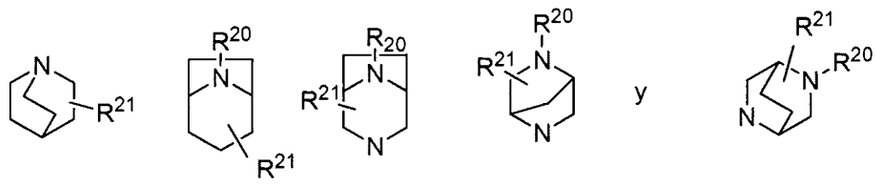
A menos que se defina otra cosa, el término "heteroarilo", como se usa en el presente documento, significa un sistema de anillos heterocíclico, aromático, por ejemplo, que tiene 5-20 átomos por anillo, que puede ser un solo anillo o múltiples anillos condensados juntos o enlazados covalentemente, en el que al menos uno de los anillos es aromático. Los anillos pueden contener uno o más heteroátomos, por ejemplo de 1 a 3 heteroátomos, seleccionados entre nitrógeno, oxígeno o azufre, en los que el átomo o átomos de nitrógeno o azufre están opcionalmente oxidados, o el átomo o átomos de nitrógeno están opcionalmente cuaternizados. Cualquier posición sustituible del anillo del resto heteroarilo puede estar enlazada covalentemente a la estructura química definida. Los ejemplos adecuados de heteroarilo incluyen 3-piridinilo, 4-piridinilo, 1-*H*-indazol-4-ilo o indol-1-ilo. El grupo heteroarilo puede estar opcionalmente sustituido. Además de otros sustituyentes opcionales, el grupo heteroarilo puede estar sustituido con un sustituyente oxo, lo que significa que uno de los átomos de carbono del anillo es parte de un grupo carbonilo.

Los términos "heterocíclico", "heterociclo" o "heterociclilo", como se usan en el presente documento, pueden usarse indistintamente para referirse a un sistema de anillos heterocíclico, monocíclico o multicíclico, saturado o

parcialmente insaturado, estable, incluyendo un sistema de anillos espirocíclico y heterocíclico puenteado, por ejemplo, que tiene de 5 a 7 miembros por anillo. Los miembros de anillos heterocíclicos son átomos de carbono y uno o más heteroátomos, por ejemplo de 1 a 3 heteroátomos, seleccionados entre átomos de nitrógeno, oxígeno y azufre, en los que el átomo o átomos de nitrógeno o azufre están opcionalmente oxidados, o el átomo o átomos de nitrógeno están opcionalmente cuaternizados. El grupo heterocíclico, heterociclo o heterociclilo puede estar opcionalmente sustituido. Además de otros sustituyentes opcionales, el grupo heterocíclico, heterociclo o heterociclilo puede estar sustituido con un sustituyente oxo, lo que significa que uno de los átomos de carbono del anillo es parte de un grupo carbonilo. El grupo heterocíclico, heterociclo o heterociclilo puede contener uno o más anillos condensados.

El término "espiroheterocíclico" se refiere a al menos un sistema de anillos heterocíclico unido a otro sistema de anillos en el mismo átomo.

El término "bicíclico, puenteado" se refiere a un sistema de anillos heterocíclico condensado con otro sistema de anillos en átomos no adyacentes, donde al menos uno de los sistemas de anillos es un anillo heterocíclico. Ejemplos adecuados de sistemas de anillos "bicíclicos, puenteados" se proporcionan en la sección de Ejemplos de la memoria descriptiva e incluyen, pero sin limitación:



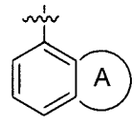
opcionalmente sustituidos en el nitrógeno con R^{20} y opcionalmente sustituidos

en uno o más carbonos con R^{21}, en los que

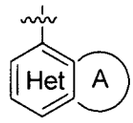
R^{20} se selecciona entre H, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-C(O)R^7$, $-S(O)_mR^7$, alquilo de 1-6 átomos de carbono, alquilo ramificado de 1-8 átomos de carbono, anillo cicloalquilo de 3-10 carbonos, anillo arilo, anillo heterocíclico de 5-7 miembros y anillo heteroarilo de 5-10 miembros, comprendiendo cada anillo heterocíclico o anillo heteroarilo 1-3 heteroátomos seleccionados entre N, O o S, cada uno del alquilo de 1-6 átomos de carbono, alquilo ramificado de 1-8 átomos de carbono, anillo arilo, anillo heterocíclico y anillo heteroarilo opcionalmente sustituido con uno a cuatro sustituyentes seleccionados entre -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$ o $-R^8NR^7C(O)NR^7R^7$ e YR^{10}; y

R^{21} se selecciona entre H, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$ o $-R^8NR^7C(O)NR^7R^7$ e YR^{10}; en los que R^{7-10} se han definido anteriormente.

La expresión "anillo arilo bicíclico o anillo heteroarilo" se refiere a una estructura de anillo de fórmula



o

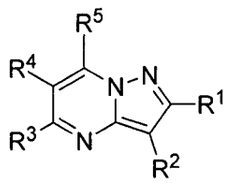


El símbolo  se refiere a un anillo heteroarilo de 5-7 miembros que comprende 1-3 heteroátomos seleccionados entre N, O o S. El término "Het" se refiere a un anillo heteroarilo de 6 miembros que contiene 1-2 átomos de nitrógeno. Cada uno del anillo arilo bicíclico o anillo heteroarilo bicíclico está opcionalmente sustituido con sustituyentes seleccionados entre -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$, $-R^8NR^7C(O)NR^7R^7$, $-YR^8R^{10}$, $-YR^8NR^7R^7$ y $-YR^{10}$.

Como se usa en el presente documento, la expresión "vehículo farmacéuticamente aceptable" incluye diluyentes y excipientes farmacéuticamente aceptables.

Como se usan en el presente documento, los términos "individuo", "sujeto" o "paciente", usados indistintamente, se refieren a cualquier animal, incluyendo mamíferos, preferentemente ratones, ratas, otros roedores, conejos, perros, gatos, cerdos, ganado, ovejas, caballos o primates, y más preferentemente seres humanos.

De acuerdo con una realización a modo de ejemplo, la invención proporciona un compuesto de fórmula A:



A

y sales farmacéuticamente aceptables del mismo;

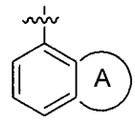
en la que R^1-R^{10}, J, m, W, X, Y y Z son como se han definido anteriormente.

Los ejemplos adecuados de R^1 incluyen, pero sin limitación, tienilo, furilo, indolilo, pirrolilo, tiofenilo, benzofurilo, benzotiofenilo, quinolilo, isoquinolilo, imidazolilo, tiazolilo, oxazolilo, piridinilo, pirrolidilo, oxolanilo, tiolanilo, piperidinilo, piperazinilo, tiazolilo, triazolilo, pirazolilo, pirazinilo, piridazinilo, pirimidinilo y morfolinilo. El anillo heterocíclico o anillo heteroarilo puede estar sustituido para la estructura del anillo de pirazolo[1,5-a]pirimidina en cualquier posición aceptable. De acuerdo con una realización, R^1 es 4-piridinilo o 4-morfolinilo, opcionalmente sustituido con uno a cuatro sustituyentes seleccionados entre -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$, $-R^8NR^7C(O)NR^7R^7$, $-OPO(OR^7)_2$, $-YR^8R^{10}$, $-YR^8NR^7R^7$ y $-YR^{10}$.

Los ejemplos adecuados de R^2 incluyen, pero sin limitación, fenilo sustituido con halógeno, fenilo sustituido con alquil C_1-C_6-sulfonamido, fenilo

sustituido con carbamato, fenilcarbamato sustituido con alcoxi C_1-C_6, benzonitrilo, benzonitrilo sustituido con hidroxilo, benzonitrilo sustituido con alcoxi C_1-C_6, hidroxifenilo (fenol), hidroxifenilo (fenol) sustituido con alquilo C_1-C_6, hidroxifenilo (fenol) sustituido con halógeno, alcoxi C_1-C_6-fenilo, alcoxi C_1-C_6-fenilo sustituido con halógeno, hidroxipiridinilo, alcoxi C_1-C_6-piridinilo, aminofenilo (anilina), aminofenilo (anilina) sustituido con halógeno, aminofenilo (anilina) sustituido con hidroxilo, fenilo sustituido con formamida, fenilformamida sustituida con hidroxilo, fenilformamida sustituida con alcoxi C_1-C_6, aminofenilo (anilina) sustituido con alcoxi C_1-C_6, fenilo sustituido con urea, benzamido, benzamido sustituido con alquilo C_1-C_6, benzamido sustituido con halógeno, indazolilo, indazolilo sustituido con alquilo C_1-C_6, indazolilo sustituido con halógeno, haloindazolilo sustituido con alquilo C_1-C_6, perfluoroindazolilo sustituido con alquilo C_1-C_6, benzamidazolilo, benzamidazolilo sustituido con halógeno, oxo-dihidro-benzamidazolilo, dihidro-pirrolodinilo, dihidro-pirrolodinilo sustituido, dihidro-indolilo, dihidro-indolilo sustituido y fenilo sustituido con oxadiazolilo. Otros ejemplos adecuados de R^2 incluyen, pero sin limitación, indolilo, benzotriazolilo, oxindolilo, benzotiazolonilo y benzooxazolonilo. El anillo arilo monocíclico y el anillo heteroarilo bicíclico pueden estar sustituidos para la estructura del anillo de pirazolo[1,5-a]pirimidina en cualquier posición aceptable.

De acuerdo con una realización, R^2 es un anillo arilo o un anillo arilo bicíclico de fórmula



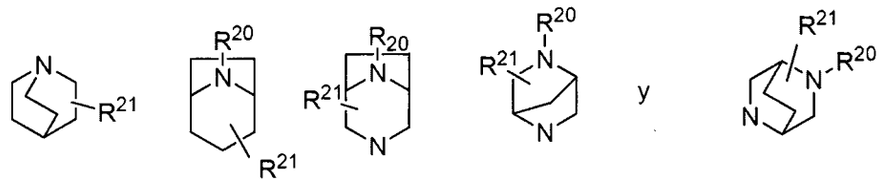
en la que (A) se refiere a un anillo heteroarilo de 5-7 miembros que comprende 1-3 heteroátomos seleccionados entre N, O y S, estando dicho anillo opcionalmente sustituido con uno a cuatro sustituyentes seleccionados entre -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$, $-R^8NR^7C(O)NR^7R^7$, $-YR^8R^{10}$, $-YR^8NR^7R^7$ y $-YR^{10}$.

De acuerdo con una realización separada, R^2 es un anillo fenilo o un anillo indazolilo, opcionalmente sustituido con uno a cuatro sustituyentes seleccionados entre -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$, $-R^8NR^7C(O)NR^7R^7$, $-YR^8R^{10}$, $-YR^8NR^7R^7$ y $-YR^{10}$.

De acuerdo con una realización separada, R^2 se selecciona entre fenilo sustituido con halógeno, fenilo sustituido con alquil C_1-C_6-sulfonamido, fenilo sustituido con carbamato, fenilcarbamato sustituido con alcoxi C_1-C_6, benzonitrilo, benzonitrilo sustituido con hidroxilo, benzonitrilo sustituido con alcoxi C_1-C_6, hidroxifenilo, hidroxifenilo sustituido con alquilo C_1-C_6, hidroxifenilo sustituido con halógeno, alcoxi C_1-C_6-fenilo, alcoxi C_1-C_6-fenilo sustituido con

halógeno, hidroxipiridinilo, alcoxi C_1-C_6-piridinilo, aminofenilo, aminofenilo sustituido con halógeno, aminofenilo sustituido con hidroxilo, fenilo sustituido con formamida, fenilformamida sustituida con hidroxilo, fenilformamida sustituida con alcoxi C_1-C_6, aminofenilo sustituido con alcoxi C_1-C_6, fenilo sustituido con urea, benzamido, benzamido sustituido con alquilo C_1-C_6, benzamido sustituido con halógeno, indazolilo, indazolilo sustituido con alquilo C_1-C_6, indazolilo sustituido con halógeno, haloindazolilo sustituido con alquilo C_1-C_6, perfluoroindazolilo sustituido con alquilo C_1-C_6, benzamidazolilo, benzamidazolilo sustituido con halógeno, dihidro-pirrolodinilo, dihidro-pirrolodinilo sustituido, dihidro-indolilo, dihidro-indolilo sustituido y fenilo sustituido con oxadiazolilo.

Los ejemplos adecuados de R^6 incluyen, pero sin limitación, anillos heterocíclicos bicíclicos, puenteados, seleccionados entre:



opcionalmente sustituidos en el nitrógeno con R^{20} y opcionalmente sustituidos en uno o más carbonos con R^{21}, en los que

R^{20} se selecciona entre H, -C(O)OR^7, -C(O)NR^7R^7, -C(O)R^7, -C(O)R^{10}, -$S(O)_mR^7$, alquilo de 1-6 átomos de carbono, alquilo ramificado de 1-8 átomos de carbono, anillo cicloalquilo de 3-10 carbonos, anillo arilo, anillo heterocíclico de 5-7 miembros y anillo heteroarilo de 5-10 miembros, comprendiendo cada anillo heterocíclico o anillo heteroarilo 1-3 heteroátomos seleccionados entre N, O o S, cada uno del alquilo de 1-6 átomos de carbono, alquilo ramificado de 1-8 átomos de carbono, anillo arilo, anillo heterocíclico y anillo heteroarilo

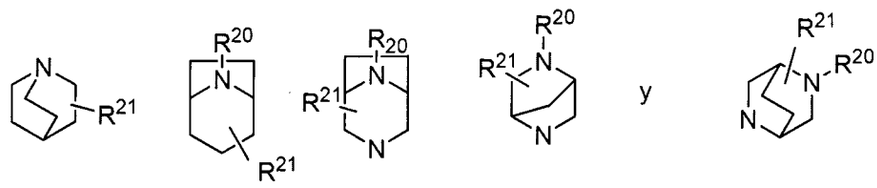
opcionalmente sustituido con uno a cuatro sustituyentes seleccionados entre -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$ o $-R^8NR^7C(O)NR^7R^7$ e YR^{10}; y

R^{21} se selecciona entre H, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$ o $-R^8NR^7C(O)NR^7R^7$ e YR^{10}; en los que R^{7-10} se han definido anteriormente.

R^6 puede estar unido directamente, a través de un carbono (denominado unido a carbono), a la estructura de anillo de pirazolo[1,5-a]pirimidina en una diversidad de posiciones aceptables. R^6 también puede estar unido directamente a la estructura de anillo de pirazolo[1,5-a]pirimidina en una diversidad de posiciones aceptables, que se juntan usando grupos espaciadores definidos por X-W-R^6. De acuerdo con una realización, al menos uno de R^3, R^4 y R^5 se selecciona independientemente entre R^6 unido a carbono. De acuerdo con una realización separada, al menos uno de R^3, R^4 y R^5 se selecciona independientemente entre X-W-R^6.

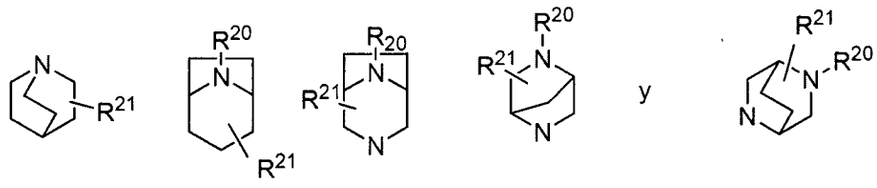
De acuerdo con una realización, R^5 es R^6 unido a carbono y comprende

un anillo heterocíclico, bicíclico, puenteado, seleccionado entre:



opcionalmente sustituidos en el nitrógeno con R^{20} y opcionalmente sustituidos en uno o más carbonos con R^{21}.

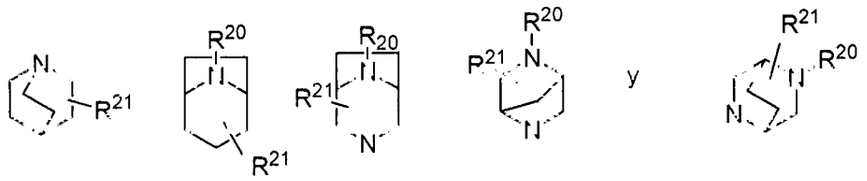
De acuerdo con una realización separada, R^5 es X-W-R^6, en el que R^6 comprende un anillo arilo o un anillo heteroarilo sustituido con un anillo heterocíclico, bicíclico, puenteado, seleccionado entre:



opcionalmente sustituidos en el nitrógeno con R^{20} y opcionalmente sustituidos en uno o más carbonos con R^{21}, X es arilo o heteroarilo, cada uno opcionalmente sustituido adicionalmente con uno a cuatro sustituyentes seleccionados entre -J, -NO_2, -CN, -N_3, -CHO, -CF_3, -OCF_3, -R^7, -OR^7, -$S(O)_mR^7$, -NR^7R^7, -$NR^7S(O)_mR^7$, -OR^9OR^7, -$OR^9NR^7R^7$, -$N(R^7)R^9OR^7$, -$N(R^7)R^9NR^7R^7$, -$NR^7C(O)R^7$, -$C(O)R^7$, -$C(O)OR^7$, -$C(O)NR^7R^7$, -$OC(O)R^7$, -$OC(O)OR^7$, -$OC(O)NR^7R^7$, $NR^7C(O)R^7$, -$NR^7C(O)OR^7$, -$NR^7C(O)NR^7R^7$, -R^8OR^7, -$R^8NR^7R^7$, -$R^8S(O)_mR^7$, -$R^8C(O)R^7$, -$R^8C(O)OR^7$, -$R^8C(O)NR^7R^7$, -$R^8OC(O)R^7$, -$R^8OC(O)OR^7$, -$R^8OC(O)NR^7R^7$, -$R^8NR^7C(O)R^7$, -$R^8NR^7C(O)OR^7$ o -$R^8NR^7C(O)NR^7R^7$ e YR^{10} y W es un enlace.

De acuerdo con una realización separada, R^6 es R^5 es X-W-R^6, en el que R^6 comprende un anillo heterocíclico, bicíclico, puenteado, seleccionado

entre:



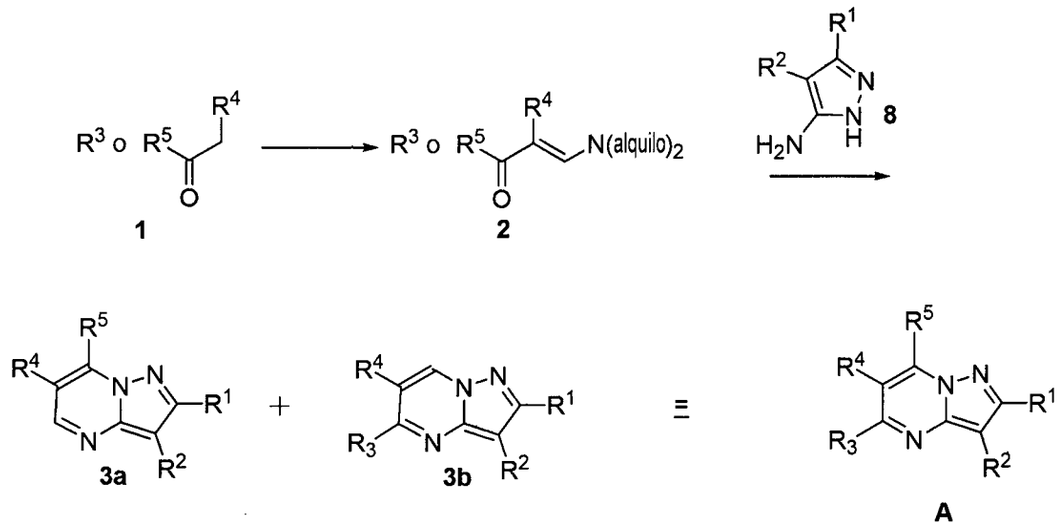
opcionalmente sustituidos en el nitrógeno con R^{20} y opcionalmente sustituidos en uno o más carbonos con R^{21}, X es arilo o heteroarilo, cada uno opcionalmente sustituido adicionalmente con uno a cuatro sustituyentes seleccionados entre -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$ o $-R^8NR^7C(O)NR^7R^7$ e YR^{10} y W es ZN R^7 o NR^7Z.

De acuerdo con una realización separada, R^6 es un anillo espiroheterocíclico bicíclico que comprende 1-3 heteroátomos seleccionados entre N, O y S, opcionalmente sustituido con uno a cuatro sustituyentes seleccionados entre -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$ o $-R^8NR^7C(O)NR^7R^7$ e YR^{10}.

Los compuestos de la presente invención pueden prepararse a partir de:

(a) materiales de partida disponibles en el mercado (b) materiales de partida conocidos que pueden prepararse como se describe en procedimientos bibliográficos o (c) nuevos intermedios descritos en los esquemas y procedimientos experimentales del presente documento. Las reacciones se realizan en un disolvente apropiado para los reactivos y materiales usados y adecuado para la transformación que se efectúe. Se entiende por los expertos en la materia de la síntesis orgánica que las diversas funcionalidades presentes en la molécula deben ser coherentes con la transformación química propuesta. Puede ser necesario un criterio para el orden de las etapas sintéticas.

Los compuestos de la presente invención pueden prepararse como se ilustra en los ejemplos y en los siguientes Esquemas de reacción 1 a 5:



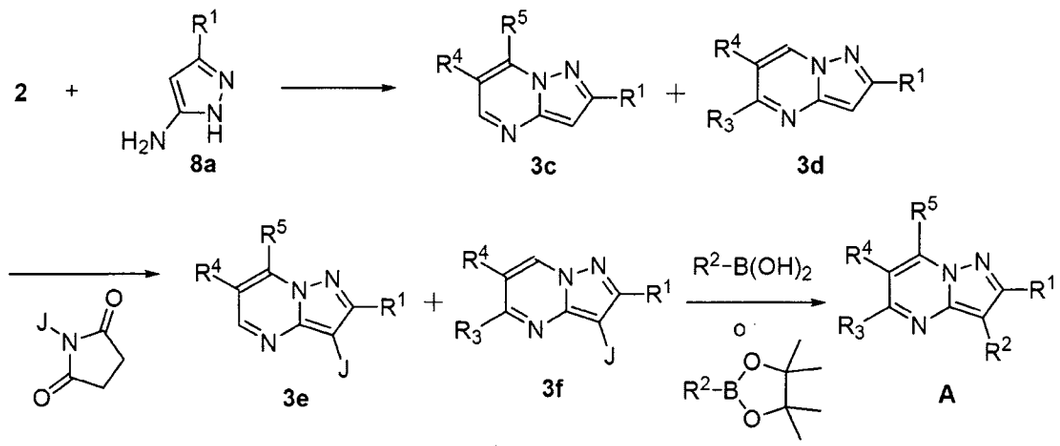
Esquema 1

Con respecto al Esquema 1, la reacción de una cetona de fórmula **1**, opcionalmente sustituida con R^3, R^4 y R^5 con un acetal de N,N-dialquilformamida o un acetal de N,N-dialquilacetamida, realizada en un disolvente inerte o sin disolvente, proporciona una enaminona, concretamente

una 3-dialquilamino-2-propen-1-ona, de fórmula **2.** La reacción del 3-aminopirazol sustituido de fórmula **8**, en la que R^1 y R^2 se han definido anteriormente o son hidrógeno, con una 3-dialquilamino-2-propen-1-ona apropiadamente sustituida en un ácido débil, tal como ácido acético glacial, o en un disolvente inerte, tal como tolueno, acetonitrilo o dimetoxietano, a la temperatura de reflujo durante varias horas, o sin disolvente a 50-150 ºC, proporciona los compuestos deseados de fórmula **3a** y **3b**. En algunos casos, la modificación química de compuestos de fórmula **3a** y **3b**, de acuerdo con procedimientos conocidos por los expertos en la materia de la síntesis orgánica, puede realizarse por los expertos en la materia para proporcionar compuestos adicionales de la invención. Por ejemplo, cuando cualquiera de R^3, R^4 o R^5 en los compuestos de fórmula **3a** y **3b** es un halógeno, o un grupo haloarilo, o similar, las reacciones de acoplamiento de Suzuki o Buchwald catalizadas con paladio proporcionan compuestos adicionales de la invención. Además, cuando cualquiera de R^3, R^4 o R^5 en los compuestos de fórmula **3a** y **3b** es un resto 2-bromopiridilo, la reacción de dicho compuesto a temperatura elevada, de 50-150 ºC con una amina, alcohol o tiol, en DMSO u otro disolvente aprótico polar, en presencia de una base de amina terciaria, tal como base de Hunig, o hidruro sódico o similar, proporciona compuestos de la invención.

Los compuestos de la invención también pueden sintetizarse de acuerdo con la ruta mostrada en el Esquema 2. Por lo tanto, la enaminona de fórmula **2** puede reaccionar con el compuesto de aminopirazol de fórmula **8a** en un ácido débil, tal como ácido acético glacial, o en un disolvente inerte, tal como tolueno, acetonitrilo o dimetoxietano, a la temperatura de reflujo durante varias horas, o

sin disolvente a 50-150 °C, para proporcionar uno o los dos compuestos de fórmula **3c** y **3d**. Los compuestos de fórmula **3c** y **3d** pueden separarse, cromatográficamente o por recristalización, y halogenarse para proporcionar los derivados de halo-pirazol correspondientes, usando *N*-halosuccininmidas de la temperatura ambiente a 50 °C en disolventes de hidrocarburos clorados, para dar uno o los dos compuestos de fórmula **3e** o **3f**. Como alternativa, la mezcla de compuestos de fórmula **3c** y **3d** puede halogenarse en estas condiciones con separación posterior de los compuestos de fórmula **3e** o **3f**. Los compuestos de halopirazol de fórmula **3e** o **3f** pueden experimentar después reacciones de acoplamiento de Suzuki catalizadas con paladio con ácidos aril o heteroarilborónicos o ésteres boronato correspondientes para proporcionar los compuestos de la invención.



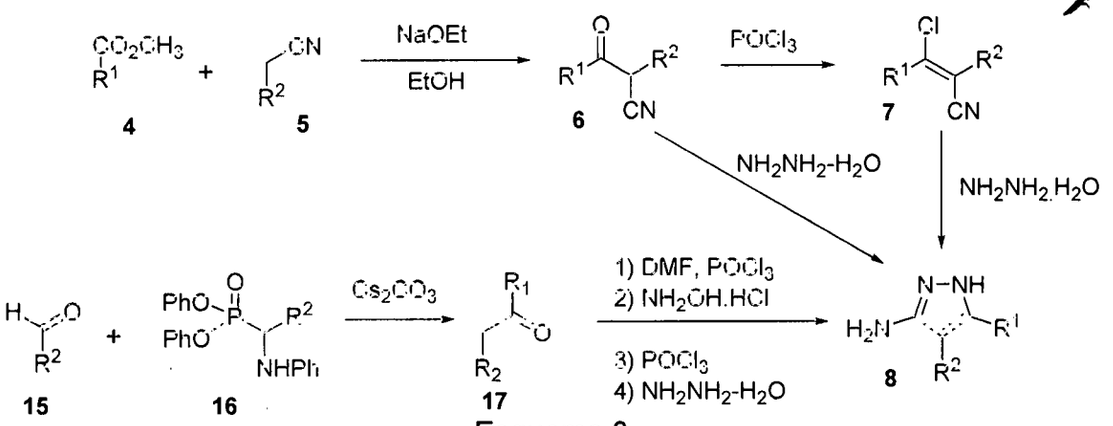
Esquema 2

Se describen 3-dimetilamino-1-(3-heteroaril)-2-propen-1-onas sustituidas en las Patentes de Estados Unidos Nº 4.281.000 y 4.521.422 y se desvelan 3-dialquilamino-1-fenil-2-propen-1-onas en las Patentes de Estados Unidos Nº 4.178.449 y 4.236.005. Se desvelan diversos 3-amino-4-pirazoles en las

Patentes de Estados Unidos Nº 4.236.005; 4.281.000; 4.521.422; 4.626.538; 4.654347; y 4.900.836. Se preparan pirazolo[1,5-a]pirimidinas por condensación de 3-aminopirazoles y 3-aminopirazoles sustituidos con compuestos de 1,3-dicarbonilo como se describe en *J. Med. Chem., 18*, 645 (1974); *J. Med. Chem. 18*, 460 (1975); *J. Med. Chem., 20*, 386 (1977); *Synthesis*, 673 (1982) y referencias contenidas en esos documentos.

Están disponibles compuestos intermedios de aminopirazol adicionales de fórmula **8** de acuerdo con la ruta que se muestra en el Esquema 3. Con respecto al Esquema 3, la reacción de condensación de compuestos de acetonitrilo sustituidos de fórmula **5**, en la que R^2 es como se ha definido anteriormente o es hidrógeno, con compuestos de éster sustituidos de fórmula **4,** puede realizarse en presencia de una base tal como, pero sin limitación, etóxido sódico, en un disolvente adecuado, tal como etanol, para proporcionar compuestos intermedios de fórmula **6.** Los compuestos intermedios de fórmula **6** pueden hacerse reaccionar posteriormente con hidrazina hidrato en un disolvente adecuado, tal como etanol, para proporcionar compuestos de aminopirazol de fórmula **8** en la que R^1 y R^2 se han definido anteriormente. Para ciertos compuestos intermedios sustituidos de fórmula **6**, es necesario hacerlos reaccionar en primer lugar con oxicloruro de fósforo a temperaturas elevadas, típicamente a la temperatura de reflujo, para proporcionar compuestos intermedios de fórmula **7.** Los compuestos intermedios de fórmula **7** pueden convertirse en compuestos de aminopirazol sustituido de fórmula **8** mediante una reacción posterior con hidrazina hidrato en un disolvente adecuado, tal como etanol. Los compuestos de éster sustituidos de fórmula **4** y los compuestos de acetonitrilo sustituidos de fórmula **5** pueden obtenerse de

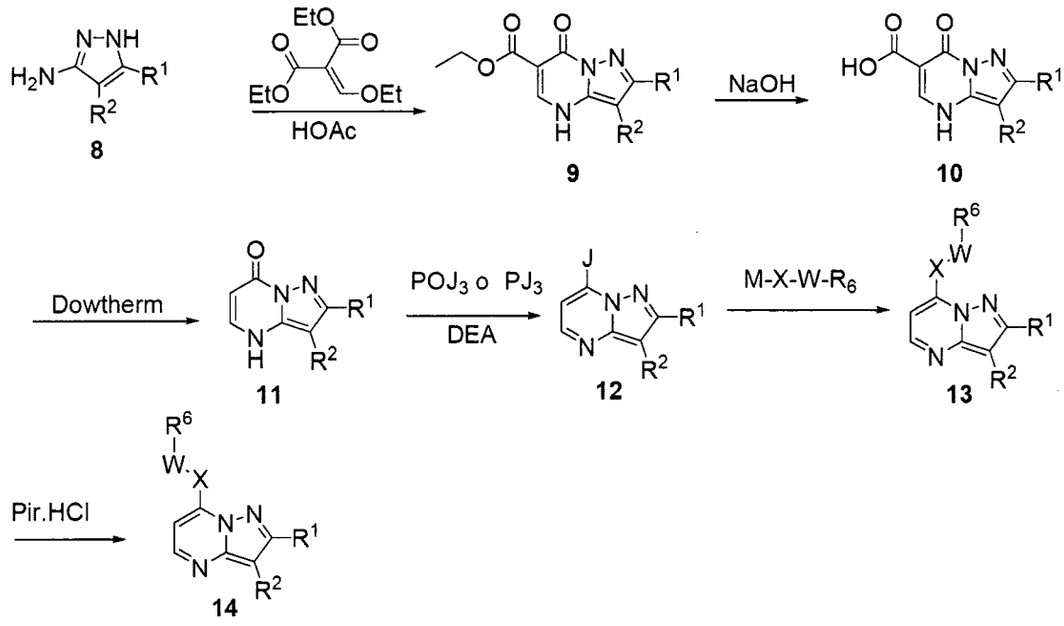
fuentes comerciales o prepararse fácilmente por los expertos en la materia mediante numerosos procedimientos bibliográficos. Los compuestos de aminopirazol de fórmula **8** también pueden prepararse a partir de una ruta alternativa partiendo de compuestos de aldehído de fórmula **15**, como se muestra en el Esquema 3. En la primera etapa de esta ruta alternativa, los compuestos de aldehído **15**, que están disponibles en el mercado o pueden prepararse por procedimientos conocidos, se hacen reaccionar típicamente a temperatura ambiente con compuestos de fosfonato de fórmula **16** (que pueden prepararse de acuerdo con el procedimiento de Tet. Lett., **1988**, *39*, 1717-1720) en un disolvente adecuado, tal como tetrahidrofurano, usando una base apropiada, tal como, pero sin limitación, carbonato de cesio, para proporcionar compuestos intermedios de fórmula **17.** Después, los compuestos intermedios de fórmula **17** se calientan, típicamente a 80 °C, en una mezcla de cloroformo, oxicloruro de fósforo o similar, y dimetilformamida para dar los 3-cloropropenales sustituidos correspondientes. Los 3-cloropropenales en bruto se tratan con hidroxilamina en un disolvente adecuado, tal como dimetilformamida, típicamente a temperatura ambiente, para proporcionar las 3-cloropropenal oximas correspondientes, que después se tratan con un agente deshidratante adecuado tal como, pero sin limitación, oxicloruro de fósforo, típicamente a temperatura ambiente, para dar los 3-cloroacrilonitrilos correspondientes. Los 3-cloroacrilonitrilos intermedios pueden convertirse después en los compuestos de aminopirazol sustituidos deseados de fórmula **8** mediante una reacción posterior con hidrazina hidrato en un disolvente adecuado, tal como etanol.



Esquema 3

Con respecto al Esquema 4, los compuestos de la invención también están disponibles por condenación de los compuestos de aminopirazol deseados de fórmula **8**, con malonatos de alcoximetileno en un ácido débil, tal como ácido acético a temperatura elevada, típicamente a la temperatura de reflujo, para proporcionar compuestos derivados de dihidropirazolo[1,5-a]pirimidina de fórmula **9.** La hidrólisis de la funcionalidad éster de compuestos de fórmula **9** mediada por una base acuosa tal como hidróxido sódico proporciona compuestos de pirimidona de fórmula **10,** que después se descarboxilan a temperatura elevada para formar compuestos de fórmula **11.** La transformación de los compuestos de pirimidona de fórmula **11** en los compuestos de halo-pirimidina correspondientes de fórmula **12** se realiza con oxicloruro de fósforo, o un agente de halogenación similar, a temperatura elevada, en presencia de una base de amina, tal como *N,N*-dietilanilina. La reacción de compuestos de halo-pirimidina de fórmula **12** con M-X-W-R^6, en la que M es un hidrógeno, ácido borónico, éster boronato, estanano o silano, en presencia de un catalizador de metal de transición, da después compuestos de fórmula **13** de la invención que pueden estar funcionalizados adicionalmente de acuerdo con procedimientos conocidos por los expertos en la materia. Los

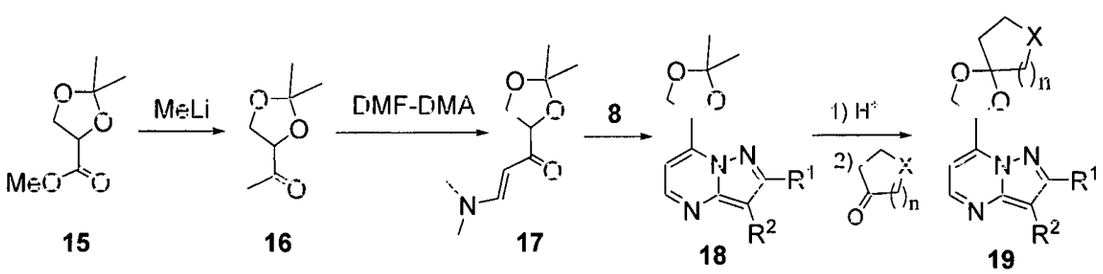
compuestos de halo-pirimidina de fórmula **12** pueden convertirse análogamente en compuestos de fórmula **13** de la invención por reacción con M-X-W-R^6 en la que M es un metal incluyendo, pero sin limitación, cinc, litio y magnesio. En el caso de compuestos en los que R^2 es un resto metoxifenilo, el fenol correspondiente (compuestos de fórmula **14**, R_2 = PhOH) se proporciona por reacción con clorhidrato de piridina a temperatura elevada, o tribromuro de boro.



Esquema 4

Con respecto al Esquema 5, ciertos compuestos de la invención en los que R^6 es un resto espirobicíclico están disponibles partiendo de compuestos de cetona-cetal de fórmula **16**, preparados en una sola etapa a partir de compuestos de éster metílico de fórmula **15** disponibles en el mercado [D. Tanner, P. Somfai, Syn. Commun., 16(12), 1517-1522 (1986)]. La conversión de compuestos de metil cetona de fórmula **16** en compuestos de enaminona de

fórmula **17** se realiza por reacción con acetales de N,N-dialquilformamida o acetales de N,N-dialquilacetamida, en un disolvente inerte o sin disolvente, a una temperatura de 50-100 °C. La reacción de los compuestos de 3-aminopirazol sustituidos de fórmula **8**, en la que R^1 y R^2 se han definido anteriormente o son hidrógeno, con compuestos de enaminona de fórmula **17** en un ácido débil, tal como ácido acético glacial, o en un disolvente inerte, tal como tolueno, acetonitrilo o dimetoxietano, a la temperatura de reflujo durante varias horas, o sin disolvente a 50-150 °C, produce los compuestos de cetal deseados de fórmula **18.** La hidrólisis de los compuestos de cetal de fórmula **18** en condiciones ácidas, tales como ácido acético acuoso, ácido trifluoroacético, ácido tósico o ácido canforsulfónico de la temperatura ambiente a 100 °C, seguido de reacción del diol resultante con cetonas carbocíclicas y heterocíclicas en condiciones ácidas, proporciona los compuestos de fórmula **19** de la invención.



Esquema 5

Los compuestos a modo de ejemplo de Fórmula A preparados por procedimientos de la presente invención incluyen los siguientes compuestos: 3-(7-{6-[(1-azabiciclo[2.2.2]oct-4-ilmetil)amino]piridin-3-il}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol, 3-(7-{6-[(3*S*)-1-azabiciclo[2.2.2]oct-3-ilamino]piridin-3-il}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol, 3-(7-{6-[(3*R*)-1-azabiciclo[2.2.2]oct-3-ilamino]piridin-3-il}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol, (3*R*)-*N*-{4-[3-

(3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]piridin-2-il}quinuclidin-3-amina, (3*R*)-*N*-{5-[3-(4-cloro-3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]piridin-2-il}quinuclidin-3-amina, 3-{7-[(1-azabiciclo[2.2.2]oct-4-ilmetil)amino]-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il}fenol, 3-[3-(3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, 3-[3-(3-hidroxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]-octano-8-carboxilato de etilo, 3-[7-(8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]fenol, 3-[3-(4-cloro-3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, 3-[3-(4-cloro-3-hidroxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, 5-[7-(8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]-2-clorofenol, 5-[7-(8-acetil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]-2-clorofenol, 2-cloro-5-{7-[8-(metilsulfonil)-8-azabiciclo[3.2.1]oct-3-il]-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il}fenol, acetato de 5-[7-(8-acetil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]-2-clorofenilo, 7-(8-azabiciclo[3.2.1]oct-3-il)-3-(4-cloro-3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(4-cloro-3-metoxifenil)-7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 2-cloro-5-[7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]fenol, 7-(8-azabiciclo[3.2.1]oct-3-il)-3-(3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-3-(2-metoxipiridin-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 4-[7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]piridin-2-ol, 4-[7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]anilina, 1-{4-[7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-

il]fenil}urea, 3-(3-metoxifenil)-7-[4-(8-metil-3,8-diazabiciclo[3.2.1]oct-3-il)fenil]-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-{7-[4-(8-metil-3,8-diazabiciclo[3.2.1]oct-3-il)fenil]-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il}fenol, 3-(4-cloro-3-metoxifenil)-7-[4-(8-metil-3,8-diazabiciclo[3.2.1]oct-3-il)fenil]-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 2-cloro-5-{7-[4-(8-metil-3,8-diazabiciclo[3.2.1]oct-3-il)fenil]-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il}fenol, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol, 3-(7-{4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol, 3-(4-cloro-3-metoxifenil)-7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(4-fluoro-3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 5-(7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)-2-fluorofenol, 3-(1*H*-indazol-4-il)-7-{6-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]piridin-3-il}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-7-{4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(3-metoxifenil)-7-{4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]-hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(4-fluoro-3-metoxifenil)-7-{4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 5-(7-{4-[(1*S*,4*S*)-5-etil-2,5-diazabiciclo[2.2.1]-hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)-2-fluorofenol, 5-(7-{4-[(1*S*,4*S*)-5-acetil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)-2-fluorofenol, 7-{6-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]piridin-3-il}-3-(7-metil-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(7-cloro-1*H*-

indazol-4-il)-7-{6-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]piridin-3-il}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(7-fluoro-1*H*-indazol-4-il)-7-{6-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]piridin-3-il}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(7-{6-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]piridin-3-il}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)benzamida, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-2-metilfenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-7-{2-metil-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-4-fluorofenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-fluoro-2-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, (1*S*,4*S*)-5-{2-[3-(4-cloro-3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-5-fluorofenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo, 3-(4-cloro-3-metoxifenil)-7-{2-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-4-fluorofenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(4-cloro-3-metoxifenil)-7-{4-fluoro-2-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo-[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-2-fluorofenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2-fluoro-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 2-fluoro-5-(7-{4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol, 3-(4-fluoro-3-metoxifenil)-7-{2-metil-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 2-fluoro-5-(7-{2-metil-4-[(1*S*,4*S*)-5-metil-2,5-

diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol, 3-(7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-2-metilfenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol, 3-(7-{2-metil-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol, 3-(7-{2-cloro-4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol, 3-(7-{2-cloro-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol, 7-{2-cloro-4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2-cloro-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-[3-(3-hidroxi-4-metilfenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, 5-[7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]-2-fluorofenol, 3-[3-(2,3-difluorofenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, 3-(3-{3-[(metilsulfonil)amino]-fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, {4-[7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]fenil}carbamato de metilo, 4-[7-(8-etil-8-azabiciclo[3.2.1]-oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]-2-hidroxibenzonitrilo, {4-[7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]-2-metoxifenil}carbamato de terc-butilo, 4-[7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]-2-metoxianilina, 2-amino-5-[7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]fenol, *N*-{4-[7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]-2-hidroxifenil}formamida, *N*-{4-[7-(8-etil-8-

azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]-2-metoxifenil}formamida, 3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, 7-(8-azabiciclo[3.2.1]oct-3-il)-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo-[1,5-a]pirimidina, 3-[3-(7-cloro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, 3-{2-piridin-4-il-3-[7-(trifluorometil)-1*H*-indazol-4-il]pirazolo[1,5-a]pirimidin-7-il}-8-azabiciclo[3.2.1]-octano-8-carboxilato de etilo, 7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-3-(7-metil-1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-[3-(7-metil-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, 3-(7-cloro-1*H*-indazol-4-il)-7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-il-3-[7-(trifluorometil)-1*H*-indazol-4-il]pirazolo[1,5-a]pirimidina, 3-[3-(7-fluoro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, 3-(7-cloro-6-fluoro-1*H*-indazol-4-il)-7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-[3-(2-oxo-2,3-dihidro-1*H*-benzoimidazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]-octano-8-carboxilato de etilo, 3-[3-(1*H*-indol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, 3-[3-(1*H*-indol-6-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, 3-[3-(2-oxo-2,3-dihidro-1*H*-pirrolo[2,3-b]piridin-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, 7-(8-etil-8-azabiciclo-[3.2.1]oct-3-il)-3-(1*H*-indol-6-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-[3-(2-oxo-2,3-dihidro-1*H*-indol-6-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-

8-carboxilato de etilo, 2-cloro-5-[7-(2,2-dimetil-1,3-dioxolan-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]fenol, 7-(8-Etil-8-azabiciclo[3.2.1]-octan-3-il)-3-(1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina, 3-(3-(3-(1,3,4-oxadiazol-2-il)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, (1S,4S)-5-{3-fluoro-4-[3-(1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]fenil}-2,5-diazabiciclo-[2.2.1]heptano-2-carboxilato de *terc*-butilo, 7-{4-[(1S,4S)-2,5-diazabiciclo[2.2.1]hept-2-il]-2-fluorofenil}-3-(1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2-Fluoro-4-[(1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2-fluoro-4-[(1S,4S)-5-metil-5-oxido-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1H-indazol-4-il)-2-piridin-4-ilpirazolo-[1,5-a]pirimidina, Éster terc-Butílico del ácido (1S,4S)-5-{3-cloro-4-[3-(1H-indazol-4-il)-2-piridin-4-il-pirazolo[1,5-a]pirimidin-7-il]-fenil}-2,5-diaza-biciclo[2.2.1]heptano-2-carboxílico, Sal bis-clorhidrato de 7-[2-cloro-4-((1S,4S)-2,5-diaza-biciclo[2.2.1]hept-2-il)-fenil]-3-(1H-indazol-4-il)-2-piridin-4-il-pirazolo[1,5-a]pirimidina, 7-[2-Cloro-4-((1S,4S)-5-metil-2,5-diaza-biciclo[2.2.1]hept-2-il)-fenil]-3-(1H-indazol-4-il)-2-piridin-4-il-pirazolo[1,5-a]pirimidina, (1S,4S)-5-{3,5-Difluoro-4-[3-(1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]fenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo, 7-(4-((1S,4S)-2,5-diazabiciclo[2.2.1]-heptan-2-il)-2,6-difluorofenil)-3-(1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina, 7-{2,6-difluoro-4-[(1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, (1S,4S)-5-{4-[3-(7-Fluoro-1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]fenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo, 7-[4-(2,5-Diaza-biciclo[2.2.1]hept-2-il)-fenil]-3-(7-fluoro-1H-indazol-4-il)-2-piridin-4-il-pirazolo[1,5-a]pirimidina, clorhidrato de 3-(7-

fluoro-1H-indazol-4-il)-7-{4-[(1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, (1S,4S)-5-{3-Fluoro-4-[3-(7-fluoro-1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]fenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo, 7-{4-[(1S,4S)-2,5-diazabiciclo[2.2.1]hept-2-il]-2-fluorofenil}-3-(7-fluoro-1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(7-fluoro-1H-indazol-4-il)-7-{2-fluoro-4-[(1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, (1S,4S)-5-{3,5-Difluoro-4-[3-(7-fluoro-1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]fenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo, 7-{4-[(1S,4S)-2,5-Diazabiciclo[2.2.1]hept-2-il]-2,6-difluorofenil}-3-(7-fluoro-1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2,6-Difluoro-4-[(1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(7-fluoro-1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-5-il]-8-azabiciclo[3.2.1]-octano-8-carboxilato de etilo, 2-{3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]oct-8-il}etanol, 3-(1*H*-indazol-4-il)-7-(8-isopropil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-7-[8-(metilsulfonil)-8-azabiciclo[3.2.1]oct-3-il]-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxamida, 2-{3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]oct-8-il}-*N*,*N*-dimetil-2-oxoetanamina, {3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]oct-8-il}acetonitrilo, *N*-etil-3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxamida, 7-(8-acetil-8-azabiciclo[3.2.1]oct-3-il)-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-[3-(1*H*-indazol-4-il)-2-

piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-*N*,*N*-dimetil-8-azabiciclo[3.2.1]octano-3-carboxamida, (1*S*,4*S*)-5-{[3-(4-cloro-3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]metil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo, (1*S*,4*S*)-5-{4-[3-(7-fluoro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-5-il]fenil}-2,5-diazabiciclo-[2.2.1]heptano-2-carboxilato de *terc*-butilo, (1*S*,4*S*)-5-{3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]fenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo, 7-{3-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, (1*S*,4*S*)-5-{4-[3-(7-cloro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]fenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo, 3-(1*H*-indazol-4-il)-7-{3-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(7-cloro-1*H*-indazol-4-il)-7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, (2*S*)-2-({3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]oct-8-il}carbonil)pirrolidin-1-carboxilato de *terc*-butilo, 3-(1*H*-indazol-4-il)-7-(8-L-prolil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 1-{3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]oct-8-il}propan-2-ona, 3-[3-(7-fluoro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-5-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-2-fluorofenil}-3-(3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-2-fluorofenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol, 3-(7-{2-fluoro-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-2-metilfenil}-3-(7-fluoro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(7-fluoro-1*H*-

indazol-4-il)-7-{2-metil-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo-[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-(8-azabiciclo[3.2.1]oct-3-il)-3-(7-fluoro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, {3-[3-(7-fluoro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]oct-8-il}acetonitrilo, 3-(7-cloro-1*H*-indazol-4-il)-5-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-7-[6-(8-metil-3,8-diazabiciclo[3.2.1]oct-3-il)piridin-3-il]-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(7-cloro-1*H*-indazol-4-il)-7-{4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-(1,4-dioxaespiro[4.5]dec-8-il)-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-7-{4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.2]oct-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo-[2.2.2]oct-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-4,6-difluorofenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 5-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-2-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-*N*,*N*-dimetilanilina, 7-{2,4-difluoro-6-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 2-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-*N*,*N*-dimetil-5-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]anilina, 7-{*cis*-4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]ciclohexil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-7-[*cis*-4-(3-oxa-8-azabiciclo[3.2.1]oct-8-il)ciclohexil]-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-7-[*trans*-4-(3-oxa-8-azabiciclo[3.2.1]-oct-8-il)ciclohexil]-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-7-[*cis*-4-(8-oxa-3-azabiciclo[3.2.1]oct-3-il)ciclohexil]-2-piridin-4-

ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-7-[*trans*-4-(8-oxa-3-azabiciclo[3.2.1]oct-3-il)ciclohexil]-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-7-{*cis*-4-[(1*S*,4*S*)-2-oxa-5-azabiciclo[2.2.1]hept-5-il]ciclohexil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-7-{*trans*-4-[(1*S*,4*S*)-2-oxa-5-azabiciclo[2.2.1]hept-5-il]ciclohexil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{*trans*-4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]ciclohexil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-3-(trifluorometil)fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-1-naftil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-7-{4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]-3-(trifluorometil)fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-7-{4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]-1-naftil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-3,5-difluorofenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-2,3-difluorofenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-2,5-difluorofenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{3,5-difluoro-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2,3-difluoro-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2,5-difluoro-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-[(1*S*,4*S*)-5-etil-2,5-diazabiciclo[2.2.1]-hept-2-il]-2,6-difluorofenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2,6-difluoro-4-[(1*S*,4*S*)-5-isobutil-2,5-diazabiciclo[2.2.1]hept-2-

il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2,6-difluoro-4-[(1*S*,4*S*)-5-isopropil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-[(1*S*,4*S*)-5-ciclobutil-2,5-diazabiciclo[2.2.1]hept-2-il]-2,6-difluorofenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-(1,4-dioxaespiro[4.5]dec-8-il)-3-(7-fluoro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.2]oct-2-il]-2-fluorofenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2-fluoro-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.2]oct-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-2-piridin-4-il-7-{2,3,5,6-tetrafluoro-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}pirazolo[1,5-a]pirimidina, (1*S*,4*S*)-5-{3-cloro-4-[3-(7-fluoro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]fenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo, 7-{*cis*-4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]ciclohexil}-3-(7-fluoro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(7-fluoro-1*H*-indazol-4-il)-7-{*cis*-4-[(1*S*,4*S*)-2-oxa-5-azabiciclo[2.2.1]hept-5-il]ciclohexil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(7-fluoro-1*H*-indazol-4-il)-7-{*trans*-4-[(1*S*,4*S*)-2-oxa-5-azabiciclo[2.2.1]hept-5-il]ciclohexil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(7-fluoro-1*H*-indazol-4-il)-7-[*cis*-4-(8-oxa-3-azabiciclo[3.2.1]oct-3-il)ciclohexil]-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(7-fluoro-1*H*-indazol-4-il)-7-[*trans*-4-(8-oxa-3-azabiciclo[3.2.1]oct-3-il)ciclohexil]-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(7-fluoro-1*H*-indazol-4-il)-7-[*cis*-4-(3-oxa-8-azabiciclo[3.2.1]oct-8-il)ciclohexil]-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(7-fluoro-1*H*-indazol-4-il)-7-[*trans*-4-(3-oxa-8-azabiciclo[3.2.1]oct-8-il)ciclohexil]-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{*trans*-4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]ciclohexil}-3-(7-fluoro-1*H*-

indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2-cloro-4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]-hept-2-il]fenil}-3-(7-fluoro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-3-fluorofenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-2-(trifluorometil)fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2-bromo-4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{3-fluoro-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-7-{4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]-2-(trifluorometil)fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2-bromo-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-(1,4-dioxaespiro[4.5]dec-7-en-8-il)-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2,6-difluoro-4-[(1*S*,4*S*)-5-metil-5-oxido-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-7-{5-[(1*S*,4*S*)-2-oxa-5-azabiciclo[2.2.1]hept-5-ilmetil]furan-3-il}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, (1*S*,4*S*)-5-({4-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]furan-2-il}metil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo, 7-{5-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-ilmetil]furan-3-il}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, (1*S*,4*S*)-5-({5-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]tiofen-2-il}metil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo, 3-(1*H*-indazol-4-il)-7-{5-[(1*S*,4*S*)-2-oxa-5-azabiciclo[2.2.1]hept-5-ilmetil]tiofen-2-il}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{5-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-ilmetil]tiofen-2-il}-3-(1*H*-indazol-4-il)-2-

piridin-4-ilpirazolo[1,5-a]pirimidina, (3-endo)-3-[3-(1*H*-indazol-4-il)-6-metil-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, 3-(1*H*-indazol-4-il)-7-[6-(8-oxa-3-azabiciclo[3.2.1]oct-3-il)piridin-3-il]-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-7-{6-[(1*S*,4*S*)-2-oxa-5-azabiciclo-[2.2.1]hept-5-il]piridin-3-il}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, (1*S*,4*S*)-5-{3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]bencil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo, (1*S*,4*S*)-5-{4-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]bencil}-2,5-diazabiciclo[2.2.1]-heptano-2-carboxilato de *terc*-butilo, 3-(1*H*-indazol-4-il)-7-{4-[(1*S*,4*S*)-2-oxa-5-azabiciclo[2.2.1]-hept-5-ilmetil]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-ilmetil]-2-fluorofenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2-fluoro-4-[(1*S*,4*S*)-2-oxa-5-azabiciclo[2.2.1]hept-5-ilmetil]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2-fluoro-4-[(1*R*,4*R*)-2-oxa-5-azabiciclo[2.2.1]hept-5-ilmetil]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{3-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-ilmetil]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-ilmetil]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 9-{3-fluoro-4-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]bencil}-3,7-dioxa-9-azabiciclo[3.3.1]nonano y sales farmacéuticamente aceptables de los mismos.

Los compuestos de Fórmula A pueden obtenerse en forma de sales inorgánicas u orgánicas usando procedimientos conocidos por los expertos en la materia, por ejemplo, Richard C. Larock, Comprehensive Organic Transformations, VCH publishers, 411-415, 1989. Se sabe bien por un experto en la materia que una forma de sal apropiada se elige basándose en su

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estabilidad física y química, fluidez, higroscopicidad y solubilidad.

Pueden formarse sales farmacéuticamente aceptables de los compuestos de Fórmula A con un resto ácido a partir de bases orgánicas e inorgánicas. Por ejemplo, con metales alcalinos o alcalinotérreos, tales como sodio, potasio, litio, calcio, o magnesio o bases orgánicas y sales de N-tetraalquilamonio, tales como sales de N-tetrabutilamonio. De forma análoga, cuando un compuesto de la presente invención contiene un resto básico, pueden formares sales a partir de ácidos orgánicos e inorgánicos. Por ejemplo, pueden formarse sales a partir de ácido acético, propiónico, láctico, cítrico, tartárico, succínico, fumárico, maleico, malónico, mandélico, málico, ftálico, clorhídrico, bromhídrico, fosfórico, nítrico, sulfúrico, metanosulfónico, naftalenosulfónico, bencenosulfónico, toluenosulfónico, canforsulfónico y ácidos aceptables conocidos de forma similar. Los ejemplos adecuados de sales farmacéuticamente aceptables incluyen, pero sin limitación, sulfato; citrato, acetato; oxalato; cloruro; bromuro; yoduro; nitrato; bisulfato; fosfato; fosfato ácido; isonicotinato; lactato; salicilato; citrato ácido; tartrato; oleato; tanato; pantotenato; bitartrato; ascorbato; succinato; maleato; gentisinato; fumarato; gluconato; glucaronato; sacarato; formiato; benzoato; glutamato; metanosulfonato; etanosulfonato; bencenosulfonato; p-toluenosulfonato; pamoato (es decir, 1,1'-metileno-bis-(2-hidroxi-3-naftoato)); y sales de ácidos grasos tales como sales caproato, laurato, miristato, palmitato, estearato, oleato, linoleato y linolenato. Los compuestos también pueden usarse en forma de ésteres, carbamatos y otras formas de profármacos convencionales, que cuando se administran en dicha forma, se convierten en el resto activo *in vivo*.

Por consiguiente, la presente invención proporciona una composición

farmacéutica que comprende una cantidad eficaz de un compuesto de Fórmula A en combinación o asociación con un vehículo farmacéuticamente aceptable. Las composiciones farmacéuticas se preparan de acuerdo con procedimientos farmacéuticos aceptables, tales como los descritos en Remingtons Pharmaceutical Sciences, 17ª edición, ed. Alfonoso R. Gennaro, Mack Publishing Company, Easton, Pa. (1985). Son vehículos farmacéuticamente aceptables los que son compatibles con los otros ingredientes de la formulación y biológicamente aceptables. Como se usa en el presente documento, el término "cantidad eficaz" se refiere a la cantidad de compuesto activo o agente farmacéutico que suscita la respuesta biológica o médica en un tejido, sistema, animal, individuo o ser humano que se espera por un investigador, veterinario, doctor en medicina u otro médico, que incluye uno o más de los siguientes: (1) prevenir la enfermedad; por ejemplo, prevenir una enfermedad, afección o trastorno en un individuo que puede estar predispuesto a la enfermedad, afección o trastorno pero que aún no ha experimentado o mostrado la patología o sintomatología de la enfermedad; (2) inhibir la enfermedad; por ejemplo, inhibir una enfermedad, afección o trastorno en un individuo que está experimentando o mostrando la patología o sintomatología de la enfermedad, afección o trastorno (es decir, detener o retrasar el desarrollo adicional de la patología y/o sintomatología); y (3) mejorar la enfermedad; por ejemplo, mejorar una enfermedad, afección o trastorno en un individuo que está experimentando o mostrando la patología o sintomatología de la enfermedad, afección o trastorno (es decir, revertir la patología y/o sintomatología).

Los compuestos de la presente invención pueden formularse en forma pura o pueden combinarse con uno o más vehículos farmacéuticamente

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aceptables para la administración. Los vehículos adecuados incluyen, pero sin limitación, por ejemplo, disolventes, diluyentes y similares, y pueden administrarse por vía oral en formas tales como comprimidos, cápsulas, polvos dispersables, gránulos o suspensiones que contienen, por ejemplo, de aproximadamente el 0,05 al 5 % de agente de suspensión, jarabes que contienen, por ejemplo, de aproximadamente el 10 al 50 % de azúcar, y elixires que contienen, por ejemplo, de aproximadamente el 20 al 50 % de etanol, y similares, o por vía parenteral, en forma de solución o suspensión inyectable estéril que contiene de aproximadamente el 0,05 al 5 % de agente de suspensión en un medio isotónico. Dichas preparaciones farmacéuticas pueden contener, por ejemplo, de aproximadamente el 0,05 hasta aproximadamente el 90 % del principio activo junto con el vehículo, más habitualmente entre aproximadamente el 5 % y el 60 % en peso.

En algunas realizaciones, las formulaciones se administran por vía transdérmica, que incluye todos los procedimientos de administración a través de la superficie del cuerpo y de los revestimientos internos de los conductos corporales, incluyendo tejidos epiteliales y mucosos. Dicha administración puede realizarse en forma de una loción, crema, coloide, espuma, parche, suspensión o solución.

La dosificación eficaz de principio activo usada puede variar dependiendo del compuesto particular usado, el modo de administración y la gravedad de la afección que se trate. Sin embargo, en general, se obtienen resultados satisfactorios cuando los compuestos de la invención se administran a una dosificación diaria de aproximadamente 0,5 a aproximadamente 1000 mg/kg de peso corporal del animal, opcionalmente dada en dosis divididas de

dos a cuatro veces al día, o en una forma de liberación sostenida. Para la mayoría de los mamíferos grandes, la dosificación diaria total es de aproximadamente 1 a 1000 mg, preferentemente de aproximadamente 2 a 500 mg. Las formas farmacéuticas adecuadas para uso interno comprenden de aproximadamente 0,5 a 1000 mg del compuesto activo en mezcla íntima con un vehículo sólido o líquido farmacéuticamente aceptable. Este régimen de dosificación puede ajustarse para proporcionar la respuesta terapéutica óptima. Por ejemplo, pueden administrarse varias dosis divididas diariamente o la dosis puede reducirse proporcionalmente según determinen las exigencias de la situación terapéutica.

Los compuestos de la presente invención pueden administrarse por vía oral así como por vías intravenosa, intramuscular o subcutánea. Los vehículos sólidos incluyen almidón, lactosa, fosfato dicálcico, celulosa microcristalina, sacarosa y caolín, mientras que los vehículos incluyen agua estéril, polietilenglicoles, tensioactivos no iónicos y aceites comestibles tales como aceites de maíz, cacahuete y sésamo, que son apropiados para la naturaleza del principio activo y la forma de administración particular deseada. Pueden incluirse ventajosamente adyuvantes usados habitualmente en la preparación de composiciones farmacéuticas, tales como agentes saporíferos, agentes colorantes, agentes conservantes y antioxidantes, por ejemplo, vitamina E, ácido ascórbico, BHT y BHA.

Las composiciones farmacéuticas preferidas desde el punto de vista de la facilidad de preparación y administración son composiciones sólidas, particularmente comprimidos y cápsulas rellenas duras o rellenas de líquido. En algunas ocasiones, es deseable la administración oral de los compuestos. En

algunos casos, puede ser deseable administrar los compuestos directamente en las vías respiratorias en forma de un aerosol.

Los compuestos de la presente invención también pueden administrarse por vía parenteral o intraperitoneal. Pueden prepararse soluciones o suspensiones de estos compuestos activos en forma de una base libre o sal farmacológicamente aceptable en agua adecuadamente mezclada con un tensioactivo tal como hidroxi-propilcelulosa. También pueden prepararse dispersiones en glicerol, polietilenglicoles líquidos y mezclas de los mismos en aceites. En condiciones convencionales de almacenamiento y uso, estas preparaciones contienen un conservante para prevenir el crecimiento de microorganismos.

Las formas farmacéuticas adecuadas para el uso inyectable incluyen soluciones o dispersiones acuosas estériles y polvos estériles para la preparación extemporánea de soluciones o dispersiones inyectables estériles. En todos los casos, la forma debe ser estéril y debe ser fluida hasta el punto en que exista una fácil inyectabilidad. Debe ser estable en las condiciones de fabricación y almacenamiento y debe conservarse frente a la acción contaminante de microorganismos tales como bacterias y hongos. El vehículo puede ser un disolvente o medio de dispersión que contenga, por ejemplo, agua, etanol, poliol (por ejemplo, glicerol, propilenglicol y polietilenglicol líquido), mezclas adecuadas de los mismos, y aceites vegetales.

Para el tratamiento del cáncer, los compuestos de la presente invención pueden administrarse junto con otras sustancias antitumorales o con terapia de radiación. Estas otras sustancias o tratamientos de radiación pueden darse al mismo tiempo o en momentos diferentes de los compuestos de la presente

invención. Estas terapias combinadas pueden tener sinergía y dar como resultado una eficacia mejorada. Por ejemplo, los compuestos de la presente invención pueden usarse junto con inhibidores mitóticos tales como taxol o vinblastina, agentes alquilantes tales como cisplatino o ciclofosamida, antimetabolitos tales como 5-fluorouracilo o hidroxiurea, intercaladores de ADN tales como adriamicina o bleomicina, inhibidores de la topoisomerasa tales como etopósido o camptotecina, agentes antiantiogénicos tales como angiostatina, y antiestrógenos tales como tamoxifeno. Como se usa de acuerdo con la presente invención, el término una "cantidad eficaz" de un compuesto significa administrar directamente dicho compuesto, o administrar un profármaco, derivado o análogo que formará una cantidad eficaz del compuesto dentro del cuerpo.

Como se usa de acuerdo con la presente invención, el término una "cantidad eficaz" de un compuesto significa administrar directamente dicho compuesto, o administrar un profármaco, derivado o análogo que formará una cantidad eficaz del compuesto dentro del cuerpo.

Los procedimientos de administración de una composición farmacéutica de la invención no se limitan específicamente, y puede administrarse en diversas preparaciones, dependiendo de la edad, sexo y síntomas del paciente. Por ejemplo, pueden administrarse por vía oral comprimidos, píldoras, soluciones, suspensiones, emulsiones, gránulos y cápsulas. Las preparaciones para inyección pueden administrarse por vía oral o mezcladas con transfusiones de inyección tales como soluciones de glucosa y soluciones de aminoácidos por vía intravenosa. Si es necesario, las preparaciones para inyección se administran individualmente por vía intramuscular, intracutánea,

subcutánea o intraperitoneal. Los supositorios pueden administrarse en el recto.

La cantidad del compuesto de fórmula A contenida en una composición farmacéutica de acuerdo con la presente invención no se limita específicamente, sin embargo, la dosis debería ser suficiente para tratar, mejorar o reducir los síntomas a los que está dirigida. La dosificación de una composición farmacéutica de acuerdo con la presente invención dependerá del procedimiento de uso, la edad, sexo y afección del paciente.

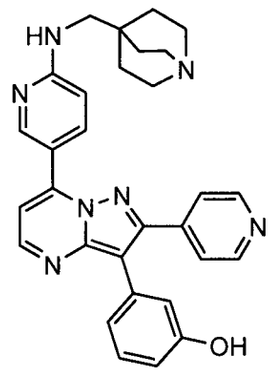
La presente invención también proporciona procedimientos de inhibición y tratamiento que comprenden adicionalmente administrar un inhibidor adicional de una oncoproteína quinasa de la ruta Ras/Raf/MEK.

Las composiciones farmacéuticas de la presente invención pueden comprender el compuesto de la presente invención solo o junto con otros compuestos inhibidores de oncoproteína quinasas o agentes quimioterapéuticos. Los agentes quimioterapéuticos incluyen, pero sin limitación, exemestano, formestano, anastrozol, letrozol, fadrozol, taxano y derivados tales como paclitaxel o docetaxel, taxanos encapsulados, CPT-11, derivados de camptotecina, glicósidos de antraciclina, por ejemplo, doxorrubicina, idarrubicina, epirrubicina, etopósido, navelbina, vinblastina, carboplatino, cisplatino, estramustina, celecoxib, tamoxifeno, raloxifeno, Sugen SU-5416, Sugen SU-6668 y Herceptina.

Habiendo descrito la invención, la invención se ilustra adicionalmente por los siguientes ejemplos no limitantes.

EJEMPLOS

Ejemplo 1: 3-(7-{6-[(1-Azabiciclo[2.2.2]oct-4-ilmetil)amino]piridin-3-il}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol



Etapa 1: Una suspensión de 5-acetil-2-bromopiridina (5 g, 0,025 mol) en 45 ml de dimetilformamida dimetil acetal se calentó a 110 °C durante 2,5 h. La mezcla de reacción se enfrió a temperatura ambiente para precipitar un sólido de color amarillo, que se filtró, se aclaró con éter y se secó a 40 °C al vacío durante una noche, proporcionando 5,20 g (rendimiento del 82 %) de (2E)-1-(6-bromopiridin-3-il)-3-(dimetilamino)prop-2-en-1-ona, que se usó sin purificación adicional.

Etapa 2: A 5 ml de etanol seco se le añadieron 0,73 g (31,84 mmol) de metal sodio (después de la retirada del aceite mineral con hexano) y la mezcla se agitó a 45 °C durante 1 hora hasta que la solución se volvió transparente. Después, se añadió una mezcla de 3 g (20,38 mmol) de 3-(metoxifenil)acetonitrilo y 3,9 g (28,66 mmol) de isonicotinato de metilo en 26 ml de etanol seco y la solución de color pardo resultante se calentó a reflujo durante 3 horas. Después de un periodo de refrigeración, el residuo se evaporó y se purificó por cromatografía sobre gel de sílice eluyendo con 9:1 a 4:1 de cloruro de metileno/metanol para proporcionar 1,75 g (rendimiento del 34 %) de

2-(3-metoxifenil)-3-oxo-3-piridin-4-il-propionitrilo.

Una mezcla de 1,7 g (6,74 mmol) de 2-(3-metoxifenil)-3-oxo-3-piridin-4-il-propionitrilo y 17 ml de $POCl_3$ se calentó a 80 °C durante 18 horas. Después de un periodo de refrigeración, el $POCl_3$ se retiró por evaporación. Al residuo resultante se le añadió tolueno y después la mezcla se evaporó a sequedad. Esta etapa se repitió hasta retirar completamente el $POCl_3$. Al residuo se le añadieron hielo y bicarbonato sódico saturado y precipitó un sólido, proporcionando 1 g (rendimiento del 57 %) de 3-cloro-2-(3-metoxifenil)-3-piridin-4-il-acrilonitrilo en forma de un sólido de color blanco. EM: 271,1 [M+H].

Una mezcla de 1 g (3,69 mmol) de 3-cloro-2-(3-metoxifenil)-3-piridin-4-il-acrilonitrilo y 0,9 ml (18,6 mmol) de hidrazina hidrato en 30 ml de etanol se calentó a reflujo durante 6,5 horas. La mezcla se dejó enfriar a temperatura ambiente y el disolvente se retiró por evaporación. Se agitó bicarbonato sódico acuoso en el residuo y el sólido resultante se recogió por filtración. El sólido se lavó con agua y después se secó al vacío, proporcionando 0,92 g (rendimiento del 94 %) de 4-[3-metoxi-fenil]-5-piridin-4-il-1H-pirazol-3-amina. EM: 267,2 [M+H].

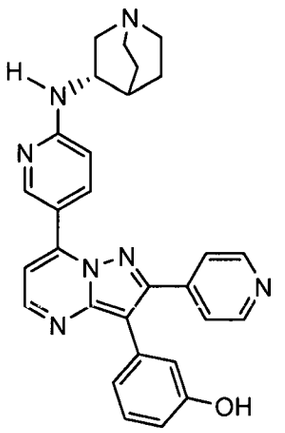
Una mezcla de 4-(3-metoxifenil)-5-piridin-4-il-1H-pirazol-3-amina (3,0 g, 11,27 mmol) y clorhidrato de piridina (6,0 g, 51,92 mmol) se calentó a 202 °C durante una hora. Después, la reacción se enfrió a temperatura ambiente, se diluyó con 10 ml de hidróxido de amonio, se agitó durante 30 min y después el disolvente se retiró al vacío. El residuo resultante se lavó con metanol al 15 %/diclorometano y los lavados recogidos se secaron sobre sulfato sódico, se filtraron y se evaporaron, dando un residuo que se purificó por cromatografía ultrarrápida sobre sílice eluyendo con metanol al 5 %-12 %/diclorometano,

proporcionando 2,21 g (rendimiento del 78 %) de 3-(3-amino-5-piridin-4-il-1H-pirazol-4-il)fenol en forma de un sólido de color beige.

Etapa 3: Se combinaron 1-(6-bromo-piridin-3-il)-3-dimetilamino-propenona (258 mg, 1,0 mmol), 3-(3-amino-5-piridin-4-il-1H-pirazol-4-il)fenol (254 mg, 1,0 mmol) y 3 ml de ácido acético glacial y se calentaron en el microondas a 120 °C durante 3000 seg. Después de la refrigeración, el precipitado de color amarillo obtenido se filtró, se aclaró con acetato de etilo al 10 %/éter y después con éter y se secó a 40 °C a presión reducida, dando 575 mg (rendimiento del 94 %) de 3-[7-(6-bromopiridin-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]fenol en forma de una sal del ácido acético, un sólido de color amarillo naranja. EM: 444,1 [M+H].

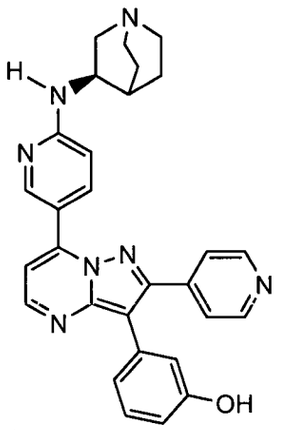
Etapa 4: A una suspensión agitada de 3-[7-(6-bromopiridin-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]fenol (117 mg, 0,25 mmol) en 1,2 ml de DMSO se le añadió diisopropiletilamina (0,13 ml, 0,75 mmol) seguido de 1-(1-azabiciclo[2.2.2]oct-4-il)metanamina (74 mg, 0,5 mmol). La mezcla se calentó a 125 °C durante 16 horas, se enfrió a temperatura ambiente y se purificó por RP-HPLC sobre una columna Gemini™ C18 eluyendo con acetonitrilo al 5-95 %/agua (TFA al 0,02 %), dando 18 mg de 3-(7-{6-[(1-azabiciclo[2.2.2]oct-4-ilmetil)amino]piridin-3-il}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol en forma de un sólido de color amarillo-naranja, rendimiento del 11 %. EM: 504,4 [M+H].

Ejemplo 2: 3-(7-{6-[(3S)-1-Azabiciclo[2.2.2]oct-3-ilamino]piridin-3-il}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol



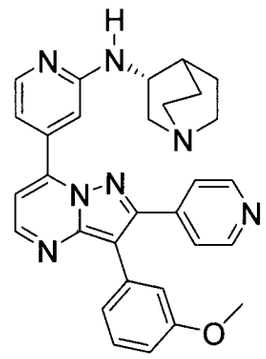
A una suspensión agitada de 3-[7-(6-bromopiridin-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]fenol (117 mg, 0,25 mmol) en 1,0 ml de DMSO se le añadieron diisopropiletilamina (0,23 ml, 1,35 mmol) y diclorhidrato de 3-(S)-aminoquinuclidina (60 mg, 0,3 mmol) y la mezcla resultante se sometió a microondas a 150 °C durante 1 hora y después se purificó por RP-HPLC sobre una columna Gemini™ C18, eluyendo con acetonitrilo al 5-95 %/agua (TFA al 0,02 %), dando 21 mg (rendimiento del 14 %) de 3-(7-{6-[(3S)-1-azabiciclo[2.2.2]oct-3-ilamino]piridin-3-il}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol en forma de un sólido de color amarillo-naranja. EM: 490,4 [M+H].

Ejemplo 3: 3-(7-{6-[(3R)-1-Azabiciclo[2.2.2]oct-3-ilamino]piridin-3-il}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol



Siguiendo el procedimiento para el Ejemplo 2, se hicieron reaccionar 3-[7-(6-bromopiridin-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]fenol y diclorhidrato de 3-(R)-aminoquinuclidina, dando 29 mg (rendimiento del 14 %) de 3-(7-{6-[(3R)-1-azabiciclo[2.2.2]oct-3-ilamino]piridin-3-il}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol en forma de un sólido de color amarillo. EM: 490,4 [M+H].

Ejemplo 4: (3R)-N-{4-[3-(3-Metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]piridin-2-il}quinuclidin-3-amina



Etapa 1: A una solución de acetilpiridina (2,2 ml, 20 mmol) en 22 ml de diclorometano se le añadió ácido 3-cloroperoxibenzoico (3,45 g, 20 mmol) y la mezcla resultante se calentó a reflujo durante 16 horas. Después, el disolvente se evaporó y el residuo en bruto se cromatografió sobre gel de sílice, eluyendo con metanol al 0-40 %/acetato de etilo, proporcionando 1 g (rendimiento del 38 %) de 1-(1-oxi-piridin-4-il)-etanona en forma de un sólido de color blanco que se usó directamente en la siguiente etapa.

Etapa 2: Una solución de 1-(1-oxi-piridin-4-il)-etanona (231 mg, 1,7 mmol) en 2,2 ml de dimetilformamida dimetil acetal en un vial de proceso Smith de 5 ml se sometió a microondas a 110 °C durante una hora. La mezcla resultante se enfrió a TA y el precipitado se recogió por filtración y después se

aclaró con acetato de etilo al 2 %/éter seguido de éter. El sólido se secó a 40 °C a presión reducida, dando 222 mg (rendimiento del 68 %) de 3-dimetilamino-1-(1-oxi-piridin-4-il)-propenona en forma de un sólido de color beige que se usó directamente en la siguiente etapa.

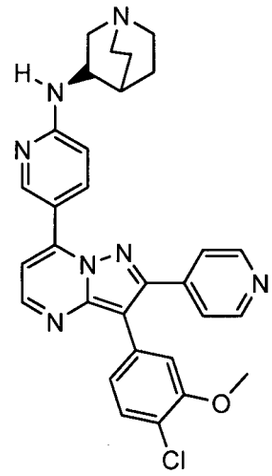
Etapa 3: Una mezcla de 3-dimetilamino-1-(1-oxi-piridin-4-il)-propenona (222 mg, 1,15 mmol) y 4-(3-metoxifenil)-5-piridin-4-il-1H-pirazol-3-amina (308 mg, 1,15 mmol) en 2 ml de ácido acético glacial se calentó en el microondas a 120 °C durante una hora. Después, la mezcla de reacción se enfrió a temperatura ambiente y el precipitado de color amarillo resultante se recogió por filtración y se aclaró con acetato de etilo al 10 %/éter y después con éter. El sólido se secó a 40 °C a presión reducida, dando 330 mg (rendimiento del 65 %) de 3-(3-metoxifenil)-7-(1-oxidopiridin-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina en forma de un sólido de color amarillo que se usó directamente en la siguiente etapa. EM: 396,1 [M+H].

Etapa 4: Una solución de 3-(3-metoxifenil)-7-(1-oxidopiridin-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina (264 mg, 0,67 mmol) se calentó a reflujo en $POCl_3$ durante una hora y después se enfrió a temperatura ambiente. Después, la mezcla se evaporó con tolueno, se inactivó con $NaHCO_3$ saturado frío y se extrajo en éter. La fase orgánica se secó y se evaporó al vacío, dando 272 mg (rendimiento del 99 %) de 7-(2-cloropiridin-4-il)-3-(3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidina en forma de un sólido de color amarillo que se usó directamente en la siguiente etapa. EM: 414,1 [M+H].

Etapa 5: Una mezcla de 7-(2-cloropiridin-4-il)-3-(3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidina (272 mg, 0,66 mmol), diclorhidrato de 3-(S)-aminoquinuclidina (654 mg, 3,29 mmol) y DIPEA (1,28 g, 9,9 mmol) en 2,0 ml

de DMSO anhidro se sometió a microondas a 170 °C durante una hora. La mezcla de reacción en bruto resultante se purificó por HPLC, dando 43 mg (rendimiento del 13 %) de (3R)-N-{4-[3-(3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]piridin-2-il}quinuclidin-3-amina en forma de un sólido de color amarillo. EM: 504,5 [M+H].

Ejemplo 5: 5-(7-{6-[(3R)-1-Azabiciclo[2.2.2]oct-3-ilamino]piridin-3-il}-3-(4-cloro-3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidina

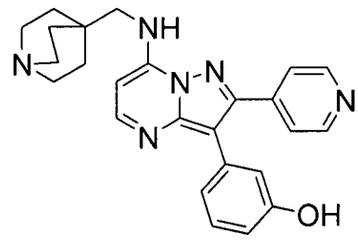


Etapa 1: Una mezcla de (2E)-1-(4-bromofenil)-3-(dimetilamino)prop-2-en-1-ona (125 mg, 0,5 mmol), (4-cloro-3-metoxifenil)-5-piridin-4-il-1H-pirazol-3-amina (150 mg, 0,5 mmol; preparada siguiendo el procedimiento del Ejemplo 1, Etapa 2, partiendo con (4-cloro-3-metoxifenil)acetonitrilo) y 1,5 ml de ácido acético glacial, se calentó en el microondas a 120 °C durante 1 hora. Después, el ácido acético se retiró a presión reducida, se añadió $NaHCO_3$ saturado y la mezcla resultante se extrajo con diclorometano con MeOH al 3 %. La fase orgánica se secó y se evaporó al vacío y el producto en bruto recuperado se cromatografió sobre gel de sílice, dando 98 mg (rendimiento del 40 %) de 7-(6-bromopiridin-3-il)-3-(4-cloro-3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidina

en forma de un sólido de color amarillo. EM: 494,1 [M+H].

Etapa 2: Una mezcla de 7-(6-bromopiridin-3-il)-3-(4-cloro-3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidina (90 mg, 0,18 mmol), diclorhidrato de 3-(R)-aminoquinuclidina (35 mg, 0,22 mmol), DIPEA (47 mg, 0,36 mmol) y 1,0 ml de DMSO anhidro se calentó en el microondas a 150 °C durante 3900 seg. Después, la mezcla de reacción en bruto se purificó por HPLC, dando 48 mg (rendimiento del 44 %) de 5-(7-{6-[(3R)-1-azabiciclo[2.2.2]oct-3-ilamino]piridin-3-il}-3-(4-cloro-3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidina en forma de un sólido de color amarillo. EM: 538,3 [M+H].

Ejemplo 6: 3-{7-[(1-Azabiciclo[2.2.2]oct-4-ilmetil)amino]-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il}fenol



Etapa 1: Una mezcla de 4-[3-(metoxi)fenil]-5-piridin-4-il-1H-pirazol-3-amina (1,5 g, 5,63 mmol) y malonato de dietil etoximetileno (1,4 ml, 6,9 mmol) en ácido acético glacial (15 ml) se calentó a reflujo durante 2,5 horas. La mezcla se enfrió y se trituró con éter. El sólido se recogió por filtración, se lavó con éter y se secó. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice (metanol/cloruro de metileno), dando 1,28 g (rendimiento del 58 %) de 3-(3-metoxifenil)-7-oxo-2-piridin-4-il-4,7-dihidropirazolo[1,5-a]pirimidin-6-carboxilato de etilo en forma de un sólido de color pardo. EM: 391,2 [M+H].

Etapa 2: Una mezcla de 3-(3-metoxifenil)-7-oxo-2-piridin-4-il-4,7-

dihidropirazolo[1,5-a]pirimidin-6-carboxilato de etilo (1,2 g, 3,07 mmol) y solución 2,5 N de hidróxido sódico (5,5 ml) se calentó a reflujo durante 4 horas. La mezcla se enfrió, se acidificó con HCl 2 N y el sólido se recogió por filtración y después se lavó con agua y se secó, produciendo 1,03 g (92 %) de ácido 3-(3-metoxifenil)-7-oxo-2-piridin-4-il-4,7-dihidropirazolo[1,5-a]pirimidin-6-carboxílico en forma de un sólido de color beige, 220-225 °C. EM: 363,2 [M+H].

Etapa 3: A Dowtherm™ (30 ml) en calentamiento a reflujo se le añadió en una porción ácido 3-(3-metoxifenil)-7-oxo-2-piridin-4-il-4,7-dihidropirazolo[1,5-a]pirimidin-6-carboxílico (1,0 g, 2,76 mmol) y la mezcla resultante se calentó a 250 °C durante 45 minutos. Después de enfriar a temperatura ambiente, el sólido se recogió por filtración, se lavó con éter y se secó, proporcionando 0,86 g (rendimiento del 98 %) de 3-(3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7(4H)-ona en forma de un sólido de color amarillo, 110-115 °C. EM: 319,2 [M+H].

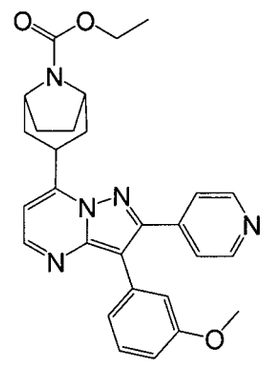
Etapa 4: Una mezcla de 3-(3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7(4H)-ona (0,85 g , 2,6 mmol), N,N-dietilanilina (0,9 ml) y oxicloruro de fósforo (9,0 ml) se calentó a 110 °C durante 2 horas. La mezcla se dejó enfriar y el exceso de oxicloruro de fósforo se evaporó a sequedad, seguido de re-evaporación dos veces en tolueno. El residuo se enfrió en un baño de hielo, se neutralizó con una solución saturada de bicarbonato sódico y se extrajo con metanol al 10 % en cloruro de metileno. La fase orgánica se secó sobre sulfato sódico anhidro, se filtró y el filtrado se evaporó, produciendo un aceite. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice, eluyendo con metanol al 1 % en cloruro de metileno, dando 1,28 g (rendimiento del 58 %) de 7-cloro-3-(3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidina en

forma de un sólido de color amarillo, 135-140 °C. EM: 337,2 [M+H].

Etapa 5: A una solución enfriada (0-5 °C) de 1-(1-azabiciclo[2.2.2]oct-4-il)metanamina (0,13 g, 0,9 mmol) y N,N-diisopropiletilamina (0,3 ml, 1,76 mmol) en acetonitrilo (5 ml) se le añadió en porciones 7-cloro-3-(3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidina (0,15 g, 0,44 mmol) durante un periodo de 5 minutos y la mezcla resultante se agitó a 5 °C durante 2 horas. El disolvente se evaporó y el residuo se agitó con una solución saturada de bicarbonato sódico. El sólido se recogió por filtración, se lavó con agua y se secó. El sólido en bruto resultante se purificó por HPLC preparativa de fase inversa (acetonitrilo/agua/ácido trifluoroacético), dando 0,12 g (rendimiento del 49 %) de (1-aza-biciclo[2.2.2]oct-4-ilmetil)-3-(3-metoxi-fenil)-2-piridin-4-il-pirazolo[1,5,a]pirimidin-7-il]-amina en forma de un sólido de color amarillo. EM: 441,3 [M+H].

Etapa 6: Una mezcla de (1-aza-biciclo[2.2.2]oct-4-ilmetil)-3-(3-metoxi-fenil)-2-piridin-4-il-pirazolo[1,5,a]pirimidin-7-il]-amina (0,092 g, 0,21 mmol) y clorhidrato de piridina (1,2 g, 10,4 mmol) se calentó a 205 °C durante 1 hora. Después de un periodo de refrigeración, la mezcla se basificó con una solución de hidróxido de amonio y el disolvente se evaporó a sequedad, produciendo un residuo en bruto. El residuo se lavó con metanol al 10 % en cloruro de metileno y el filtrado se secó sobre sulfato sódico anhidro, se filtró y el filtrado se evaporó, produciendo un aceite. El aceite en bruto se purificó por HPLC preparativa de fase inversa (acetonitrilo/agua/ácido trifluoroacético), proporcionando 0,025 g (rendimiento del 28 %) de 3-{7-[(1-azabiciclo[2.2.2]oct-4-ilmetil)amino]-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il}fenol en forma de un sólido de color amarillo. EM: 427,3 [M+H].

Ejemplo 7: 3-(3-(3-Metoxifenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo



Etapa 1: Una mezcla de isocianuro de tosilmetilo (5 g, 25,6 mmol) y 3-oxo-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo (3,8 g, 19,7 mmol) en DME (60 ml) y Etanol (1,85 ml) se agitó a -10 °C mientras se añadía en porciones *terc*-butóxido potásico durante el transcurso de 1 hora, en el que la temperatura se mantuvo a < 5 °C. Cuando la adición se completó, la reacción se agitó a -10 °C durante 1 hora y después se agitó durante 2 horas más a temperatura ambiente. Después, los disolventes se retiraron a presión reducida, dando un sólido de color naranja pardo. A este sólido se le añadió agua (200 ml) y se extrajo con éter (4 x 150 ml). El extracto orgánico se secó sobre sulfato de magnesio anhidro, se filtró y el filtrado se evaporó, produciendo un aceite de color pardo. La mezcla en bruto se purificó sobre una columna de sílice eluyendo con acetato de etilo al 30 % en hexanos, dando 2,43 g de 3-ciano-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo (rendimiento del 60 %). EM: 209,2 [M+H].

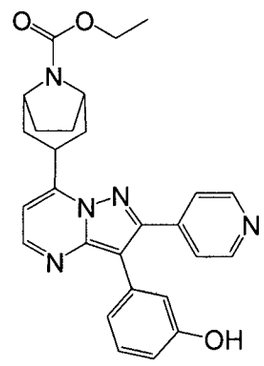
Etapa 2: Se añadió una solución 1,4 M de bromuro de metil magnesio (35,4 ml) en THF/tolueno a una solución de 3-ciano-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo (2,4 g, 11,5 mmol) en THF (50 ml) a ta. La reacción se agitó

durante 3 horas y se inactivó con cloruro de amonio (100 ml). Después, la mezcla se extrajo con éter (4 x 100 ml). Los extractos orgánicos combinados se secaron sobre sulfato de magnesio anhidro, después se filtraron y el filtrado se evaporó, produciendo 3-acetil-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo en forma de un aceite. EM: 226,2 [M+H].

Etapa 3: Una mezcla de 3-acetil-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo (1,7 g, 7,68 mmol) en 25 ml de dimetilformamida dimetil acetal se calentó a 110 °C durante 48 horas. Después, la mezcla de reacción se enfrió a temperatura ambiente y el disolvente se evaporó, proporcionando un aceite de color naranja. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice, eluyendo con acetona al 50 % en diclorometano, dando 0,86 g (rendimiento del 50 %) de 3-(3-(dimetilamino)acriloil)-8-azabiciclo[3.2.1]octano-8-carboxilato de (*E*)-etilo, que se usó sin purificación adicional. EM: 281,2 [M+H].

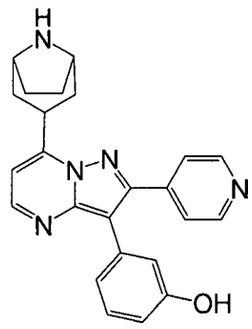
Etapa 4: Una mezcla de 3-(3-(dimetilamino)acriloil)-8-azabiciclo[3.2.1]octano-8-carboxilato de (E)-etilo (0,37 g, 1,3 mmol) y 4-(3-metoxifenil)-3-(piridin-4-il)-1H-pirazol-5-amina (0,35 g, 1,3 mmol) en ácido acético (5 ml) se agitó a 80 °C durante 2 h. La reacción se enfrió a temperatura ambiente y el disolvente se evaporó. La mezcla en bruto se purificó sobre sílice eluyendo con acetona al 50 % en diclorometano, dando 3-(3-(3-metoxifenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo en forma de un sólido de color amarillo. EM: 484,4 [M+H].

Ejemplo 8: 3-(3-(3-Hidroxifenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo



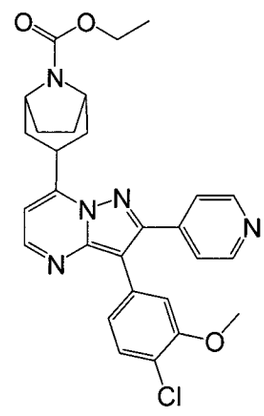
Una solución de 3-(3-(3-metoxifenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo (0,3 g, 0,6 mmol) en diclorometano se enfrió a 0 °C. Después, se añadió una solución 1 M de tribromuro de boro en diclorometano (3,7 ml) mientras se mantenía la temperatura a 0 °C. La reacción se agitó a 0 °C durante 3 horas y después se dejó calentar a temperatura ambiente. Después, la reacción se interrumpió con agua enfriada con hielo y el pH se ajustó a aproximadamente 7, seguido de extracción usando diclorometano (3 x 100 ml). Los extractos orgánicos combinados se secaron sobre sulfato sódico anhidro, se filtraron y el filtrado se evaporó. La mezcla en bruto se purificó sobre sílice eluyendo con acetona al 20 % en diclorometano, dando 3-(3-(3-hidroxifenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo en forma de un sólido de color amarillo. RMN ^{1}H (400 MHz, $CDCl_3$) δ 8,48 (d, J = 4,4 Hz, 1H), 8,41 (d, J = 4,8 Hz, 2H), 7,64 (d, J = 6 Hz, 2H), 7,38 (t, J = 8 Hz, 1H), 7,21 (d, J = 7,6 Hz, 1H), 6,92 (m, 2H), 6,74 (d, J = 4,4 Hz, 1H), 4,19 (m, 3H), 2,18-1,97 (m, 8H), 1,60 (s a, 2H), 1,26 (t, J = 7,2 Hz, 3H). EM: 470,3 [M+H].

Ejemplo 9: 3-(7-(8-Azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)fenol



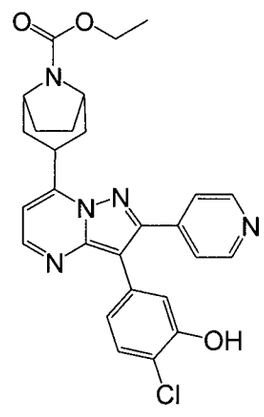
Una solución de 3-(3-(3-hidroxifenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo (0,1 g, 0,21 mmol) y yodotrimetilsilano (0,64 g, 3,2 mmol) en cloroformo se agitó a la temperatura de reflujo durante 5 horas. La reacción se enfrió a temperatura ambiente y el disolvente se evaporó. La mezcla en bruto se purificó usando HPLC prep., dando la sal trifluoroacetato (TFA) de 3-(7-(8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)fenol en forma de un sólido de color amarillo. RMN ^{1}H (400 MHz, DMSO) δ 9,49 (s, 1H), 8,75 (s, 1H), 8,67 (d, J = 4,8 Hz, 2H), 8,62 (d, J = 4 Hz, 1H), 7,68 (d, J = 4,8 Hz, 2H), 7,22 (t, J = 8 Hz, 1H), 7,08 (d, J = 4 Hz, 1H), 6,89 (d, J = 4 Hz, 1H), 6,83 (d, J = 6 Hz, 1H), 6,77 (d, J = 6,8 Hz, 1H), 4,10 (dt, J = 4,8 Hz, 7,6 Hz, 1H), 2,48 (m, 2H), 2,30 (m, 2H), 2,15 (m, 6H). EM: 398,3 [M+H].

Ejemplo 10: 3-(3-(4-Cloro-3-metoxifenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo



Se sintetizó 3-(3-(4-cloro-3-metoxifenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo de acuerdo con el procedimiento para el Ejemplo 7, Etapa 4, partiendo de 3-(3-(dimetilamino)acriloil)-8-azabiciclo[3.2.1]octano-8-carboxilato de (E)-etilo y (4-cloro-3-metoxifenil)-5-piridin-4-il-1H-pirazol-3-amina. EM: 518,3 [M+ H].

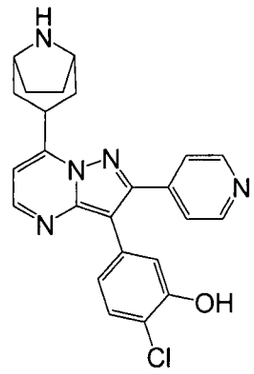
Ejemplo 11: 3-(3-(4-Cloro-3-hidroxifenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo



Se sintetizó 3-(3-(4-cloro-3-hidroxifenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo partiendo de 3-(3-(4-cloro-3-metoxifenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, el producto del Ejemplo 10, por

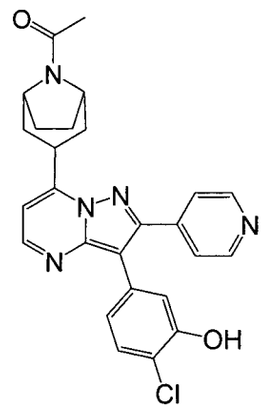
reacción con tribromuro de boro de acuerdo con el procedimiento para el Ejemplo 8. EM: 504,3 [M+H].

Ejemplo 12: 5-(7-(8-Azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)-2-clorofenol



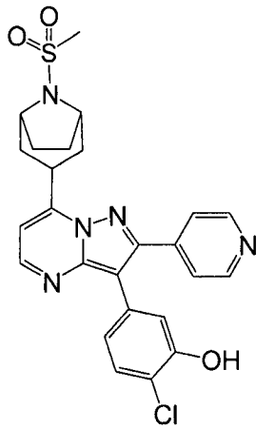
La reacción de 3-(3-(4-cloro-3-hidroxifenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, el producto del Ejemplo 11, con yodotrimetilsilano, de acuerdo con el procedimiento para el Ejemplo 9, proporcionó 5-(7-(8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)-2-clorofenol. RMN ^{1}H (400 MHz, DMSO) δ 10,28 (s, 1H) 8,80 (s, 1H), 8,73 (d, J = 8 Hz, 2H), 8,65 (d, J = 4 Hz, 1 Hz), 7,76 (d, J = 4 Hz, 2H), 7,39 (d, J = 8 Hz, 1H), 7,12 (m, 2H), 6,87 (d, J = 8 Hz, 1H), 4,10 (dt, J = 5,2 Hz, 7,2 Hz, 1H), 2,48 (m, 2H), 2,30 (m, 2H), 2,15 (m, 6H). EM: 432,3 [M+H].

Ejemplo 13: 5-[7-(8-Acetil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]-2-clorofenol



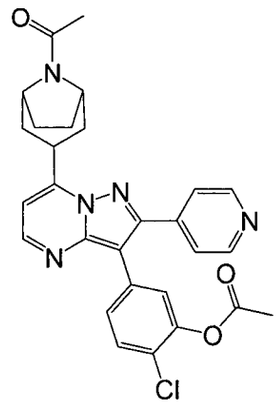
Una solución de 5-(7-(8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)-2-clorofenol (0,15 g, 0,35 mmol), el producto del Ejemplo 12 y trietilamina (140 µl, 1,05 mmol) en 1-metil-2-pirrolidinona se enfrió a 0 ºC. Después, se añadió cloruro de acetilo (23 µl, 0,33 mmol) y la reacción se agitó a 0 ºC durante 1 hora. La reacción se calentó a temperatura ambiente y se diluyó con agua y diclorometano seguido de extracción con bicarbonato sódico saturado (2 x 50 ml). Los extractos orgánicos combinados se secaron sobre sulfato sódico anhidro, se filtraron y el filtrado se evaporó. La mezcla en bruto se purificó por HPLC de fase inversa (acetonitrilo/agua/ácido trifluoroacético), proporcionando 0,015 g (rendimiento del 7 %) de 5-[7-(8-acetil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]-2-clorofenol. EM: 474,3 [M+H].

Ejemplo 14: 2-Cloro-5-{7-[8-(metilsulfonil)-8-azabiciclo[3.2.1]oct-3-il]-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il}fenol



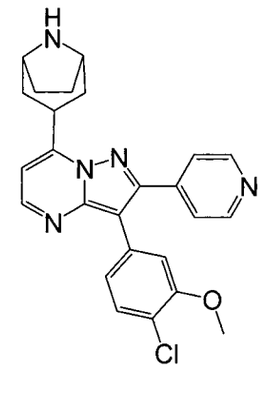
Una solución de 5-(7-(8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)-2-clorofenol (0,15 g, 0,35 mmol), el producto del Ejemplo 12 y trietilamina (140 µl, 1,05 mmol) en 1-metil-2-pirrolidinona se enfrió a 0 ºC. Después, se añadió cloruro de metilsulfonilo (25 µl, 0,33 mmol) y la reacción se agitó a 0 ºC durante 1 hora. La reacción se calentó a temperatura ambiente y se diluyó con agua y diclorometano seguido de extracción con bicarbonato sódico saturado (2 x 50 ml). Los extractos orgánicos combinados se secaron sobre sulfato sódico anhidro, se filtraron y el filtrado se evaporó. La mezcla en bruto se purificó por HPLC de fase inversa (acetonitrilo/agua/ácido trifluoroacético), proporcionando 0,017 g (rendimiento del 9 %) de 2-cloro-5-{7-[8-(metilsulfonil)-8-azabiciclo[3.2.1]oct-3-il]-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il}fenol. EM: 510,3 [M+H].

Ejemplo 15: Acetato de 5-[7-(8-acetil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]-2-clorofenilo



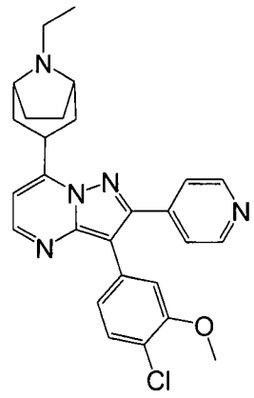
A una solución de 5-(7-(8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)-2-clorofenol (0,10 g, 0,23 mmol) y el producto del Ejemplo 12 en diclorometano se le añadió trietilamina (200 µl, 1,4 mmol). Después, se añadió cloruro de acetilo (36 µl, 0,51 mmol) y la reacción se agitó durante 1 hora. La reacción se extrajo con cloruro de amonio saturado (2 x 50 ml). Los extractos orgánicos combinados se secaron sobre sulfato sódico anhidro, se filtraron y el filtrado se evaporó. La mezcla en bruto se purificó por TLC preparativa usando metanol al 5 %/diclorometano, proporcionando 0,058 g (rendimiento del 48 %) de acetato de 5-[7-(8-acetil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]-2-clorofenilo. EM: 516,4 [M+H].

Ejemplo 16: 7-(8-Azabiciclo[3.2.1]oct-3-il)-3-(4-cloro-3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidina



Se preparó 7-(8-azabiciclo[3.2.1]oct-3-il)-3-(4-cloro-3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidina a partir de 3-(3-(4-cloro-3-metoxifenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo-[3.2.1]octano-8-carboxilato de etilo, el producto del Ejemplo 10, usando yodotrimetilsilano de acuerdo con el procedimiento para el Ejemplo 9. EM 446: [M+H].

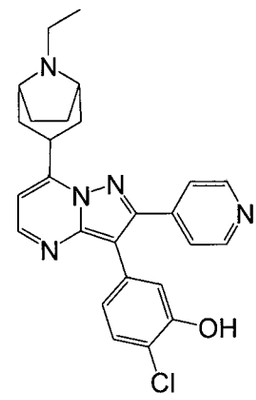
Ejemplo 17: 3-(4-Cloro-3-metoxifenil)-7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina



A una solución de 7-(8-azabiciclo[3.2.1]oct-3-il)-3-(4-cloro-3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidina (0,258 g, 0,58 mmol), el producto del Ejemplo 16 y carbonato potásico (321 mg, 2,3 mmol) en N,N-dimetilformamida se le añadió yodoetano (92 µl, 1,16 mmol) y la reacción se agitó durante 3 horas. Después, la reacción se añadió a agua (25 ml) y el sólido en bruto resultante se filtró y se secó. El sólido en bruto se purificó por cromatografía sobre gel de sílice eluyendo con un gradiente del 5 %-10 %-15 %-20 % de metanol en diclorometano, proporcionando 0,172 g (rendimiento del 63 %) de 3-(4-cloro-3-metoxifenil)-7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina. EM: 474,3 [M+H].

Ejemplo 18: 2-Cloro-5-[7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-

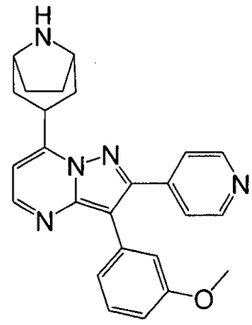
ilpirazolo[1,5-a]pirimidin-3-il]fenol



Una solución de 3-(4-cloro-3-metoxifenil)-7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina (0,09 g, 0,19 mmol) y el producto del Ejemplo 17 en diclorometano se enfrió a 0 °C. Después, se añadió una solución 1 M de tribromuro de boro en diclorometano (1,12 ml) mientras se mantenía la temperatura a 0 °C. La reacción se agitó a 0 °C durante 3 horas y después se dejó calentar a temperatura ambiente. Después, la reacción se interrumpió con agua enfriada con hielo y el pH se ajustó a aproximadamente 7 seguido de extracción con diclorometano (3 x 100 ml). Los extractos orgánicos combinados se extrajeron con HCl acuoso al 10 % (2 x 15 ml). El pH de los extractos acuosos combinados se ajustó a aproximadamente pH 10 con carbonato sódico. El sólido resultante se filtró y se secó, dando el producto en bruto. Los extractos acuosos restantes se concentraron y el sólido resultante se lavó con metanol al 10 %/diclorometano. Los extractos orgánicos se concentraron al vacío, dando más cantidad de producto en bruto. Los productos en bruto se combinaron y se purificaron sobre gel de sílice eluyendo con metanol al 10 %/diclorometano, dando 56 mg (rendimiento del 64 %) de 2-cloro-5-[7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]fenol. EM:

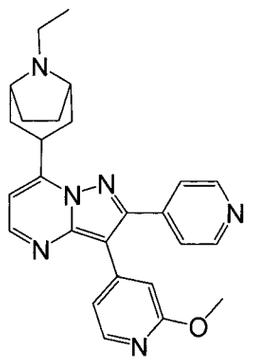
460,4 [M+H].

Ejemplo 19: 7-(8-Azabiciclo[3.2.1]oct-3-il)-3-(3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidina



3-(3-(3-Metoxifenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo (0,4 g, 0,8 mmol), el producto del Ejemplo 7, se calentó a reflujo en cloroformo. Se añadió en dos alícuotas yodotrimetilsilano (0,8 g + 0,4 g, 6,0 mmol en total) mientras se supervisaba la reacción para determinar si se había completado en 5 horas. El sólido de color naranja resultante se recogió por filtración, se disolvió en diclorometano/metanol (9:1), se adsorbió sobre sílice y se cromatografió en metanol al 5-15 %/diclorometano, proporcionando 0,11 g (rendimiento del 33 %) de 7-(8-azabiciclo[3.2.1]oct-3-il)-3-(3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidina en forma de un sólido de color amarillo. EM: 412,4 [M+H].

Ejemplo 20: 7-(8-Etil-8-azabiciclo[3.2.1]octan-3-il)-3-(2-metoxipiridin-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina



Etapa 1: Se sintetizó 3-(2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo de acuerdo con el procedimiento para el Ejemplo 7, Etapa 4, partiendo de 3-(3-(dimetilamino)acriloil)-8-azabiciclo[3.2.1]octano-8-carboxilato de (*E*)-etilo y 3-(piridin-4-il)-1H-pirazol-5-amina. EM: 378,4 [M+ H].

Etapa 2: Se sintetizó 7-(8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina de acuerdo con el procedimiento para el Ejemplo 9 partiendo de 3-(2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo. EM: 306,3 [M+ H].

Etapa 3: Una mezcla de 7-(8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina (3,1 g, 10,2 mmol), anhídrido trifluoroacético (1,48 ml, 10,7 mmol) y trietilamina (4,26 ml, 30,6 mmol) en diclorometano (100 ml) se agitó durante 1 hora. Después, la reacción se extrajo una vez con bicarbonato sódico saturado (200 ml) y cloruro de amonio saturado (200 ml). La fase orgánica se secó sobre sulfato sódico anhidro, se filtró y el filtrado se evaporó, produciendo un sólido. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice, eluyendo con metanol al 5-20 % en diclorometano, dando 2,1 g (rendimiento del 51 %) de 2,2,2-trifluoro-1-(3-(2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octan-8-il)etanona.

EM: 402,3 [M+H].

Etapa 4: A una solución de 2,2,2-trifluoro-1-(3-(2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octan-8-il)etanona (2,1 g, 5,2 mmol) en diclorometano (125 ml) se le añadió en tres porciones N-yodosuccinamida (17 g, 52,3 mmol) durante un periodo de 3 horas y después la reacción se agitó durante 16 horas más. La reacción se extrajo con tiosulfato sódico saturado (2 x 200 ml). La fase orgánica se secó sobre sulfato sódico anhidro, se filtró y el filtrado se evaporó, dando 3,0 g de 2,2,2-trifluoro-1-(3-(3-yodo-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octan-8-il)etanona en forma de un sólido de color amarillo. Este producto se usó en la siguiente etapa sin purificación adicional. EM: 528,1 [M+H].

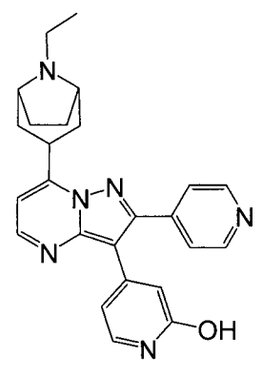
Etapa 5: Una mezcla de 2,2,2-trifluoro-1-(3-(3-yodo-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octan-8-il)etanona (3,0 g, 5,7 mmol), carbonato potásico (3,5 g, 25 mmol), metanol (50 ml) y agua (10 ml) se agitó durante 4 días. Después, el disolvente se retiró y el sólido en bruto restante se agitó en metanol al 10 % en diclorometano. Los sólidos restantes se retiraron por filtración y se lavaron con diclorometano. El filtrado se concentró al vacío, dando 7-(8-azabiciclo[3.2.1]octan-3-il)-3-yodo-2-(piridin-4-il)pirazolo[1,5-a]pirimidina en forma de un sólido de color amarillo que se usó directamente en la siguiente etapa.

Etapa 6: Siguiendo el procedimiento del Ejemplo 17, se hizo reaccionar 7-(8-azabiciclo[3.2.1]octan-3-il)-3-yodo-2-(piridin-4-il)pirazolo[1,5-a]pirimidina (2,9 g, 5,7 mmol) con carbonato potásico y yodoetano en dimetilformamida, proporcionando 2,3 g (rendimiento del 86 %) de 7-(8-etil-8-azabiciclo[3.2.1]octan-3-il)-3-yodo-2-(piridin-4-il)pirazolo[1,5-a]pirimidina en

forma de un sólido de color amarillo. EM: 460,3 [M+H].

Etapa 7: Se disolvieron 7-(8-etil-8-azabiciclo[3.2.1]octan-3-il)-3-yodo-2-(piridin-4-il)pirazolo[1,5-a]pirimidina (150 mg, 0,32 mmol) y ácido 2-metoxipiridin-4-ilborónico (100 mg, 0,65 mmol) en éter dimetílico de etilenglicol (3 ml) y a la solución resultante se le añadió complejo de (1,1'-bis(difenilfosfino)ferroceno)dicloropaladio (II) y diclorometano (53 mg). Después, a la mezcla de reacción se le añadió una solución de carbonato potásico (90 mg, 2,24 mmol) en agua (0,5 ml) y la reacción se calentó a 80 ºC durante 3 horas. Después, la reacción se enfrió y se añadió bicarbonato sódico saturado (20 ml). Después, la mezcla se extrajo con diclorometano (2 x 50 ml). La fase orgánica se secó sobre sulfato sódico anhidro, se filtró y el filtrado se evaporó, produciendo un sólido. El sólido en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice, eluyendo con metanol al 15 % en diclorometano, dando 0,07 g (rendimiento del 50 %) de 7-(8-etil-8-azabiciclo[3.2.1]octan-3-il)-3-(2-metoxipiridin-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina. EM: 441,3 [M+H].

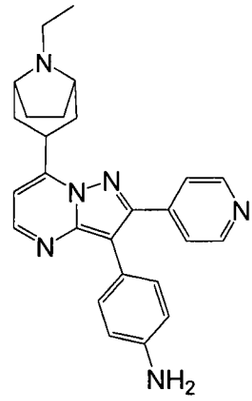
Ejemplo 21: 4-(7-(8-Etil-8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)piridin-2-ol



Una mezcla de 7-(8-etil-8-azabiciclo[3.2.1]octan-3-il)-3-(2-metoxipiridin-4-

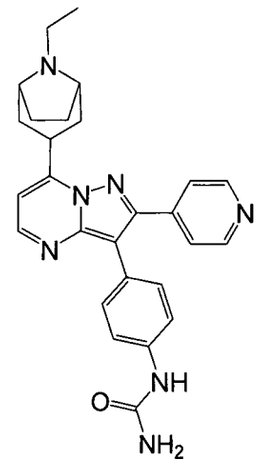
il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina (0,68 g, 0,15 mmol) y clorhidrato de piridina (0,68 g) se agitó a 180 °C durante 30 minutos. Después, la reacción se enfrió y se diluyó con bicarbonato sódico saturado. El disolvente se retiró y el sólido en bruto restante se lavó con metanol al 10 % en diclorometano. La fase orgánica se secó sobre sulfato sódico anhidro, se filtró y el filtrado se evaporó, dando 0,049 g (rendimiento del 75 %) de 4-(7-(8-etil-8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)piridin-2-ol en forma de un sólido de color amarillo. EM: 427,3 [M+H].

Ejemplo 22: 4-(7-(8-Etil-8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)anilina



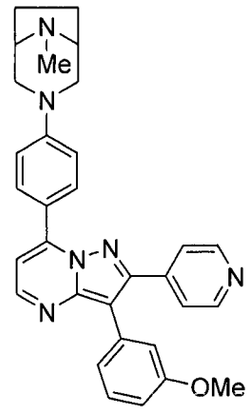
Siguiendo el procedimiento del Ejemplo 20, Etapa 7, se hizo reaccionar 7-(8-etil-8-azabiciclo[3.2.1]octan-3-il)-3-yodo-2-(piridin-4-il)pirazolo[1,5-a]pirimidina con 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina, proporcionando 81 mg (rendimiento del 60 %) de 4-(7-(8-etil-8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)anilina en forma de un sólido de color amarillo. EM: 425,3 [M+H].

Ejemplo 23: 1-(4-(7-(8-Etil-8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)fenil)urea



Una mezcla de 4-(7-(8-etil-8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)anilina (23 mg, 0,05 mmol), el producto del Ejemplo 22 y trietilamina (22 µl, 0,16 mmol) en diclorometano (1,5 ml) se añadió a una solución de trifosgeno (8 mg, 0,025 mmol) en diclorometano (0,5 ml) y se agitó durante 10 minutos. A esta mezcla se le añadió una solución 2 M de amoniaco en dioxano (2 ml) y la mezcla resultante se agitó durante 30 minutos más. La reacción se diluyó con diclorometano (5 ml) y se extrajo con bicarbonato sódico saturado (2 x 5 ml). La fase orgánica se secó sobre sulfato sódico anhidro, se filtró y el filtrado se evaporó, dando un sólido. El sólido en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice, eluyendo con metanol al 15 % en diclorometano, dando 5,1 mg (rendimiento del 20 %) de 1-(4-(7-(8-etil-8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)fenil)urea en forma de un sólido de color amarillo. EM: 468,3 [M+H].

Ejemplo 24: 3-(3-Metoxi-fenil)-7-[4-(8-metil-3,8-diaza-biciclo[3.2.1]oct-3-il)-fenil]-2-piridin-4-il-pirazolo[1,5-a]pirimidina

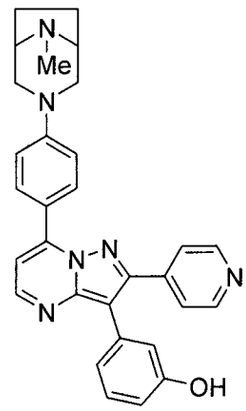


Etapa 1: Siguiendo el procedimiento del Ejemplo 1, Etapa 1, se hizo reaccionar 1-(4-bromo-fenil)-etanona con dimetilformamida dimetil acetal, proporcionando 1-(4-bromo-fenil)-3-dimetilamino-propenona. EM: 254,2 [M+H].

Etapa 2: Siguiendo el procedimiento del Ejemplo 7, Etapa 4, se hizo reaccionar 1-(4-bromo-fenil)-3-dimetilamino-propenona con 4-(3-metoxifenil)-3-(piridin-4-il)-1H-pirazol-5-amina, proporcionando 7-(4-bromo-fenil)-3-(3-metoxi-fenil)-2-piridin-4-il-pirazolo[1,5-a]pirimidina. EM: 457,3 [M+H].

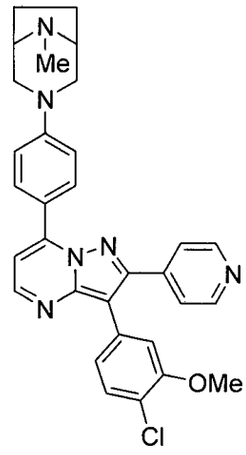
Etapa 3: Un tubo cerrado herméticamente se cargó con 7-(4-bromo-fenil)-3-(3-metoxi-fenil)-2-piridin-4-il-pirazolo[1,5-a]pirimidina (65 mg, 0,14 mmol), diclorhidrato de 8-metil-3,8-diaza-biciclo[3.2.1]octano (25 mg, 0,13 mmol), terc-butóxido sódico (37 mg, 0,39 mmol), tris(dibencilidenoacetona)dipaladio (0) (25 mg, 0,027 mmol,), BINAP (66 mg, 0,1 mmol) y THF (3 ml) en una atmósfera de nitrógeno. El tubo se calentó a 100 °C durante una noche. Después, la solución se dejó enfriar a temperatura ambiente, se concentró, se disolvió en DMSO, se filtró y se purificó por HPLC, dando la sal TFA de 3-(3-metoxi-fenil)-7-[4-(8-metil-3,8-diaza-biciclo[3.2.1]oct-3-il)-fenil]-2-piridin-4-il-pirazolo[1,5-]pirimidina en forma de un sólido de color amarillo. EM: 503,5 [M+H].

Ejemplo 25: 3-{7-[4-(8-Metil-3,8-diaza-biciclo[3.2.1]oct-3-il)-fenil]-2-piridin-4-il-pirazolo[1,5-a]pirimidin-3-il}-fenol



Siguiendo el procedimiento del Ejemplo 8, se hizo reaccionar 3-(3-metoxi-fenil)-7-[4-(8-metil-3,8-diaza-biciclo[3.2.1]oct-3-il)-fenil]-2-piridin-4-il-pirazolo[1,5-]pirimidina con tribromuro de boro y después se purificó usando HPLC, proporcionando 3-{7-[4-(8-metil-3,8-diaza-biciclo[3.2.1]oct-3-il)-fenil]-2-piridin-4-il-pirazolo[1,5-a]pirimidin-3-il}-fenol. EM: 489,5 [M+H].

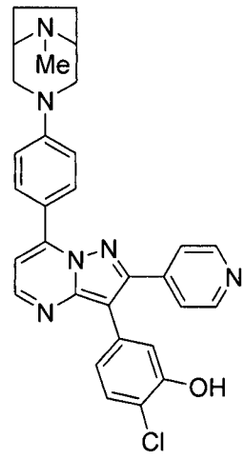
Ejemplo 26: 3-(4-Cloro-3-metoxi-fenil)-7-[4-(8-metil-3,8-diaza-biciclo[3.2.1]oct-3-il)-fenil]-2-piridin-4-il-pirazolo[1,5-a]pirimidina



Siguiendo el procedimiento del Ejemplo 24, partiendo de 4-(4-cloro-3-metoxi-fenil)-5-piridin-4-il-2H-pirazol-3-ilamina, se obtuvo 3-(4-cloro-3-metoxi-

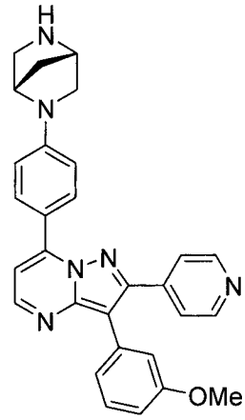
fenil)-7-[4-(8-metil-3,8-diaza-biciclo[3.2.1]oct-3-il)-fenil]-2-piridin-4-il-pirazolo[1,5-a]pirimidina en forma de la sal TFA como un sólido de color amarillo. EM: 537,5 [M+H].

Ejemplo 27: 2-Cloro-5-{7-[4-(8-metil-3,8-diaza-biciclo[3.2.1]oct-3-il)-fenil]-2-piridin-4-il-pirazolo[1,5-a]pirimidin-3-il}-fenol



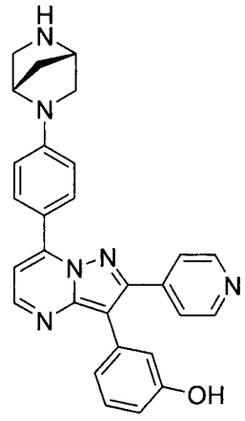
Siguiendo el procedimiento del Ejemplo 8, se hizo reaccionar 3-(4-cloro-3-metoxi-fenil)-7-[4-(8-metil-3,8-diaza-biciclo[3.2.1]oct-3-il)-fenil]-2-piridin-4-il-pirazolo[1,5-a]pirimidina con tribromuro de boro y después se purificó usando HPLC, proporcionando 2-cloro-5-{7-[4-(8-metil-3,8-diaza-biciclo[3.2.1]oct-3-il)-fenil]-2-piridin-4-il-pirazolo[1,5-a]pirimidin-3-il}-fenol. EM: 523,5 [M+H].

Ejemplo 28: 7-[4-((1S,4S)-2,5-Diaza-biciclo[2.2.1]hept-2-il)-fenil]-3-(3-metoxi-fenil)-2-piridin-4-il-pirazolo[1,5-a]pirimidina



Siguiendo el procedimiento del Ejemplo 24, partiendo de 4-(3-metoxi-fenil)-5-piridin-4-il-2H-pirazol-3-ilamina y dibromhidrato de (1S,4S)-2,5-diaza-biciclo[2.2.1]heptano, se obtuvo sal trifluoroacetato de 7-[4-((1S,4S)-2,5-diaza-biciclo[2.2.1]hept-2-il)-fenil]-3-(3-metoxi-fenil)-2-piridin-4-il-pirazolo[1,5-a]pirimidina en forma de un sólido de color amarillo. EM: 475,5 [M+H].

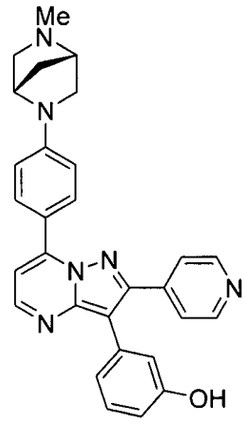
Ejemplo 29: 3-{7-[4-((1S,4S)-2,5-Diaza-biciclo[2.2.1]hept-2-il)-fenil]-2-piridin-4-il-pirazolo[1,5-a]pirimidin-3-il}-fenol



Siguiendo el procedimiento del Ejemplo 8, se hizo reaccionar 7-[4-((1S,4S)-2,5-diaza-biciclo[2.2.1]hept-2-il)-fenil]-3-(3-metoxi-fenil)-2-piridin-4-il-pirazolo[1,5-a]pirimidina con tribromuro de boro y después se purificó usando HPLC, proporcionando sal trifluoroacetato de 3-{7-[4-((1S,4S)-2,5-diaza-

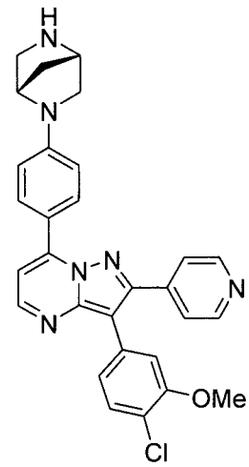
biciclo[2.2.1]hept-2-il)-fenil]-2-piridin-4-il-pirazolo[1,5-a]pirimidin-3-il}-fenol. EM: 461,4 [M+H].

Ejemplo 30: 3-{7-[4-((1S,4S)-5-Metil-2,5-diaza-biciclo[2.2.1]hept-2-il)-fenil]-2-piridin-4-il-pirazolo[1,5-a]pirimidin-3-il}-fenol



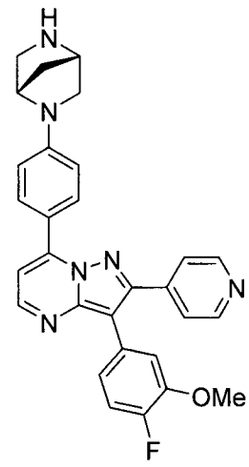
Se añadieron tres gotas de formaldehído (37 % en agua) a una solución de 3-{7-[4-((1S,4S)-2,5-diaza-biciclo[2.2.1]hept-2-il)-fenil]-2-piridin-4-il-pirazolo[1,5-a]pirimidin-3-il}-fenol (18 mg), el producto del Ejemplo 25, y exceso de triacetoxiborohidruro sódico en 2 ml de DMF. Después de 3 horas, la mezcla de reacción se filtró y el producto en bruto se purificó por HPLC, proporcionando sal trifluoroacetato de 3-{7-[4-((1S,4S)-5-metil-2,5-diaza-biciclo[2.2.1]hept-2-il)-fenil]-2-piridin-4-il-pirazolo[1,5-a]pirimidin-3-il}-fenol. EM: 475,5 [M+H].

Ejemplo 31: 7-(4-((1S,4S)-2,5-Diaza-biciclo[2.2.1]heptan-2-il)fenil)-3-(4-cloro-3-metoxifenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina



Siguiendo el procedimiento del Ejemplo 24, Etapas 1-3, 4-(4-cloro-3-metoxifenil)-5-piridin-4-il-2H-pirazol-3-ilamina y dibromhidrato de (1S,4S)-2,5-diaza-biciclo[2.2.1]heptano dieron 7-(4-((1S,4S)-2,5-diaza-biciclo[2.2.1]heptan-2-il)fenil)-3-(4-cloro-3-metoxifenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina en forma de una sal trifluoroacetato. EM: 509,3 [M+H].

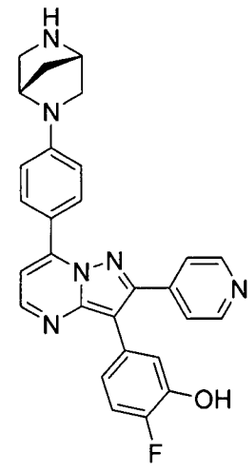
Ejemplo 32: 7-(4-((1S,4S)-2,5-Diaza-biciclo[2.2.1]heptan-2-il)fenil)-3-(4-fluoro-3-metoxifenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina



El compuesto 4-(4-fluoro-3-metoxifenil)-5-piridin-4-il-2H-pirazol-3-ilamina se preparó de acuerdo con el procedimiento del Ejemplo 1, Etapa 2, partiendo

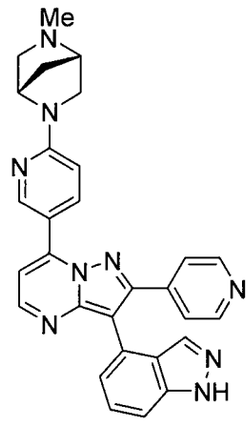
de 4-fluoro-3-metoxi-bencenoacetonitrilo. Siguiendo el procedimiento del Ejemplo 24, Etapas 1-3, y usando dibromhidrato de (1S,4S)-2,5-diaza-biciclo[2.2.1]heptano en la etapa 3, 4-(4-fluoro-3-metoxifenil)-5-piridin-4-il-2H-pirazol-3-ilamina dio sal trifluoroacetato de 7-(4-((1S,4S)-2,5-diaza-biciclo[2.2.1]heptan-2-il)fenil)-3-(4-fluoro-3-metoxifenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina. EM: 493,5 [M+H].

Ejemplo 33: 5-(7-(4-((1S,4S)-2,5-Diazabiciclo[2.2.1]heptan-2-il)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)-2-fluorofenol



Siguiendo el procedimiento del Ejemplo 8, se hizo reaccionar 7-(4-((1S,4S)-2,5-diaza-biciclo[2.2.1]heptan-2-il)fenil)-3-(4-fluoro-3-metoxifenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina con tribromuro de boro y el producto resultante se purificó por HPLC, proporcionando sal trifluoroacetato de 5-(7-(4-((1S,4S)-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)-2-fluorofenol. EM: 479,5 [M+H].

Ejemplo 34: 3-(1H-Indazol-4-il)-7-(6-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)piridin-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina



Etapa 1: Siguiendo el procedimiento del Ejemplo 1, Etapa 3, se hizo reaccionar 1-(6-bromo-piridin-3-il)-3-dimetilamino-propenona con 3-(piridin-4-il)-1H-pirazol-5-amina, dando 7-(6-bromopiridin-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina en forma de un sólido de color amarillo.

Etapa 2: Siguiendo el procedimiento del Ejemplo 1, Etapa 4, se hizo reaccionar 7-(6-bromopiridin-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina con dibromhidrato de (1S,4S)-2,5-diaza-biciclo[2.2.1]heptano y se purificó por cromatografía sobre gel de sílice, dando 7-(6-((1S,4S)-2,5-diazabiciclo[2.2.1]heptan-2-il)piridin-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina. EM: 370,4 [M+H].

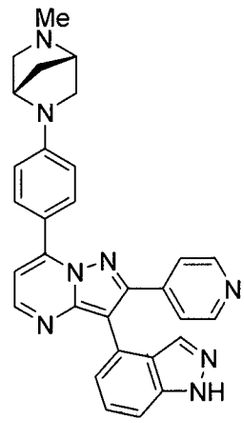
Etapa 3: Se disolvió 7-(6-((1S,4S)-2,5-diazabiciclo[2.2.1]heptan-2-il)piridin-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina (100 mg, 0,27 mmol) en 5 ml de DMF y después se añadieron formaldehído al 37 % (0,10 ml, 1,35 mmol) y una gota de ácido acético. La solución se agitó durante 5 minutos y después se añadió triacetoxiborohidruro sódico (286 mg, 1,35 mmol). La reacción se interrumpió con 2 ml de una solución de amoniaco metanólico después de una hora. Después, la mezcla se concentró y se purificó por cromatografía sobre gel de sílice, dando 7-(6-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-

il)piridin-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina. EM: 384,4 [M+H].

Etapa 4: Se disolvió 7-(6-((1S,4S)-5-Metil-2,5-diazabiciclo[2.2.1]heptan-2-il)piridin-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina (200 mg, 0,52 mmol) en 10 ml de diclorometano y 1 ml de ácido acético y después se añadió *N*-yodosuccinimida (175 mg, 0,78 mmol). Después de una hora, la reacción resultante se interrumpió con una solución de amoniaco metanólico, se concentró y se purificó por cromatografía sobre gel de sílice, dando 3-yodo-7-(6-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)piridin-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina. EM: 510,4 [M+H].

Etapa 5: A una suspensión de 3-yodo-7-(6-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)piridin-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina (110 mg, 0,22 mmol) en 3 ml de dimetoxietano se le añadieron carbonato sódico 2 M (0,22 ml, 0,44 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-indazol (100 mg [pureza del 79 %, 0,32 mmol) y una cantidad catalítica de tetraquis(trifenilfosfina)paladio (0). La mezcla se calentó a 130 °C durante 50 minutos en un reactor de microondas. El producto en bruto se purificó por HPLC y después por cromatografía sobre gel de sílice, dando el producto deseado en forma de una base libre. La base libre se disolvió en metanol y después se añadió 1 ml de HCl metanólico 1,25 M. La solución se concentró al vacío y se secó, dando sal clorhidrato de 3-(1H-indazol-4-il)-7-(6-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)piridin-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina. EM: 500,3 [M+H].

Ejemplo 35: 3-(1H-indazol-4-il)-7-(4-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina



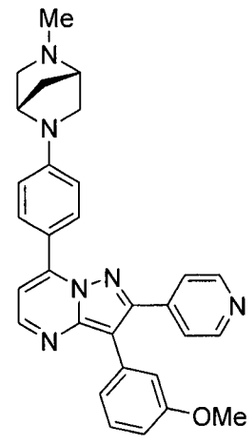
Etapa 1: Siguiendo el procedimiento del Ejemplo 1, Etapa 3, se hizo reaccionar (E)-1-(4-bromofenil)-3-(dimetilamino)prop-2-en-1-ona con 3-(piridin-4-il)-1H-pirazol-5-amina, dando 7-(4-bromofenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina en forma de un sólido de color amarillo.

Etapa 2: Siguiendo el procedimiento del Ejemplo 24, Etapa 3, Se acopló 7-(4-bromofenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina con dibromhidrato de (1S,4S)-2,5-diaza-biciclo[2.2.1]heptano, dando 7-(4-((1S,4S)-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina. EM: 369,4 [M+H].

Etapas 3-5: Siguiendo el procedimiento del Ejemplo 34, Etapas 3-5, se convirtió 7-(4-((1S,4S)-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina en sal clorhidrato de 3-(1H-indazol-4-il)-7-(4-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina, obtenida en forma de un sólido de color rojo oscuro. RMN ^{1}H (400 MHz, $CDCl_3$) δ 8,73-8,70 (m, 2H), 8,57 (d, J = 4,4 Hz, 1H), 8,41–8,36 (m, 2H), 8,26–8,21 (m, 2H), 7,73–7,67 (m, 2H), 7,58 (dd, J = 7,0, 8,2 HZ, 1H), 7,38 (d, J = 4,8 Hz, 1H), 7,35–7,31 (m, 1H), 6,99–6,93 (m, 2H), 4,51–4,47 (m, 1H), 3,92–3,82 (m, 2H), 3,60 (d, J = 11,2 Hz, 1H), 3,04 (s, 3H), 2,55-2,49

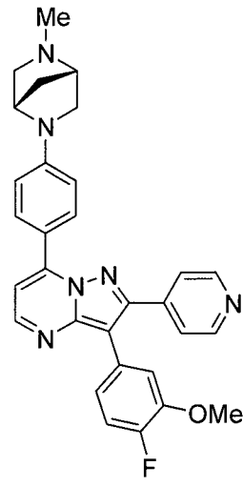
(m, 1H), 2,41–2,34 (m, 1H). EM: 499,5 [M+H].

Ejemplo 36: 3-(3-Metoxifenil)-7-(4-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina



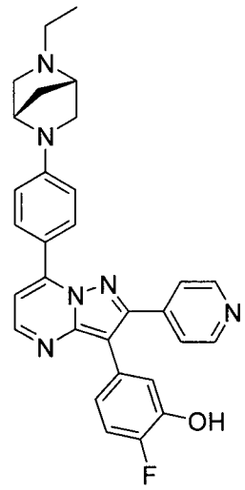
Siguiendo el procedimiento del Ejemplo 30, se convirtió 7-[4-((1S,4S)-2,5-diaza-biciclo[2.2.1]hept-2-il)-fenil]-3-(3-metoxi-fenil)-2-piridin-4-il-pirazolo[1,5-a]pirimidina en 3-(3-metoxifenil)-7-(4-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina, obtenida en forma de una sal trifluoroacetato. EM: 489,5 [M+H].

Ejemplo 37: 3-(4-Fluoro-3-metoxifenil)-7-(4-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina



Siguiendo el procedimiento del Ejemplo 30, se convirtió 7-(4-((1S,4S)-2,5-diaza-biciclo[2.2.1]heptan-2-il)fenil)-3-(4-fluoro-3-metoxifenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina en 3-(4-fluoro-3-metoxifenil)-7-(4-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina, obtenida en forma de una sal trifluoroacetato. EM: 507,5 [M+H].

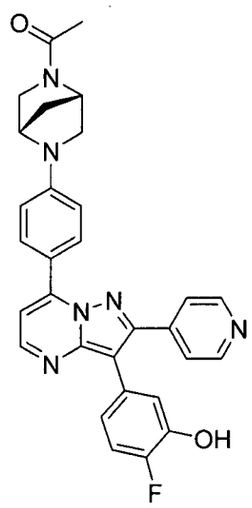
Ejemplo 38: 5-(7-(4-((1S,4S)-5-Etil-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)-2-fluorofenol



Siguiendo el procedimiento del Ejemplo 30, acetaldehído y 5-(7-(4-((1S,4S)-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-2-(piridin-4-il)pirazolo[1,5-

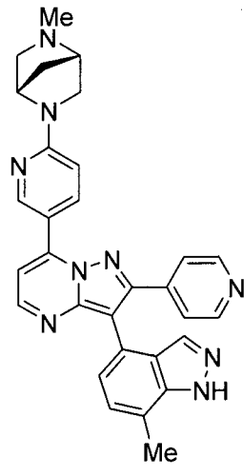
a]pirimidin-3-il)-2-fluorofenol proporcionaron 5-(7-(4-((1S,4S)-5-etil-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)-2-fluorofenol en forma de una sal trifluoroacetato. EM: 507,3 [M+H].

Ejemplo 39: 1-((1S,4S)-5-(4-(3-(4-Fluoro-3-hidroxifenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)fenil)-2,5-diazabiciclo[2.2.1]heptan-2-il)etanona



El compuesto 5-(7-(4-((1S,4S)-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)-2-fluorofenol se acetiló, dando 1-((1S,4S)-5-(4-(3-(4-fluoro-3-hidroxifenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)fenil)-2,5-diazabiciclo[2.2.1]heptan-2-il)etanona. EM: 521,5 [M+H].

Ejemplo 40: 3-(7-Metil-1H-indazol-4-il)-7-(6-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)piridin-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina



Etapa 1: Una mezcla de nitro-m-xileno (3,02 g, 20,0 mmol), yodo (2,04 g, 8,0 mmol), ácido peryódico (4,1 g, 18,0 mmol) y ácido sulfúrico concentrado (1,2 ml) en ácido acético (2,4 ml) se calentó a 90 °C durante 3 días. Después, la reacción se enfrió, se vertió en agua y se extrajo con diclorometano. Los extractos orgánicos combinados se enfriaron y se lavaron con una solución fría de hidróxido sódico 2 N y salmuera, se secaron sobre sulfato de magnesio anhidro, se filtraron y se concentraron al vacío. El residuo se trituró con hexanos y el sólido se recogió por filtración, se lavó con hexanos y se secó, produciendo 2,3 g (42 %) de 1-yodo-2,4-dimetil-3-nitrobenceno en forma de un sólido de color blanco. EM: 278,1 $[M+H]^+$

Etapa 2: A una suspensión caliente de polvo de hierro (2,3 g, 8,3 mmol), cloruro de amonio (2,16 g, 38,7 mmol) y agua (18 ml) en etanol (50 ml) se le añadió en porciones 1-yodo-2,4-dimetil-3-nitrobenceno durante un periodo de 10 minutos. La mezcla resultante se calentó a reflujo durante 1 hora y se filtró mientras permanecía caliente a través de una capa de Celite™. El Celite se lavó con etanol y acetato de etilo y el filtrado se concentró al vacío. El residuo se extrajo con diclorometano, los extractos orgánicos se secaron sobre sulfato

sódico anhidro y se filtraron y el filtrado se evaporó, produciendo 2,0 g (98 %) de 3-yodo-2,6-dimetil-fenilamina en forma de un sólido de color blanco. EM: 248,1 $[M+H]^+$

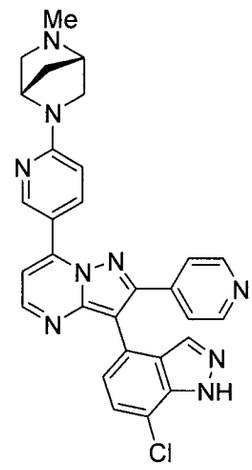
Etapa 3: A una solución fría (0-5 °C) de 3-yodo-2,6-dimetil-fenilamina (2,0 g, 8,09 mmol) en cloroformo (20 ml) se le añadió gota a gota anhídrido acético (1,8 ml, 18,63 mmol) y la mezcla resultante se agitó durante 5 minutos. La reacción se dejó calentar a temperatura ambiente, se agitó durante 1 hora y después se añadieron acetato potásico (0,24 g, 2,45 mmol) y nitrito de isoamilo (2,3 ml, 17,4 mmol). Después, la reacción se calentó a reflujo durante 20 horas. Después de enfriar a temperatura ambiente, el disolvente se evaporó, produciendo un sólido de color pardo que después se diluyó con agua. Después de evaporar el agua, el residuo sólido de color pardo resultante se trató con ácido clorhídrico concentrado y la mezcla se calentó a 50 °C durante 2 horas y después se enfrió en un baño de hielo y se basificó a pH 14 con una solución al 50 % de hidróxido potásico. El sólido se recogió por filtración, se lavó con agua y se secó, produciendo 1,96 g de sólido en forma de una mezcla 1:1 de dos isómeros. Los isómeros se separaron y se purificaron por RP-HPLC, dando 0,35 g (17 %) del isómero deseado, 4-yodo-7-metil-1H-indazol, en forma de un sólido de color blanco. EM: 259,0 $[M+H]^+$

Etapa 4: A una solución de 4-yodo-7-metil-1H-indazol (0,113 mg, 0,44 mmol) en DMSO (5 ml) se le añadieron acetato potásico (0,17 g, 1,73 mmol), cloruro de 1,1'-bis(difenilfosfino)ferrocenopaladio (11 mg, 0,013 mmol) y bis(pinacolato)diboro (0,14 g, 0,55 mmol). La mezcla se desgasificó y se calentó en un reactor de microondas a 120 °C durante 1,5 horas. Después, la mezcla de reacción se filtró a través de una capa de celite y el filtrado se diluyó

con agua y después se extrajo con acetato de etilo (3 x 50 ml). Los extractos orgánicos combinados se secaron sobre sulfato sódico, se filtraron y se concentraron al vacío. El residuo se purificó por cromatografía sobre gel de sílice, proporcionando 7-metil-4-(4,4,5,5-tetrametil-[1.3.2]dioxaborolan-2-il)-1H-indazol en forma de un sólido de color blanco con un rendimiento del 79 %. EM: 259,2 $[M+H]^+$

Etapa 5: Siguiendo el procedimiento del Ejemplo 34, Etapa 5, 3-yodo-7-(6-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)piridin-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina y 7-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-indazol proporcionaron 3-(7-metil-1H-indazol-4-il)-7-(6-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)piridin-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina en forma de una sal clorhidrato. EM: 514,7 [M+H].

Ejemplo 41: 3-(7-Cloro-1H-indazol-4-il)-7-(6-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)piridin-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina



Etapa 1: A una solución de 2,2,6,6-tetrametilpiperidina (811 mg, 5,8 mmol) en THF (10 ml) a -78 ºC se le añadió una solución de butil litio 2,5 M en hexanos (2,31 ml, 5,8 mmol) y 4-bromo-1-cloro-2-fluoro-benceno (1,0 g, 4,8

mmol). La mezcla se calentó a –20 °C durante 2 horas, después se añadió DMF (0,54 ml, 6,9 mmol) y después la reacción se agitó durante 2 horas a temperatura ambiente. La reacción se interrumpió con agua (100 ml) y la mezcla se neutralizó con HCl 1 M y después se extrajo con éter (3 x 30 ml). Los extractos orgánicos combinados se secaron sobre sulfato sódico, se filtraron y se concentraron al vacío. El residuo se purificó por cromatografía sobre gel de sílice, proporcionando 6-bromo-3-cloro-2-fluorobenzaldehído con un rendimiento del 85 %. EM: 270,0 [M+H].

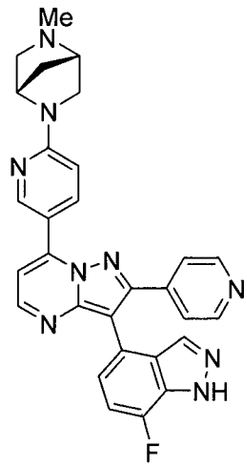
Etapa 2: A una solución de 6-bromo-3-cloro-2-fluorobenzaldehído (1,0 g, 4,24 mmol) en DME (5 ml) se le añadió hidrazina hidrato (5 ml). La mezcla se calentó a reflujo durante 3 horas y después se enfrió a temperatura ambiente. El disolvente se evaporó, se añadió agua (100 ml) y el producto orgánico se extrajo con acetato de etilo (3 x 30 ml). Los extractos orgánicos combinados se secaron sobre sulfato sódico, se filtraron y se concentraron al vacío. El residuo resultante se purificó por cromatografía sobre gel de sílice, proporcionando 4-bromo-7-cloro-1H-indazol con un rendimiento del 51 %. EM: 230,9 [M+H].

Etapa 3: A una solución de 4-bromo-7-cloro-1H-indazol (500 mg, 2,16 mmol) en dimetilsulfóxido DMSO (2 ml) se le añadieron acetato potásico (697 mg, 7,12 mmol), cloruro de 1,1'-bis(difenilfosfino)ferrocenopaladio (77 mg, 0,10 mmol) y bis(pinacolato)diboro (1,1 g, 4,32 mmol). La mezcla se desgasificó y se calentó en un reactor de microondas durante 2 horas a 120 °C. Después, el disolvente se filtró a través de una capa de celite, se añadió agua (60 ml) y el producto se extrajo con acetato de etilo (3 x 30 ml). Los extractos orgánicos combinados se secaron sobre sulfato sódico, se concentraron al vacío y el 7-cloro-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-indazol resultante se usó

en la siguiente etapa sin purificación adicional.

Etapa 4: Siguiendo el procedimiento del Ejemplo 34, Etapa 5, 3-yodo-7-(6-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)piridin-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina y 7-cloro-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-indazol proporcionaron 3-(7-cloro-1H-indazol-4-il)-7-(6-((1S,4S)-5-metil-2,5-diazabiciclo-[2.2.1]heptan-2-il)piridin-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina en forma de una sal clorhidrato. EM: 534,3 [M+H].

Ejemplo 42: 3-(7-Fluoro-1H-indazol-4-il)-7-(6-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)piridin-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina



Etapa 1: A una solución de 2,2,6,6-tetrametilpiperidina (3,12 ml, 18,4 mmol) en THF (35 ml) a -78 °C se le añadió una solución de butil litio 1,6 M en hexanos (11,5 ml, 18,4 mmol) y 1-bromo-3,4-difluorobenceno (3,38 g, 17,5 mmol). La mezcla se calentó a –20 °C durante 2 horas, después se añadió DMF (1,42 ml, 18,4 mmol) y la reacción se calentó a temperatura ambiente y se agitó durante 2 horas. La reacción se interrumpió con agua (5 ml), se neutralizó con HCl 1 M y se extrajo con éter (3 x 30 ml). Los extractos orgánicos combinados se secaron sobre sulfato sódico, se filtraron y se concentraron al

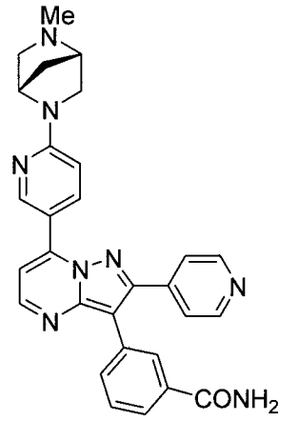
vacío. El material en bruto 6-bromo-2,3-difluorobenzaldehído se usó tal cual en la siguiente etapa.

Etapa 2: A una solución de 6-bromo-2,3-difluorobenzaldehído (5,0 g, 22,6 mmol) en DME (20 ml) se le añadió hidrazina hidrato (20 ml). La mezcla se calentó a reflujo durante 3 horas y se enfrió a temperatura ambiente. El disolvente se evaporó, se añadió agua (100 ml) y la mezcla se extrajo con acetato de etilo (3 x 40 ml). Los extractos orgánicos combinados se secaron sobre sulfato sódico, se filtraron y se concentraron al vacío. El residuo se recristalizó en diclorometano caliente, proporcionando 4-bromo-7-fluoro-1H-indazol en forma de un sólido de color blanco con un rendimiento del 21 %. EM: 215,0 [M+H].

Etapa 3: De acuerdo con el procedimiento del Ejemplo 40, Etapa 4, 4-bromo-7-fluoro-1H-indazol proporcionó 7-fluoro-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-indazol en forma de un sólido de color blanco con un rendimiento del 74 %. EM: 263,1 [M+H].

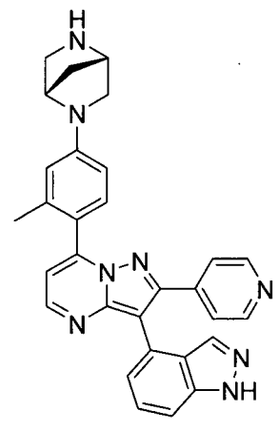
Etapa 4: Siguiendo el procedimiento del Ejemplo 34, Etapa 5, 3-yodo-7-(6-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)piridin-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina y 7-fluoro-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-indazol proporcionaron 3-(7-fluoro-1H-indazol-4-il)-7-(6-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)piridin-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina en forma de una sal clorhidrato. RMN ^{1}H (400 MHz, $CDCl_3$) δ 9,40 (d, J = 2 Hz, 1H), 8,81–8,75 (m, 3H), 8,69 (d, J = 4 Hz, 1H), 8,30–8,25 (m, 2H), 7,75 (d, J = 3,2 Hz, 1H), 7,57 (d, J = 4,4 Hz, 1H), 7,34–7,24 (m, 3H), 5,34 (s, 1H), 4,64 (s, 1H), 4,10–3,95 (m, 3H), 3,10 (s, 3H), 2,64 (d, J = 11,6, 1H), 2,45 (d, J = 11,6, 1H). EM: 518,7 [M+H].

Ejemplo 43: 3-(7-(6-((1S,4S)-5-Metil-2,5-diazabiciclo[2.2.1]heptan-2-il)piridin-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)benzamida



Siguiendo el procedimiento del Ejemplo 34, Etapa 5, 3-yodo-7-(6-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)piridin-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina y ácido 3-carbamoilfenilborónico proporcionaron 3-(7-(6-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)piridin-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)benzamida en forma de una sal clorhidrato. EM: 503,3 [M+H].

Ejemplo 44: 7-(4-((1S,4S)-2,5-Diazabiciclo[2.2.1]heptan-2-il)-2-metilfenil)-3-(1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina



Etapa 1: A una solución de 2,5-diazabiciclo[2.2.1]heptano-2-carboxilato

de (1S,4S)-terc-butilo (200 mg, 1,3 mmol) en 2 ml de 1-metilpirrolidin-2-ona se le añadieron 1-(4-fluoro-2-metilfenil)etanona (387 mg, 1,95 mmol) y N-etil-N-isopropilpropan-2-amina (0,45 ml, 2,6 mmol). Esta solución se calentó a 240 °C durante 1 hora en un reactor de microondas. Después, la mezcla se enfrió a temperatura ambiente y después se añadieron 0,54 g de dicarbonato de di-terc-butilo y 0,2 ml de trietilamina. Después de agitar durante 30 minutos, esta mezcla se diluyó con 80 ml de diclorometano y los extractos orgánicos se lavaron dos veces con agua. La fase orgánica se secó y se concentró y el residuo se purificó por cromatografía sobre gel de sílice, dando 5-(4-acetil-3-metilfenil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de (1S,4S)-terc-butilo. EM: 331,2 [M+H].

Etapa 2: Una mezcla de 5-(4-acetil-3-metilfenil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de (1S,4S)-terc-butilo (95 mg, 0,29 mmol) y 2 ml de 1,1-dimetoxi-N,N-dimetilmetanamina se calentaron a 190 °C durante 1 hora en un reactor de microondas. Después, la mezcla de reacción se diluyó con 80 ml de diclorometano y los extractos orgánicos se lavaron dos veces con agua. La fase orgánica se secó y se concentró y el residuo se purificó por cromatografía sobre gel de sílice, dando 5-(4-((E)-3-(dimetilamino)acriloil)-3-metilfenil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de (1S,4S)-terc-butilo. EM: 386,2 [M+H].

Etapa 3: A una suspensión fría (0-5 °C) de hidruro sódico (0,6 g, 15,0 mmol) en DMF (20 ml) se le añadió en porciones 1H-indazol-4-carboxilato de metilo (2,4 g, 13,62 mmol) [D.Batt, et al. J. Med. Chem., 2000, *43*, 41-58] durante un periodo de 5 minutos y la mezcla resultante se agitó a 5 °C durante 15 minutos. Después, se añadió gota a gota una solución de cloruro de

bencenosulfonilo (1,9 ml, 15,0 mmol) y la mezcla resultante se agitó a 5 °C durante 30 minutos y después a temperatura ambiente durante 3 horas. La mezcla se vertió en hielo y el sólido se recogió por filtración, se lavó con agua y se secó, produciendo 3,91 g (91 %) de 1-(fenilsulfonil)-1H-indazol-4-carboxilato de metilo en forma de un sólido de color beige. EM: 317,1 $[M+H]^+$

Etapa 4: A una suspensión de 1-(fenilsulfonil)-1H-indazol-4-carboxilato de metilo (3,11 g, 9,83 mmol) en una mezcla de THF (30 ml) y tolueno (15 ml) se le añadió borohidruro de litio en forma de una solución 2,0 M en THF (2,7 ml, 5,5 mmol) y la mezcla resultante se agitó y se calentó a 70 °C durante 30 minutos. Se añadió en porciones más cantidad de solución 2,0 M de borohidruro de litio (2,0 ml, 4,0 mmol) durante un periodo de 2,5 horas hasta que se consumió todo el éster de partida. Después, la mezcla se enfrió y se vertió en agua enfriada con hielo y las dos fases resultantes se separaron. La fase acuosa se extrajo con acetato de etilo. Las fases orgánicas combinadas se secaron sobre sulfato sódico anhidro, se filtraron y se concentraron al vacío. El aceite en bruto se purificó por cromatografía sobre gel de sílice, produciendo 2,0 g (71 %) de [1-(fenilsulfonil)-1H-indazol-4-il]metanol en forma de un sólido de color blanco. EM: 289,1 [M+H].

Etapa 5: Una mezcla de [1-(fenilsulfonil)-1H-indazol-4-il]metanol (13,0 g, 45,08 mmol) y peryodinano de Dess-Martin (22,9 g, 54,0 mmol) en diclorometano (420 ml) se agitó a temperatura ambiente durante 1 hora. La reacción se interrumpió con agitación durante 20 minutos con una solución saturada de tiosulfato sódico (100 ml) y una solución saturada de bicarbonato sódico (75 ml). Las dos fases se separaron y la fase acuosa se extrajo con cloruro de metileno. Las fases orgánicas combinadas se secaron sobre sulfato

sódico anhidro, se filtraron y se concentraron al vacío. El sólido en bruto resultante se purificó por cromatografía sobre gel de sílice, produciendo 12,65 g (98 %) de 1-(fenilsulfonil)-1H-indazol-4-carbaldehído en forma de un sólido de color blanco. EM: 287,1 [M+H].

Etapa 6: Una mezcla de 1-(fenilsulfonil)-1H-indazol-4-carbaldehído (6,4 g, 22,4 mmol) y 8,5 g (20,3 mmol) de (fenilamino)(piridin-4-il)metilfosfonato de difenilo (preparado de acuerdo con el procedimiento de Tet. Lett., 1988, *39*, 1717-1720) en THF (50 ml) y alcohol isopropílico (10 ml) se agitó a temperatura ambiente y se añadió en porciones carbonato de cesio (8,6 g, 26,4 mmol). Después de agitar la reacción durante 15 horas, se añadió HCl 3 N (20 ml) y la mezcla se agitó durante 4 horas más. Después, la reacción se diluyó con éter (150 ml) y se extrajo con HCl al 10 % (3 x 150 ml). La fase acuosa se neutralizó a pH 7-8 usando NaOH. Después, la fase acuosa se extrajo con acetato de etilo (3 x 150 ml) y las fases orgánicas combinadas se secaron sobre sulfato sódico anhidro, se filtraron y se concentraron al vacío, dando 4,6 g (rendimiento del 55 %) de 2-(1-(fenilsulfonil)-1H-indazol-4-il)-1-(piridin-4-il)etanona en forma de un sólido de color blanco. EM: 378,1 [M+ H].

Etapa 7: Se añadió oxicloruro de fósforo (1,4 ml, 14,9 mmol) a DMF (1,84 ml) a 0 °C y la mezcla se agitó durante 15 minutos. A esta solución se le añadió 2-(1-(fenilsulfonil)-1H-indazol-4-il)-1-(piridin-4-il)etanona (1,13 g, 3,0 mmol) en diclorometano (10 ml) y después la reacción se calentó a 80 °C durante 15 horas. Después, la reacción se enfrió a temperatura ambiente, se interrumpió con bicarbonato sódico saturado (300 ml) y se extrajo con metanol al 2 % en diclorometano (4 x 250 ml). La fase orgánica se secó sobre sulfato sódico anhidro, se filtró y después se concentró al vacío. El residuo resultante

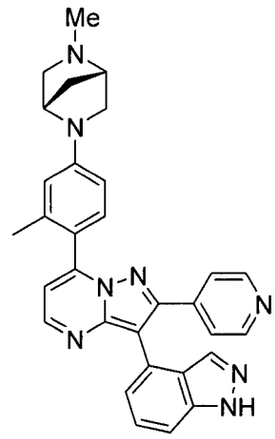
se disolvió en dimetilformamida, DMF (3 ml), se añadió clorhidrato de hidroxilamina (0,15 ml, 3,6 mmol) y la reacción se agitó durante 12 horas. Después, la reacción se enfrió a 0 °C, se añadió oxicloruro de fósforo (0,64 ml, 6,0 mmol) y la mezcla se agitó durante una noche a temperatura ambiente. La reacción se interrumpió con bicarbonato sódico saturado y se extrajo con metanol al 3 % en diclorometano (4 x 200 ml). Las fases orgánicas combinadas se secaron sobre sulfato sódico anhidro, se filtraron y después se concentraron al vacío, dando (E)-3-cloro-2-(1H-indazol-4-il)-3-(piridin-4-il)acrilonitrilo en bruto. El (E)-3-cloro-2-(1H-indazol-4-il)-3-(piridin-4-il)acrilonitrilo en bruto se disolvió en etanol (16 ml), se añadió hidrazina monohidrato (0,44 ml, 9,0 mmol) y la reacción resultante se agitó a 80 °C durante 6 horas. La reacción se enfrió a temperatura ambiente y el disolvente se retiró por evaporación. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice, eluyendo con metanol al 2-12 % en diclorometano, dando 0,58 g (rendimiento del 71 %) de 4-(1H-indazol-4-il)-3-(piridin-4-il)-1H-pirazol-5-amina. EM: 277,2 [M+H].

Etapa 8: Siguiendo el procedimiento del Ejemplo 7, Etapa 4, 5-(4-((E)-3-(dimetilamino)acriloil)-3-metilfenil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de (1S,4S)-terc-butilo (41 mg, 0,11 mmol) y 4-(1H-indazol-4-il)-3-(piridin-4-il)-1H-pirazol-5-amina (34 mg, 0,12 mmol) proporcionaron 5-(4-(3-(1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-3-metilfenil)-2,5-diazabiciclo-[2.2.1]heptano-2-carboxilato de (1S,4S)-terc-butilo, que se usó como un producto en bruto para la siguiente etapa. EM: 599,8 [M+H].

Etapa 9: Se disolvió 5-(4-(3-(1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-3-metilfenil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato en bruto en 3 ml de HCl 4 N (diluido en HCl concentrado con metanol) y se agitó

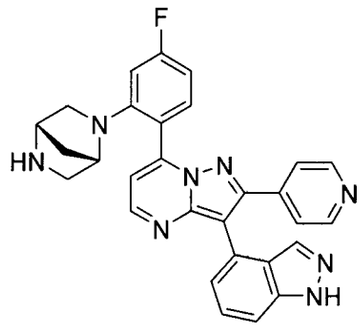
durante 1 hora a temperatura ambiente. Después, la mezcla se concentró, se basificó con solución de amoniaco metanólico y se purificó por HPLC. La base libre se disolvió en metanol y después se añadió 1 ml de HCl metanólico 1,25 M. La solución se concentró al vacío y después se secó, dando 7-(4-((1S,4S)-2,5-diazabiciclo[2.2.1]heptan-2-il)-2-metilfenil)-3-(1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-sal clorhidrato. EM: 499,4 [M+H].

Ejemplo 45: 3-(1H-Indazol-4-il)-7-(2-metil-4-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina



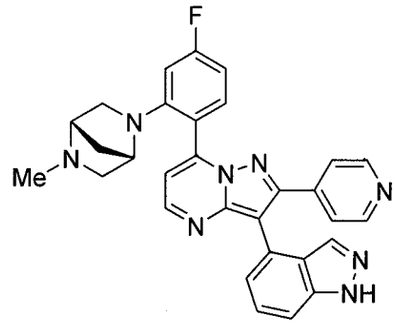
Siguiendo el procedimiento del Ejemplo 30, 7-(4-((1S,4S)-2,5-diazabiciclo[2.2.1]heptan-2-il)-2-metilfenil)-3-(1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina proporcionó 3-(1H-indazol-4-il)-7-(2-metil-4-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]-heptan-2-il)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina en forma de una sal clorhidrato. EM: 513,4 [M+H].

Ejemplo 46: 7-(2-((1S,4S)-2,5-Diazabiciclo[2.2.1]heptan-2-il)-4-fluorofenil)-3-(1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina



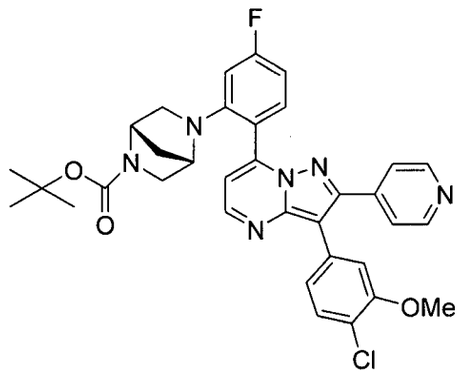
Siguiendo el procedimiento del Ejemplo 44, 1-(2,4-difluorofenil)etanona proporcionó 7-(2-((1S,4S)-2,5-diazabiciclo[2.2.1]heptan-2-il)-4-fluorofenil)-3-(1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina en forma de una sal clorhidrato. RMN ^{1}H (400 MHz, CD_3OD) δ 8,73–8,68 (m, 3H), 8,19–8,14 (m, 2H), 7,75–7,66 (m, 3H), 7,59 (dd, J = 7,4, 8,2 Hz, 1H), 7,38–7,28 (m, 2H), 7,00 (dd, J = 2,2, 11,8 Hz, 1H), 6,85 (dt, J = 2,0, 8,0 Hz, 1H), 4,65 (s, 1H), 4,22 (s, 1H), 3,57–3,5 (m, 1H), 2,20–2,08 (m, 1H), 2,02–1,94 (m, 1H). EM: 503,7 [M+H].

Ejemplo 47: 7-(4-Fluoro-2-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-3-(1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina



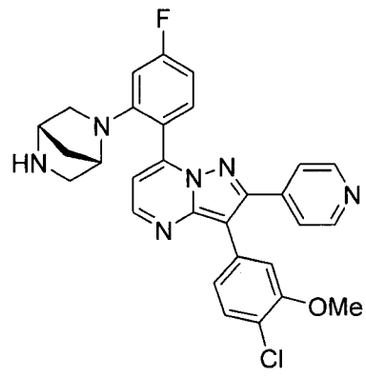
Siguiendo el procedimiento del Ejemplo 30, 7-(2-((1S,4S)-2,5-diazabiciclo[2.2.1]heptan-2-il)-4-fluorofenil)-3-(1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina proporcionó 7-(4-fluoro-2-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-3-(1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina en forma de una sal clorhidrato. EM: 517,7 [M+H].

Ejemplo 48: 5-(2-(3-(4-Cloro-3-metoxifenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-5-fluorofenil)-2,5-diazabiciclo[2.2.1]-heptano-2-carboxilato de (1S,4S)-terc-butilo



Siguiendo el procedimiento del Ejemplo 44, Etapas 1-2, partiendo de 1-(2,4-difluorofenil)etanona, seguido del procedimiento del Ejemplo 7, Etapa 4, usando 4-(4-cloro-3-metoxifenil)-3-(piridin-4-il)-1H-pirazol-5-amina, se proporcionó 5-(2-(3-(4-cloro-3-metoxifenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-5-fluorofenil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de (1S,4S)-terc-butilo en forma de una sal trifluoroacetato. EM: 627,3 [M+H].

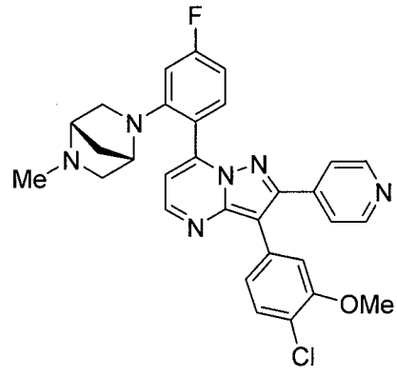
Ejemplo 49: 7-(2-((1S,4S)-2,5-Diazabiciclo[2.2.1]heptan-2-il)-4-fluorofenil)-3-(4-cloro-3-metoxifenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina



Siguiendo el procedimiento del Ejemplo 44, Etapa 9, 5-(2-(3-(4-cloro-3-

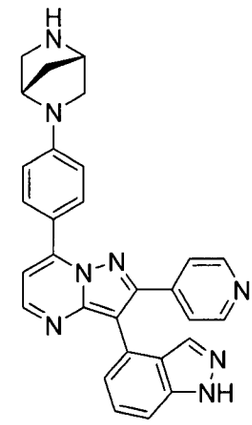
metoxifenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-5-fluorofenil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de (1S,4S)-terc-butilo dio 7-(2-((1S,4S)-2,5-diazabiciclo[2.2.1]heptan-2-il)-4-fluorofenil)-3-(4-cloro-3-metoxifenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina en forma de una sal trifluoroacetato. EM: 527,1 [M+H].

Ejemplo 50: 3-(4-Cloro-3-metoxifenil)-7-(4-fluoro-2-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina



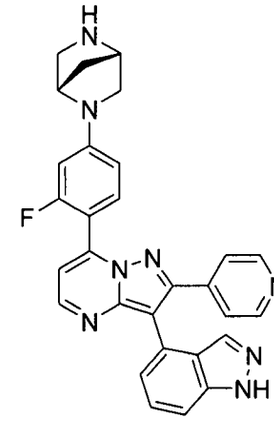
Siguiendo el procedimiento del Ejemplo 30, la alquilación reductora de 7-(2-((1S,4S)-2,5-diazabiciclo[2.2.1]heptan-2-il)-4-fluorofenil)-3-(4-cloro-3-metoxifenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina proporcionó 3-(4-cloro-3-metoxifenil)-7-(4-fluoro-2-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina en forma de una sal trifluoroacetato. EM: 541,1 [M+H].

Ejemplo 51: 7-(4-((1S,4S)-2,5-Diazabiciclo[2.2.1]heptan-2-il)fenil)-3-(1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina



Siguiendo el procedimiento del Ejemplo 44, partiendo de 1-(4-fluorofenil)etanona, se obtuvo 7-(4-((1S,4S)-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-3-(1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina en forma de una sal clorhidrato. EM: 485,7 [M+H].

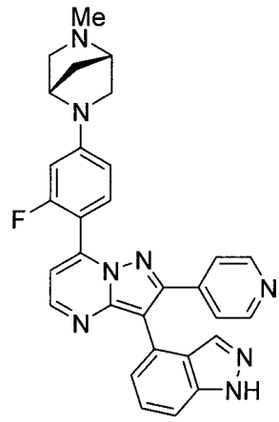
Ejemplo 52: 7-(4-((1S,4S)-2,5-Diazabiciclo[2.2.1]heptan-2-il)-2-fluorofenil)-3-(1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina



Siguiendo el procedimiento del Ejemplo 44, partiendo de 1-(2,4-difluorofenil)etanona, se obtuvo 7-(4-((1S,4S)-2,5-diazabiciclo[2.2.1]heptan-2-il)-2-fluorofenil)-3-(1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina en forma de una sal clorhidrato. EM: 503,1 [M+H].

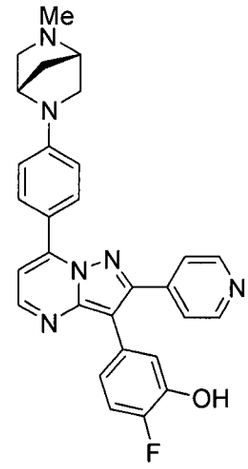
Ejemplo 53: 7-(2-Fluoro-4-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-

2-il)fenil)-3-(1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina



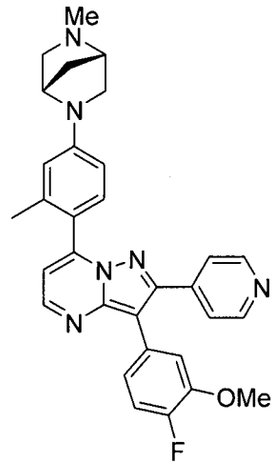
Siguiendo el procedimiento del Ejemplo 30, la alquilación reductora de 7-(4-((1S,4S)-2,5-diazabiciclo[2.2.1]heptan-2-il)-2-fluorofenil)-3-(1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina proporcionó 7-(2-fluoro-4-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-3-(1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina, aislada en forma de una sal clorhidrato. RMN ^{1}H (400 MHz, CD_3OD) δ 8,72–8,68 (m, 2H), 8,62 (d, J = 4,4 Hz, 1H), 8,2–8,16 (m, 2H), 8,05–7,96 (m, 1H), 7,79 (d, J = 0,8 Hz, 1H), 7,75–7,70 (m, 1H), 7,61 (dd, J = 6,8, 8,4 Hz, 1H), 7,35 (dd, J = 0,8, 7,2 Hz, 1H), 7,30 (dd, J = 1,2, 4,0 Hz, 1H), 6,82–6,70 (m, 2H), 4,50 (s, 1H), 3,92–3,80 (m, 2H), 3,63 (d, J = 11,2 Hz, 1H), 3,04 (s, 3H), 2,55–2,48 (m, 1H), 2,40–2,33 (m, 1H). EM: 517,1 [M+H].

Ejemplo 54: 5-(7-(4-((1S,4S)-2,5-Diazabiciclo[2.2.1]heptan-2-il)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)-2-fluorofenol



Siguiendo el procedimiento del Ejemplo 8, 3-(4-fluoro-3-metoxifenil)-7-(4-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina y tribromuro de boro proporcionaron 2-fluoro-5-(7-(4-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)fenol, aislado en forma de una sal clorhidrato. RMN ^{1}H (400 MHz, CD_3OD) δ 8,84–8,79 (m, 2H), 8,58 (d, J = 4,8 Hz, 1H), 8,38–8,32 (m, 4H), 7,35 (d, J = 4,8 Hz, 1H), 7,20 (dd, J = 8,0, 10,8 Hz, 1H), 7,13 (dd, J = 2, 8,4 Hz, 1H), 6,98–6,90 (m, 3H), 4,49 (s, 1H), 3,91–3,78 (m, 3H), 3,63 (d, J = 11,2 Hz, 1H), 3,03 (s, 3H), 2,54–2,44 (m, 1H), 2,39–2,28 (m, 1H). EM: 493,2 [M+H].

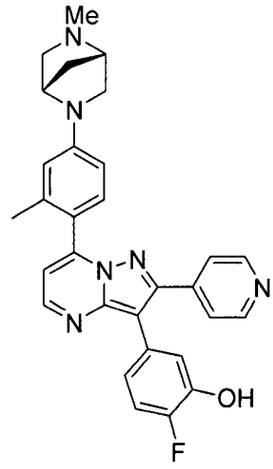
Ejemplo 55: 3-(4-Fluoro-3-metoxifenil)-7-(2-metil-4-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina



Etapa 1: Siguiendo el procedimiento del Ejemplo 7, Etapa 4, (1S,4S)- 5-(4-((E)-3-(dimetilamino)acriloil)-3-metilfenil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de terc-butilo (41 mg, 0,11 mmol) y 4-(4-fluoro-3-metoxifenil)-3-(piridin-4-il)-1H-pirazol-5-amina proporcionaron 7-(4-((1S,4S)-2,5-diazabiciclo[2.2.1]heptan-2-il)-2-metilfenil)-3-(4-fluoro-3-metoxifenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina. EM: 507,2 [M+H].

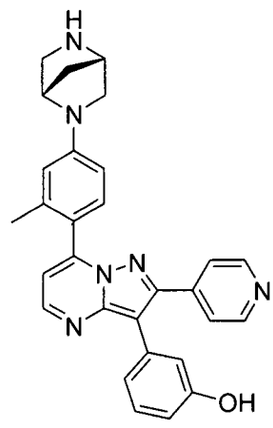
Etapa 5: Siguiendo el procedimiento del Ejemplo 30, la alquilación reductora de 7-(4-((1S,4S)-2,5-diazabiciclo[2.2.1]heptan-2-il)-2-metilfenil)-3-(4-fluoro-3-metoxifenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina dio 3-(4-fluoro-3-metoxifenil)-7-(2-metil-4-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina, aislada en forma de una sal trifluoroacetato. EM: 521,3 [M+H].

Ejemplo 56: 2-Fluoro-5-(7-(2-metil-4-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)fenol



Siguiendo el procedimiento del Ejemplo 8, 3-(4-fluoro-3-metoxifenil)-7-(2-metil-4-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina y tribromuro de boro dieron 2-fluoro-5-(7-(2-metil-4-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)fenol, aislado en forma de una sal trifluoroacetato. EM: 507,3 [M+H].

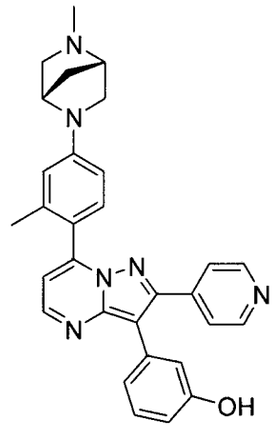
Ejemplo 57: 3-(7-(4-((1S,4S)-2,5-Diazabiciclo[2.2.1]heptan-2-il)-2-metilfenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)fenol



Siguiendo el procedimiento del Ejemplo 7, Etapa 4, 3-(3-amino-5-piridin-4-il-1H-pirazol-4-il)fenol y 5-(4-((E)-3-(dimetilamino)acriloil)-3-metilfenil)-2,5-

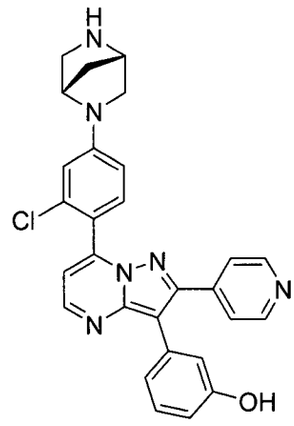
diazabiciclo[2.2.1]heptano-2-carboxilato de (1S,4S)-terc-butilo proporcionaron 3-(7-(4-((1S,4S)-2,5-diazabiciclo[2.2.1]heptan-2-il)-2-metilfenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)fenol, aislado en forma de una sal trifluoroacetato. EM: 475,3 [M+H].

Ejemplo 58: 3-(7-(2-Metil-4-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)fenol



Siguiendo el procedimiento del Ejemplo 30, la alquilación reductora de 3-(7-(4-((1S,4S)-2,5-diazabiciclo[2.2.1]heptan-2-il)-2-metilfenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)fenol proporcionó 3-(7-(2-metil-4-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)fenol, aislado en forma de una sal trifluoroacetato. EM: 489,3 [M+H].

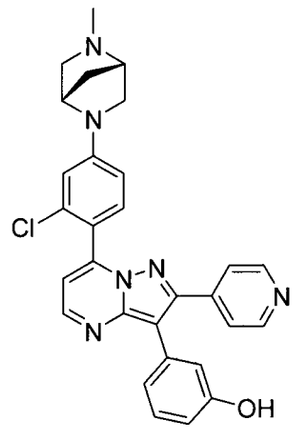
Ejemplo 59: 3-(7-(4-((1S,4S)-2,5-Diazabiciclo[2.2.1]heptan-2-il)-2-clorofenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)fenol



Etapa 1: Siguiendo el procedimiento del Ejemplo 44, Etapas 1-2, se preparó 5-(3-cloro-4-((E)-3-(dimetilamino)acriloil)fenil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de (1S,4S)-terc-butilo partiendo de 1-(2-cloro-4-fluorofenil)etanona.

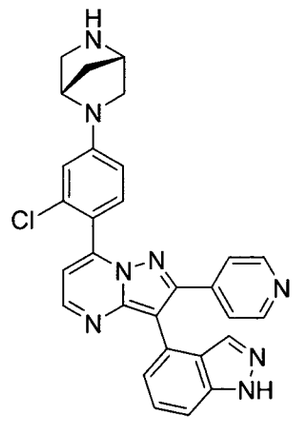
Etapa 2: Siguiendo el procedimiento del Ejemplo 7, Etapa 4, 5-(3-cloro-4-((E)-3-(dimetilamino)acriloil)fenil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de (1S,4S)-terc-butilo y 3-(3-amino-5-piridin-4-il-1H-pirazol-4-il)fenol proporcionaron 3-(7-(4-((1S,4S)-2,5-diazabiciclo[2.2.1]heptan-2-il)-2-clorofenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)fenol en forma de una sal trifluoroacetato. EM: 495,3 [M+H].

Ejemplo 60: 3-(7-(2-Cloro-4-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)fenol



Siguiendo el procedimiento del Ejemplo 30, la alquilación reductora de 3-(7-(4-((1S,4S)-2,5-diazabiciclo[2.2.1]heptan-2-il)-2-clorofenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)fenol proporcionó 3-(7-(2-cloro-4-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)fenol, aislado en forma de una sal trifluoroacetato. EM: 509,3 [M+H].

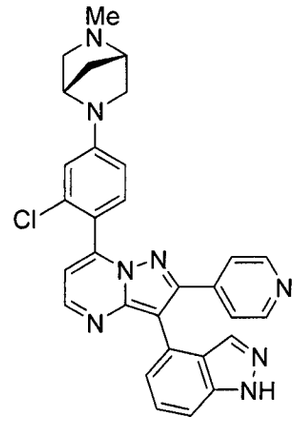
Ejemplo 61: 7-(4-((1S,4S)-2,5-Diazabiciclo[2.2.1]heptan-2-il)-2-clorofenil)-3-(1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina



Siguiendo el procedimiento del Ejemplo 44, Etapa 8, 5-(3-cloro-4-((E)-3-(dimetilamino)acriloil)fenil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de (1S,4S)-terc-butilo y 4-(1H-indazol-4-il)-3-(piridin-4-il)-1H-pirazol-5-amina (34

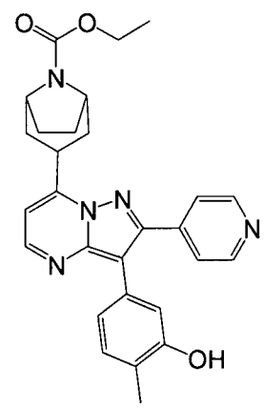
mg, 0,12 mmol) proporcionaron 7-(4-((1S,4S)-2,5-diazabiciclo[2.2.1]heptan-2-il)-2-clorofenil)-3-(1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina en forma de una sal trifluoroacetato después de la desprotección con ácido trifluoroacético. EM: 519,2 [M+H].

Ejemplo 62: 7-(2-Cloro-4-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-3-(1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina



Siguiendo el procedimiento del Ejemplo 30, la alquilación reductora de 7-(4-((1S,4S)-2,5-diazabiciclo[2.2.1]heptan-2-il)-2-clorofenil)-3-(1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina dio 7-(2-cloro-4-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-3-(1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina, aislada en forma de una sal trifluoroacetato. EM: 533,3 [M+H].

Ejemplo 63: Sal trifluoroacetato de 3-[3-(3-hidroxi-4-metilfenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo



Etapa 1: De acuerdo con el procedimiento del Ejemplo 7, Etapa 4, 3-(3-(dimetilamino)acriloil)-8-azabiciclo[3.2.1]octano-8-carboxilato de (E)-etilo (0,37 g, 1,3 mmol) y 3-(piridin-4-il)-1H-pirazol-5-amina proporcionaron 3-(2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo.

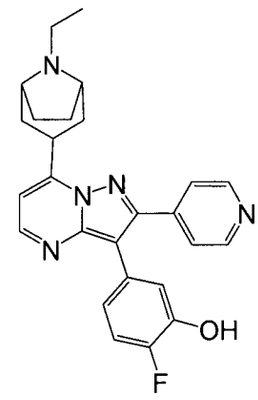
Etapa 2: A una solución de 3-(2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo (0,8 g, 2,1 mmol) en diclorometano (75 ml) se le añadió en cuatro porciones N-yodosuccinimida (5,7 g, 25 mmol) durante un periodo de 3 horas y después la reacción se agitó durante 16 horas más. La mezcla de reacción se lavó con tiosulfato sódico saturado (2 x 200 ml) y la fase orgánica se secó sobre sulfato sódico anhidro, se filtró y después se concentró al vacío, dando 0,8 g de 3-(3-yodo-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo en forma de un sólido de color amarillo. Este producto se usó en la siguiente etapa sin purificación adicional. EM: 504,3 [M+H].

Etapa 3: A una suspensión de 3-(3-yodo-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo (100 mg, 0,20 mmol) en 1,5 ml de dimetoxietano se le añadieron carbonato sódico 2 M (0,5 ml), ácido 3-metoxi-4-metilborónico (40 mg, 0,24 mmol) y una cantidad

catalítica de complejo de (1,1'-bis(difenilfosfino)ferroceno)dicloropaladio (II) y diclorometano (16 mg, 0,02 mmol). La mezcla se calentó a 100 °C durante 60 minutos en un reactor de microondas. Se añadieron porciones adicionales de ácido 3-metoxi-4-metilborónico (20 mg, 0,12 mmol) y complejo de (1,1'-bis(difenilfosfino)ferroceno)dicloropaladio (II) y diclorometano (10 mg, 0,012 mmol) y la mezcla se hizo reaccionar a 100 °C durante 40 minutos más en el reactor de microondas. El producto en bruto se purificó por cromatografía sobre gel de sílice eluyendo con un gradiente de 99:1 a 97:3 de diclorometano/metanol, proporcionando 67 mg (rendimiento del 68 %) de éster etílico del ácido 3-[3-(3-metoxi-4-metil-fenil)-2-piridin-4-il-pirazolo[1,5-a]pirimidin-7-il]-8-aza-biciclo[3.2.1]octano-8-carboxílico en forma de un aceite de color naranja. EM: 498,4 [M+H].

Etapa 4: Siguiendo el procedimiento del Ejemplo 8, se hizo reaccionar éster etílico del ácido 3-[3-(3-metoxi-4-metil-fenil)-2-piridin-4-il-pirazolo[1,5-a]pirimidin-7-il]-8-aza-biciclo[3.2.1]octano-8-carboxílico con tribromuro de boro en diclorometano, proporcionando sal trifluoroacetato de 3-[3-(3-hidroxi-4-metilfenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, en forma de un sólido de color blanco (rendimiento del 15 %) después de la purificación por HPLC preparativa (H_2O/acetonitrilo/ácido trifluoroacético). EM: 484,0 [M+H].

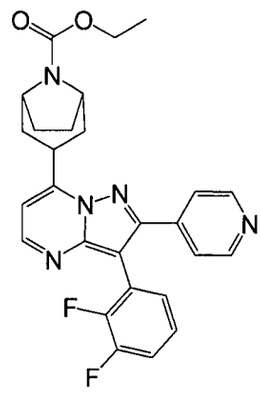
Ejemplo 64: 5-(7-(8-Etil-8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)-2-fluorofenol



Etapa 1: Siguiendo el procedimiento del Ejemplo 20, Etapa 7, se hizo reaccionar 7-(8-etil-8-azabiciclo[3.2.1]octan-3-il)-3-yodo-2-(piridin-4-il)pirazolo[1,5-a]pirimidina (150 mg, 0,326 mmol) con ácido 4-fluoro-3-metoxifenilborónico (167 mg, 0,983 mmol), produciendo 7-(8-etil-8-azabiciclo[3.2.1]octan-3-il)-3-(4-fluoro-3-metoxifenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina en forma de un sólido de color amarillo. EM 458,1 [M+H].

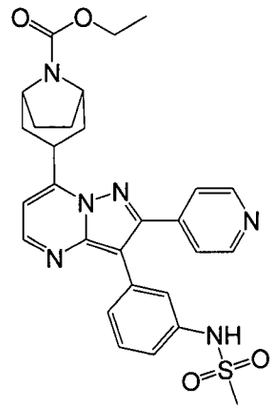
Etapa 2: Siguiendo el procedimiento del Ejemplo 8, se hizo reaccionar 7-(8-etil-8-azabiciclo[3.2.1]octan-3-il)-3-(4-fluoro-3-metoxifenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina con tribromuro de boro y después se purificó usando TLC preparativa usando un gradiente de metanol al 5-10 %/diclorometano, proporcionando 4,8 mg (rendimiento del 3,3 %) 5-(7-(8-etil-8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)-2-fluorofenol en forma de un sólido de color amarillo. EM 444,3 [M+H].

Ejemplo 65: 3-(3-(2,3-Difluorofenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo



Siguiendo el procedimiento del Ejemplo 20, Etapa 7, se hizo reaccionar 3-(3-yodo-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo (100 mg, 0,199 mmol) con ácido 2,3-difluorofenilborónico (141 mg, 0,89 mmol), produciendo 47,1 mg (48,5 %) de 3-(3-(2,3-difluorofenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo en forma de un sólido de color amarillo después de la TLC preparativa eluyendo con metanol al 4 % en diclorometano. EM 490,3 [M+H].

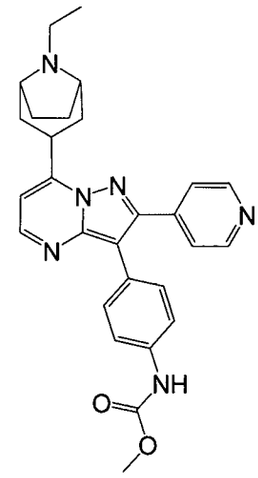
Ejemplo 66: 3-(3-(3-(Metilsulfonamido)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo



Siguiendo el procedimiento del Ejemplo 20, Etapa 7, se hizo reaccionar 3-(3-yodo-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octano-8-

carboxilato de etilo (100 mg, 0,199 mmol) con ácido 3-(metilsulfonamido)fenilborónico (192 mg, 0,89 mmol), produciendo 76,3 mg (70,3 %) de 3-(3-(3-(metilsulfonamido)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo en forma de un sólido de color amarillo después del análisis por TLC preparativa eluyendo con metanol al 4 % en diclorometano. EM 547,3 [M+H].

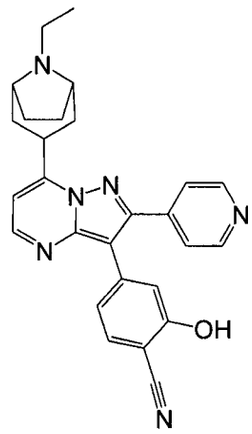
Ejemplo 67: 4-(7-(8-Etil-8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)fenilcarbamato de metilo



Una mezcla de 4-(7-(8-etil-8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)anilina (65 mg, 0,15 mmol) y trietilamina (62 µl, 0,45 mmol) en diclorometano (3 ml) se añadió a una solución de trifosgeno (23 mg, 0,075 mmol) en diclorometano (0,5 ml) y la mezcla resultante se agitó durante 10 minutos. Después, a la reacción se le añadió metanol (2 ml) y la mezcla resultante se agitó durante 30 minutos más. La reacción se diluyó con diclorometano (5 ml) y se lavó con bicarbonato sódico saturado (2 x 5 ml). La fase orgánica se secó sobre sulfato sódico anhidro, se filtró y se concentró al vacío, dando un sólido. El sólido en bruto se purificó por cromatografía

ultrarrápida sobre gel de sílice, eluyendo con metanol al 15 % en diclorometano, dando 48 mg (rendimiento del 66 %) de 4-(7-(8-etil-8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)fenilcarbamato de metilo en forma de un sólido de color amarillo. EM 483,3 [M+H].

Ejemplo 68: 4-(7-(8-Etil-8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)-2-hidroxibenzonitrilo



Etapa 1: A una solución de 4-bromo-2-fluorobenzonitrilo (5 g, 25 mmol) en tetrahidrofurano se le añadió metóxido sódico (125 mmol) en metanol (20 ml) y la reacción se agitó a 40 °C durante 3 horas. Después, la reacción se enfrió a temperatura ambiente, se añadió Amberlyst™ 15 y la mezcla se agitó durante 2 horas. La reacción se filtró y los extractos orgánicos se concentraron al vacío, dando 4-bromo-2-metoxibenzonitrilo en forma de un sólido de color blanco que se usó directamente en la siguiente reacción. EM 212,1 [M+H].

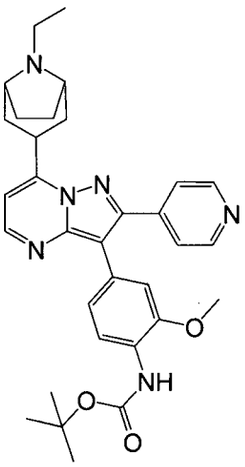
Etapa 2: De acuerdo con el procedimiento del Ejemplo 40, Etapa 4, se convirtió 4-bromo-2-metoxibenzonitrilo en 2-metoxi-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzonitrilo, que se usó directamente en la siguiente reacción.

Etapa 3: La reacción de 7-(8-etil-8-azabiciclo[3.2.1]octan-3-il)-3-yodo-2-

(piridin-4-il)pirazolo[1,5-a]pirimidina con 2-metoxi-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzonitrilo, de acuerdo con el procedimiento del Ejemplo 20, Etapa 7, proporcionó 4-(7-(8-etil-8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)-2-metoxibenzonitrilo en forma de un sólido de color pardo que se usó directamente en la siguiente reacción.

Etapa 4: Siguiendo el procedimiento del Ejemplo 8, se hizo reaccionar 4-(7-(8-etil-8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)-2-metoxibenzonitrilo (0,066 g, 0,14 mmol) con una solución 1 M de tribromuro de boro en diclorometano (4,6 ml), proporcionando 0,019 g (rendimiento del 30 %) de 4-(7-(8-etil-8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)-2-hidroxibenzonitrilo en forma de un sólido de color amarillo. EM 451,3 [M+H].

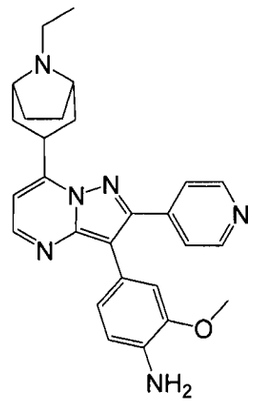
Ejemplo 69: 4-(7-(8-etil-8-Azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)-2-metoxifenilcarbamato de terc-butilo



De acuerdo con el procedimiento del Ejemplo 20, Etapa 7, la reacción de 7-(8-etil-8-azabiciclo[3.2.1]octan-3-il)-3-yodo-2-(piridin-4-il)pirazolo[1,5-a]pirimidina con 2-metoxi-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-

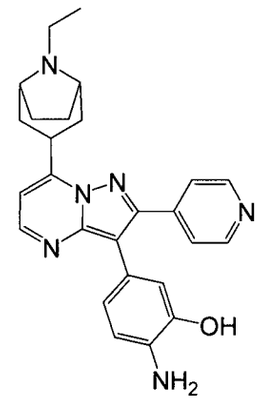
il)fenilcarbamato de terc-butilo proporcionó 0,28 g (rendimiento del 39 %) de 4-(7-(8-etil-8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)-2-metoxifenilcarbamato de terc-butilo en forma de un sólido de color amarillo. EM 555,5 [M+ H].

Ejemplo 70: 4-(7-(8-Etil-8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)-2-metoxianilina



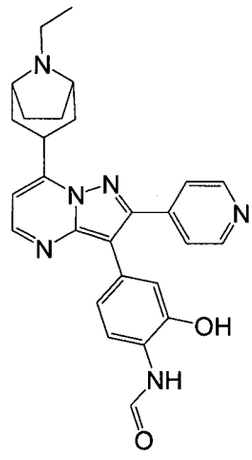
A una solución de 4-(7-(8-etil-8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)-2-metoxifenilcarbamato de terc-butilo (281 mg, 0,51 mmol) en diclorometano (5 ml) se le añadió ácido trifluoroacético (0,5 ml). La reacción se agitó durante 5 horas y después se concentró al vacío. El sólido en bruto se suspendió en bicarbonato sódico saturado (100 ml) y se extrajo con metanol al 5 % en diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico anhidro, se filtraron y se concentraron al vacío, dando 0,22 g (rendimiento del 94 %) de 4-(7-(8-etil-8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)-2-metoxianilina en forma de un sólido de color amarillo. EM 455,4 [M+ H].

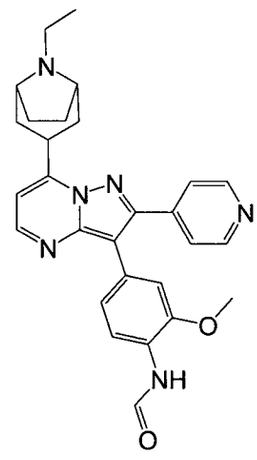
Ejemplo 71: 2-Amino-5-(7-(8-etil-8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)fenol



De acuerdo con el procedimiento del Ejemplo 8, se hizo reaccionar 4-(7-(8-etil-8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)-2-metoxianilina (0,21 g, 0,46 mmol) con una solución 1 M de tribromuro de boro en diclorometano (4,6 ml), proporcionando 0,068 g (rendimiento del 34 %) de 2-amino-5-(7-(8-etil-8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)fenol en forma de un sólido de color amarillo. EM 441,3 [M+H].

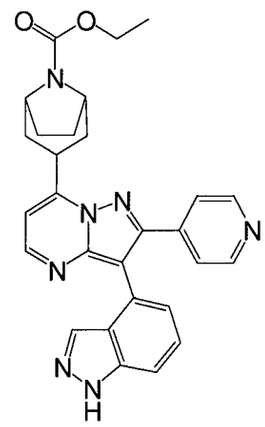
Ejemplos 72a y 72b: N-(4-(7-(8-Etil-8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)-2-hidroxifenil)formamida (WYE-126925), N-(4-(7-(8-etil-8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)-2-metoxifenil)formamida





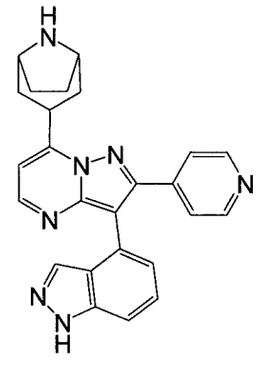
Una mezcla de ácido fórmico (19 mg, 0,42 mmol) y anhídrido acético (34,5 mg, 0,34 mmol) se agitó a 60 °C durante 2 horas y después se enfrió a temperatura ambiente y se añadió a una solución de una mezcla de 2-amino-5-(7-(8-etil-8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)fenol y 4-(7-(8-etil-8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)-2-metoxianilina (1:1, 58 mg, 0,13 mmol) en 1 ml de THF a 0 °C. La reacción se agitó durante 2 horas y después se interrumpió con carbonato potásico saturado. La mezcla se extrajo con metanol al 5 % en diclorometano y las fases orgánicas combinadas se secaron sobre sulfato sódico anhidro, se filtraron y después se concentraron al vacío. El producto en bruto se purificó por TLC preparativa eluyendo con metanol al 10 % en diclorometano, dando 4,1 mg del Ejemplo 72a, N-(4-(7-(8-etil-8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)-2-hidroxifenil)formamida, en forma de un sólido de color naranja (EM 469,4 [M+H]) y 6,4 mg del Ejemplo 72b, N-(4-(7-(8-etil-8-azabiciclo[3.2.1]octan-3-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-3-il)-2-metoxifenil)formamida, en forma de un sólido de color naranja (EM 483,3 [M+H]).

Ejemplo 73: 3-[3-(1H-Indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo



De acuerdo con el procedimiento del Ejemplo 63, Etapa 3, 6-(4,4,5,5-tetrametil-[1.3.2]dioxaborolan-2-il)- y éster etílico del ácido 3-(3-yodo-2-piridin-4-il-pirazolo[1,5-a]pirimidin-7-il)-8-aza-biciclo[3.2.1]octano-8-carboxílico proporcionaron 3-[3-(1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo con un rendimiento del 40 % después de la purificación por RP-HPLC. EM 494,3 [M+H].

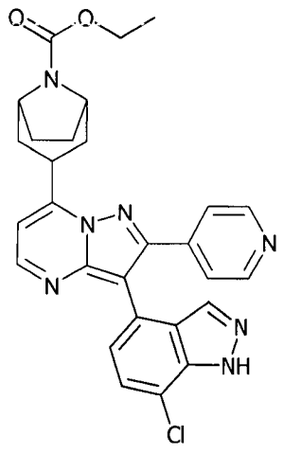
Ejemplo 74: 7-(8-Azabiciclo[3.2.1]oct-3-il)-3-(1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina



Siguiendo el procedimiento del Ejemplo 9, se hizo reaccionar 3-[3-(1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo con yodotrimetilsilano en cloroformo a la temperatura de reflujo, proporcionando 7-(8-azabiciclo[3.2.1]oct-3-il)-3-(1H-indazol-4-il)-2-

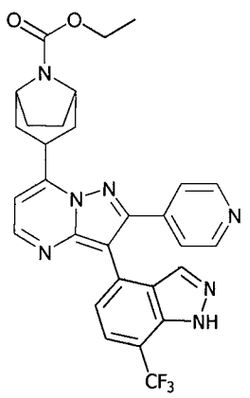
piridin-4-ilpirazolo[1,5-a]pirimidina en forma de un sólido de color amarillo con un rendimiento del 90 % después de la cromatografía sobre gel de sílice, eluyendo con un gradiente de 95:5 a 4:1 de diclorometano/metanol seguido de 80:20:1 de diclorometano/metanol/hidróxido de amonio acuoso. EM: 422,2 [M+H].

Ejemplo 75: 3-[3-(7-Cloro-1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo



De acuerdo con el procedimiento del Ejemplo 63, Etapa 3, éster etílico del ácido 3-(3-yodo-2-piridin-4-il-pirazolo[1,5-a]pirimidin-7-il)-8-aza-biciclo[3.2.1]octano-8-carboxílico y 7-cloro-4-(4,4,5,5-tetrametil-[1.3.2]dioxaborolan-2-il)-1H-indazol dieron 3-[3-(7-cloro-1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo con un rendimiento del 42 % después de la purificación por RP-HPLC. EM 528,0 [M+H].

Ejemplo 76: 3-{2-Piridin-4-il-3-[7-(trifluorometil)-1H-indazol-4-il]pirazolo[1,5-a]pirimidin-7-il}-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo



Etapa 1: A una solución de 2,2,6,6-tetrametilpiperidina (725 mg, 5,18 mmol) en THF (10 ml) a -78 ºC se le añadió una solución de butil litio 2,5 M en hexanos (2,07 ml, 5,18 mmol) y 4-bromo-2-fluoro-1-trifluorometil-benceno (1,2 g, 4,9 mmol). La mezcla se calentó a –20 ºC durante 2 horas y después la reacción se interrumpió con agua (100 ml), se neutralizó con HCl 1 M y se extrajo con éter (3 x 30 ml). Los extractos orgánicos combinados se secaron sobre sulfato sódico, se filtraron y se concentraron al vacío. El residuo se purificó por cromatografía sobre gel de sílice, proporcionando 6-bromo-2-fluoro-3-trifluorometil-benzaldehído con un rendimiento del 82 %. EM: 270,0 [M+H].

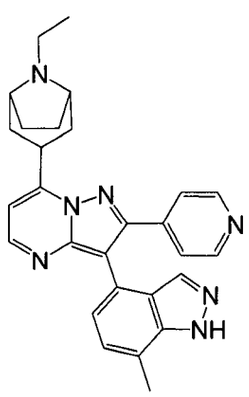
Etapa 2: A una solución de 6-bromo-2-fluoro-3-trifluorometil-benzaldehído (1,0 g, 3,7 mmol) en dimetoxietano, DME (5 ml), se le añadió hidrazina hidrato (5 ml). La mezcla se calentó a reflujo durante 3 horas y después se enfrió a temperatura ambiente. El disolvente se evaporó, se añadió agua (100 ml) y la mezcla de reacción se extrajo con acetato de etilo (3 x 30 ml). Las fases orgánicas combinadas se secaron sobre sulfato sódico, se filtraron y después se concentraron al vacío. El residuo se purificó por cromatografía sobre gel de sílice, proporcionando 4-bromo-7-(trifluorometil)-1H-indazol con un rendimiento del 42 %. EM 264,9 [M+H].

Etapa 3: A una solución de 4-bromo-7-(trifluorometil)-1H-indazol (500

mg, 1,89 mmol) en DMSO (5 ml) se le añadieron acetato potásico (610 g, 6,23 mmol), cloruro de 1,1'-bis(difenilfosfino)ferrocenopaladio (77 mg, 0,09 mmol) y bis(pinacolato)diboro (576 g, 2,27 mmol). La mezcla se desgasificó y se calentó en un baño de aceite durante una noche a 100 °C. La reacción se filtró a través de una capa de Celite™, al filtrado se le añadió agua (60 ml) y la mezcla se extrajo con acetato de etilo (3 x 30 ml). Los extractos orgánicos combinados se secaron sobre sulfato sódico, se filtraron y después se concentraron al vacío, proporcionando 4-(4,4,5,5-tetrametil-[1.3.2]dioxaborolan-2-il)-7-trifluorometil-1H-indazol que se usó en la siguiente etapa sin purificación adicional.

Etapa 4: De acuerdo con el procedimiento del Ejemplo 63, Etapa 3, éster etílico del ácido 3-(3-yodo-2-piridin-4-il-pirazolo[1,5-a]pirimidin-7-il)-8-aza-biciclo[3.2.1]octano-8-carboxílico y 4-(4,4,5,5-tetrametil-[1.3.2]dioxaborolan-2-il)-7-trifluorometil-1H-indazol dieron 3-{2-piridin-4-il-3-[7-(trifluorometil)-1H-indazol-4-il]pirazolo[1,5-a]pirimidin-7-il}-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo (32 mg, rendimiento del 37 %) después de la purificación por RP-HPLC. EM: 562,3 [M+H].

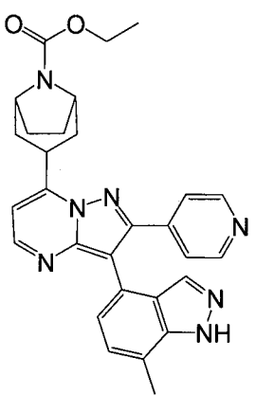
Ejemplo 77: 7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-3-(7-metil-1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, sal trifluoroacetato



De acuerdo con el procedimiento para el Ejemplo 63, Etapa 3, 7-metil-4-

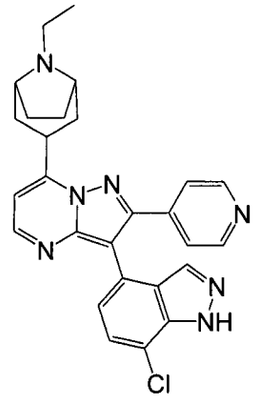
(4,4,5,5-tetrametil-[1.3.2]dioxaborolan-2-il)-1H-indazol y 7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-3-yodo-2-piridin-4-ilpirazolo[1,5-a]pirimidina proporcionaron 7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-3-(7-metil-1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, sal trifluoroacetato, en forma de un sólido de color amarillo con un rendimiento del 18 % después de la purificación por RP-HPLC. EM: 464,3 [M+H].

Ejemplo 78: 3-[3-(7-Metil-1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, sal trifluoroacetato



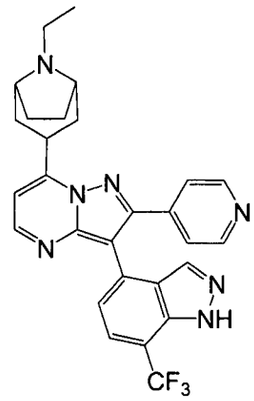
De acuerdo con el procedimiento del Ejemplo 63, Etapa 3, 7-metil-4-(4,4,5,5-tetrametil-[1.3.2]dioxaborolan-2-il)-1H-indazol y éster etílico del ácido 3-(3-yodo-2-piridin-4-il-pirazolo[1,5-a]pirimidin-7-il)-8-aza-biciclo[3.2.1]octano-8-carboxílico proporcionaron 3-[3-(7-metil-1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, sal trifluoroacetato, en forma de un sólido de color amarillo con un rendimiento del 8 % después de la purificación por RP-HPLC. EM: 508,3 [M+H].

Ejemplo 79: 3-(7-Cloro-1H-indazol-4-il)-7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, sal trifluoroacetato



De acuerdo con el procedimiento del Ejemplo 63, Etapa 3, 7-cloro-4-(4,4,5,5-tetrametil-[1.3.2]dioxaborolan-2-il)-1H-indazol y 7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-3-yodo-2-piridin-4-ilpirazolo[1,5-a]pirimidina proporcionaron 3-(7-cloro-1H-indazol-4-il)-7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, sal trifluoroacetato, en forma de un sólido de color amarillo con un rendimiento del 35 % después de la purificación por RP-HPLC. EM: 484,1 [M+H].

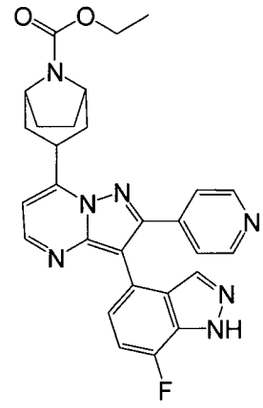
Ejemplo 80: 7-(8-Etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-il-3-[7-(trifluorometil)-1H-indazol-4-il]pirazolo[1,5-a]pirimidina, sal trifluoroacetato



De acuerdo con el procedimiento del Ejemplo 63, Etapa 3, 4-(4,4,5,5-tetrametil-[1.3.2]dioxaborolan-2-il)-7-trifluorometil-1H-indazol y 7-(8-etil-8-

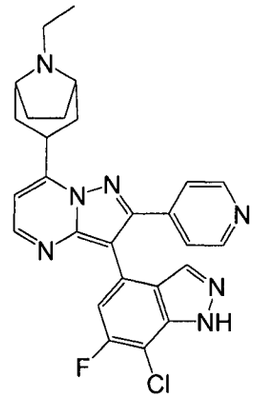
azabiciclo[3.2.1]oct-3-il)-3-yodo-2-piridin-4-ilpirazolo[1,5-a]pirimidina proporcionaron 7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-il-3-[7-(trifluorometil)-1H-indazol-4-il]pirazolo[1,5-a]pirimidina, sal trifluoroacetato, en forma de un sólido de color amarillo con un rendimiento del 8 % después de la purificación por RP-HPLC. EM: 518,3 [M+H].

Ejemplo 81: 3-[3-(7-Fluoro-1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, sal trifluoroacetato



De acuerdo con el procedimiento del Ejemplo 63, Etapa 3, 7-fluoro-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-indazol y éster etílico del ácido 3-(3-yodo-2-piridin-4-il-pirazolo[1,5-a]pirimidin-7-il)-8-aza-biciclo[3.2.1]octano-8-carboxílico dieron 3-[3-(7-fluoro-1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, sal trifluoroacetato, en forma de un sólido de color amarillo con un rendimiento del 19 % después de la purificación por RP-HPLC. EM: 512,3 [M+H].

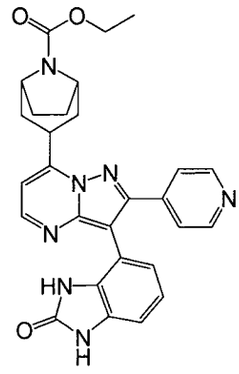
Ejemplo 82: 3-(7-Cloro-6-fluoro-1H-indazol-4-il)-7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, sal trifluoroacetato



Etapa 1: De acuerdo con el procedimiento del Ejemplo 41, Etapas 1-3, 5-bromo-2-cloro-1,3-difluorobenceno proporcionó 7-cloro-6-fluoro-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-indazol en forma de un sólido de color blanco. EM: 297,1 [M+H].

Etapa 2: De acuerdo con el procedimiento del Ejemplo 63, Etapa 3, 7-cloro-6-fluoro-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-indazol y 7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-3-yodo-2-piridin-4-ilpirazolo[1,5-a]pirimidina proporcionaron 3-(7-cloro-6-fluoro-1H-indazol-4-il)-7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, sal trifluoroacetato, en forma de un sólido de color amarillo con un rendimiento del 7 % después de la purificación por RP-HPLC. EM: 502,1 [M+H].

Ejemplo 83: 3-[3-(2-Oxo-2,3-dihidro-1H-benzoimidazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo



Etapa 1: A una solución de 4-bromo-benzo[1.2.5]tiadiazol (1,15 g, 5,35 mmol) en metanol (10 ml) se le añadieron borohidruro sódico (203 mg, 5,35 mmol) y cloruro de cobalto (II) hexahidrato (120 mg, 0,533 mmol). La mezcla se calentó a reflujo durante 3 horas, después se enfrió a temperatura ambiente y se filtró para retirar el sólido de color negro. El disolvente se evaporó, se añadió agua (100 ml) y la mezcla se extrajo con éter (3 x 30 ml). Los extractos orgánicos combinados se secaron sobre sulfato sódico, se filtraron y después se concentraron al vacío, proporcionando 3-bromo-benceno-1,2-diamina (810 mg, rendimiento del 81 %). EM: 187,0 [M+H].

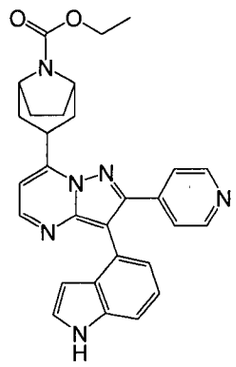
Etapa 2: A una solución de 3-bromo-benceno-1,2-diamina (810 mg, 4,33 mmol) en THF (10 ml) se le añadieron trifosgeno (2,57 g, 8,66 mmol) y trietilamina (1,15 ml, 13 mmol) y la reacción resultante se calentó a 50 °C durante una noche. Después, el disolvente se evaporó, se añadió agua (60 ml) y la mezcla se extrajo con acetato de etilo (3 x 30 ml). Los extractos orgánicos combinados se secaron sobre sulfato sódico, se filtraron y después se concentraron al vacío. El residuo se purificó por cromatografía sobre gel de sílice, dando 4-bromo-1,3-dihidro-benzoimidazol-2-ona (701 mg) con un rendimiento del 76 %. EM: 211,0 [M-H].

Etapa 3: A una solución de 4-bromo-1,3-dihidro-benzoimidazol-2-ona

(701 mg, 3,29 mmol) en DMSO (2 ml) se le añadieron acetato potásico (803 g, 10,9 mmol), cloruro de 1,1'-bis(difenilfosfino)ferrocenopaladio (134 mg, 0,16 mmol) y bis(pinacolato)diboro (1,67 g, 6,58 mmol) y la reacción se desgasificó y se calentó en un reactor de microondas durante 30 minutos a 150 °C. Después, la mezcla de reacción se filtró a través de una capa de Celite™, se añadió agua (60 ml) y la mezcla se extrajo con acetato de etilo (3 x 30 ml). Los extractos orgánicos combinados se secaron sobre sulfato sódico, se filtraron y después se concentraron al vacío, dando 4-(4,4,5,5-tetrametil-[1.3.2]dioxaborolan-2-il)-1,3-dihidro-benzoimidazol-2-ona, que se usó en la siguiente etapa sin purificación adicional.

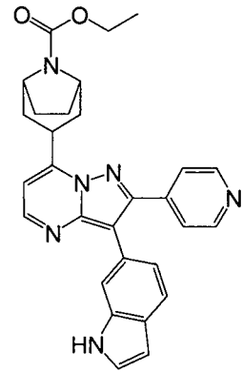
Etapa 4: De acuerdo con el procedimiento del Ejemplo 63, Etapa 3, éster etílico del ácido 3-(3-yodo-2-piridin-4-il-pirazolo[1,5-a]pirimidin-7-il)-8-aza-biciclo[3.2.1]octano-8-carboxílico y 4-(4,4,5,5-tetrametil-[1,3,2 dioxaborolan-2-il)-1,3-dihidro-benzoimidazol-2-ona proporcionaron éster etílico del ácido 3-[3-(2-oxo-2,3-dihidro-1H-benzoimidazol-4-il)-2-piridin-4-il-pirazolo[1,5-a]pirimidin-7-il]-8-aza-biciclo[3.2.1]octano-8-carboxílico (47 mg, 45 %) después de la purificación por RP-HPLC. EM: 510,4 [M+H].

Ejemplo 84: 3-[3-(1H-Indol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo



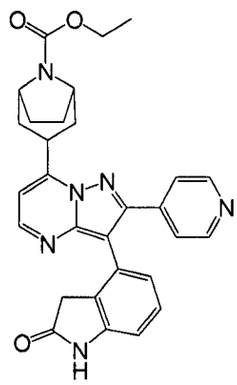
De acuerdo con el procedimiento del Ejemplo 63, Etapa 3, éster etílico del ácido 3-(3-yodo-2-piridin-4-il-pirazolo[1,5-a]pirimidin-7-il)-8-aza-biciclo[3.2.1]octano-8-carboxílico y 4-(4,4,5,5-tetrametil-[1.3.2]dioxaborolan-2-il)-1H-indol proporcionaron 3-[3-(1H-indol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo con un rendimiento del 51 % después de la purificación por RP-HPLC. EM: 493,4 [M+H].

Ejemplo 85: 3-[3-(1H-Indol-6-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo



De acuerdo con el procedimiento del Ejemplo 63, Etapa 3, éster etílico del ácido 3-(3-yodo-2-piridin-4-il-pirazolo[1,5-a]pirimidin-7-il)-8-aza-biciclo[3.2.1]octano-8-carboxílico y 6-(4,4,5,5-tetrametil-[1.3.2]dioxaborolan-2-il)-1H-indol proporcionaron 3-[3-(1H-indol-6-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo con un rendimiento del 47 % después de la purificación por RP-HPLC. EM: 493,3 [M+H].

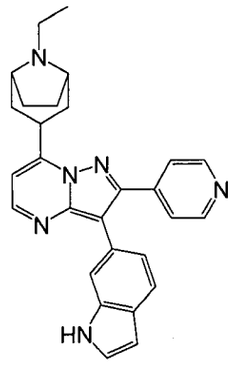
Ejemplo 86: 3-[3-(2-Oxo-2,3-dihidro-1H-pirrolo[2,3-b]piridin-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo



Etapa 1: De acuerdo con el procedimiento del Ejemplo 40, Etapa 4, 4-bromooxindol proporcionó 4-(4,4,5,5-tetrametil-[1.3.2]dioxaborolan-2-il)-1,3-dihidro-indol-2-ona, que se usó en la siguiente etapa sin purificación.

Etapa 2: De acuerdo con el procedimiento del Ejemplo 63, Etapa 3, éster etílico del ácido 3-(3-yodo-2-piridin-4-il-pirazolo[1,5-a]pirimidin-7-il)-8-aza-biciclo[3.2.1]octano-8-carboxílico y 4-(4,4,5,5-tetrametil-[1.3.2]dioxaborolan-2-il)-1,3-dihidro-indol-2-ona proporcionaron 3-[3-(2-oxo-2,3-dihidro-1H-pirrolo[2,3-b]piridin-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo con un rendimiento del 41 % después de la purificación por RP-HPLC. EM: 511,2 [M+H].

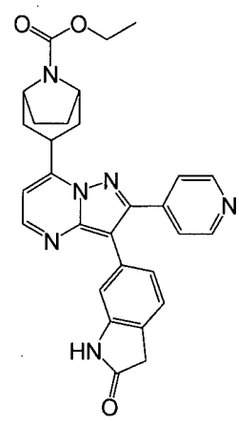
Ejemplo 87: 7-(8-Etil-8-azabiciclo[3.2.1]oct-3-il)-3-(1H-indol-6-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina



Siguiendo el procedimiento del Ejemplo 63, Etapa 3, 7-(8-etil-8-

azabiciclo[3.2.1]oct-3-il)-3-yodo-2-piridin-4-ilpirazolo[1,5-a]pirimidina y 6-(4,4,5,5-tetrametil-[1.3.2]dioxaborolan-2-il)-1H-indol dieron 7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-3-(1H-indol-6-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina con un rendimiento del 31 % después de la purificación por RP-HPLC. EM: 449,3 [M+H].

Ejemplo 88: 3-[3-(2-Oxo-2,3-dihidro-1H-indol-6-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo

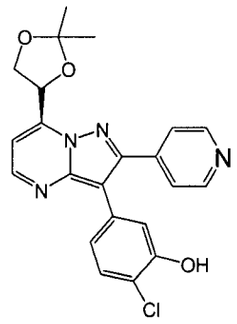


Etapa 1: De acuerdo con el procedimiento del Ejemplo 40, Etapa 4, 6-bromooxindol proporcionó 6-(4,4,5,5-tetrametil-[1.3.2]dioxaborolan-2-il)-1,3-dihidro-indol-2-ona, que se usó en la siguiente etapa sin purificación.

Etapa 2: Siguiendo el procedimiento del Ejemplo 63, Etapa 3, éster etílico del ácido 3-(3-yodo-2-piridin-4-il-pirazolo[1,5-a]pirimidin-7-il)-8-aza-biciclo[3.2.1]octano-8-carboxílico y 6-(4,4,5,5-tetrametil-[1.3.2]dioxaborolan-2-il)-1,3-dihidro-indol-2-ona proporcionaron 3-[3-(2-oxo-2,3-dihidro-1H-indol-6-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo con un rendimiento del 42 % después de la purificación por RP-HPLC. EM: 509,3 [M+H].

Ejemplo 89: 2-Cloro-5-[7-(2,2-dimetil-1,3-dioxolan-4-il)-2-piridin-4-

ilpirazolo[1,5-a]pirimidin-3-il]fenol

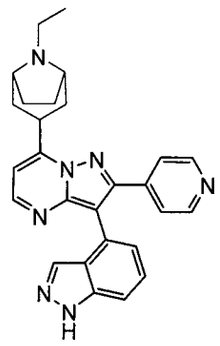


Etapa 1: Una solución de 4 g (27,74 mmol) de 1-[(4*R*)-2,2-dimetil-1,3-dioxolan-4-il]etanona (preparada de acuerdo con el procedimiento de Synthetic Communications, 16(12), 1517-22, 1986) en DMF-DMA (40 ml) se calentó a 100 ºC durante 19 horas. Después, el disolvente se retiró a presión reducida, dando un aceite viscoso de color pardo. El aceite en bruto se purificó por cromatografía Biotage™ (cartucho 40s), eluyendo con un gradiente de acetato de etilo/hexanos (1:2) y acetato de etilo al 100 %, proporcionando (2*E*)-3-(dimetilamino)-1-[(4*R*)-2,2-dimetil-1,3-dioxolan-4-il]prop-2-en-1-ona en forma de un aceite de color pardo claro (1,4 g, 25,3 %). EM: 200,2 [M+H].

Etapa 2: Una solución de (2*E*)-3-(dimetilamino)-1-[(4*R*)-2,2-dimetil-1,3-dioxolan-4-il]prop-2-en-1-ona (0,100 g, 0,5 mmol) y 3-(5-amino-3-piridin-4-il-1H-pirazol-4-il)-fenol (0,173 g, 0,606 mmol) en ácido acético (5 ml) se calentó a 100 ºC durante 19 horas. Después, el disolvente se retiró al vacío. El aceite en bruto resultante (0,194 g) se diluyó con diclorometano (20 ml) y los extractos orgánicos se lavaron con bicarbonato sódico acuoso saturado (2 x 5 ml) y salmuera (5 ml). Los extractos orgánicos se secaron sobre sulfato de magnesio, se filtraron y se concentraron al vacío. El residuo se purificó por cromatografía Biotage™ (cartucho 40s), eluyendo con acetato de etilo, proporcionando 2-cloro-5-{7-[(4*S*)-2,2-dimetil-1,3-dioxolan-4-il]-2-piridin-4-

ilpirazolo[1,5-*a*]pirimidin-3-il}fenol en forma de un sólido cristalino de color amarillo (0,048 g, 4,7 %). EM: 423 [M+H].

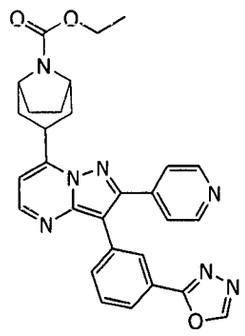
Ejemplo 90: 7-(8-Etil-8-azabiciclo[3.2.1]octan-3-il)-3-(1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina



Etapa 1: Usando el procedimiento del Ejemplo 76, Etapa 3, se convirtió 4-bromo-1H-indazol en 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-indazol que se usó en la siguiente reacción sin purificación adicional.

Etapa 2: La reacción de 7-(8-etil-8-azabiciclo[3.2.1]octan-3-il)-3-yodo-2-(piridin-4-il)pirazolo[1,5-a]pirimidina con 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-indazol, usando el procedimiento del Ejemplo 20, Etapa 7, proporcionó 6,3 mg (rendimiento del 4 %) de 7-(8-etil-8-azabiciclo[3.2.1]octan-3-il)-3-(1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina en forma de un sólido de color amarillo. RMN ^{1}H (400 MHz, CD_3OD) δ 8,57 (d, J = 4,4 Hz, 1H), 8,51 (m, 2H), 7,71 (d, J = 5,2 Hz, 2H), 7,65 (d, J = 8,4 Hz, 1H), 7,52 (m, 2H), 7,24 (d, J = 7,2 Hz, 1H), 7,13 (d, J = 4,4 Hz, 1H), 4,42 (m, 1H), 3,22 (c, J = 7,2, 2H), 2,68 (m, 2H), 2,30-2,49 (m, 8H), 1,46 (t, J = 7,2 Hz, 3H). EM: 450,3 [M+H].

Ejemplo 91: 3-(3-(3-(1,3,4-Oxadiazol-2-il)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo



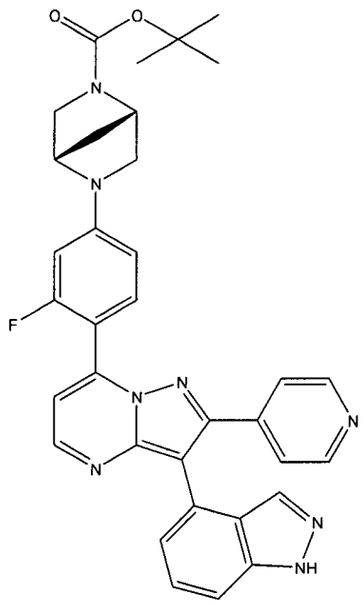
Etapa 1: Una suspensión de 3-bromobenzohidrazida (6,01 g, 27,9 mmol) en ortoformiato de trietilo (40 ml, 240 mmol) se llevó a la temperatura de reflujo en una atmósfera de nitrógeno y se agitó vigorosamente durante una noche. Después de enfriar a temperatura ambiente, el disolvente se retiró al vacío, dando un jarabe de color amarillo pálido que cristalizó después de un periodo de reposo. La recristalización en acetato de etilo/hexanos dio 2-(3-bromofenil)-1,3,4-oxadiazol (4,86 g; 77 %). EM: 223/225 [M+H].

Etapa 2: A una mezcla de 2-(3-bromofenil)-1,3,4-oxadiazol (1,06 g, 4,71 mmol), 4,4,4',4',5,5,5',5'-octametil-2,2'-bi(1,3,2-dioxaborolano) (1,40 g, 5,51 mmol) y acetato potásico (1,32 g, 13,45 mmol) se le añadieron DMSO (30 ml) y ([1,1'-bis(difenilfosfino)ferroceno]dicloropaladio (ii) (0,0993 g, 0,136 mmol). El recipiente se tapó y se puso en una atmósfera de nitrógeno, se calentó a 80 °C y se agitó vigorosamente durante aproximadamente 4,5 horas. La reacción se enfrió a temperatura ambiente durante una noche y después se vertió en agua y acetato de etilo y la mezcla resultante se filtró a través de una capa de Celite™. Las fases se separaron y la fase acuosa se lavó con una segunda porción de acetato de etilo. Los extractos orgánicos combinados se secaron sobre sulfato de magnesio, después se filtraron y se concentraron al vacío, produciendo un jarabe de color pardo que solidificó después de un periodo de reposo. El sólido en bruto se disolvió en una mezcla de diclorometano y acetato

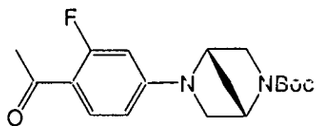
de etilo, se adsorbió sobre sílice y se purificó sobre una columna de 40 g de sílice, dando el éster boronato deseado, 2-(3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-1,3,4-oxadiazol (0,28 g; 21,8 %) en forma de un sólido de color blanquecino. EM: 273,2 [M+H].

Etapa 3: Un pequeño vial se cargó con 3-(3-yodo-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo (0,1006 g, 0,200 mmol), 2-(3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-1,3,4-oxadiazol (0,0779 g, 0,286 mmol), [1,1'-bis(difenilfosfino)ferroceno]dicloropaladio (II) (0,0102 g, 0,012 mmol) y DME (2 ml). A esta mezcla se le añadió carbonato sódico acuoso 2 M (0,3 ml, 0,600 mmol) y la mezcla de color naranja heterogénea resultante se desgasificó rigurosamente, se puso en una atmósfera de nitrógeno y se calentó a 80 °C. Después de 3 horas, la reacción se enfrió a temperatura ambiente y se agitó durante una noche. La reacción en bruto se diluyó con acetonitrilo y se filtró a través de una capa de sulfato de magnesio y Celite™. Después de la retirada del disolvente al vacío, el jarabe de color pardo oscuro resultante se purificó por RP HPLC semi-preparativa, proporcionando 3-(3-(3-(1,3,4-oxadiazol-2-il)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo en forma de un sólido de color amarillo brillante (0,0408 g; 39 %). EM: 522,1 [M+H].

Ejemplo 92: (1S,4S)-5-{3-Fluoro-4-[3-(1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]fenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo



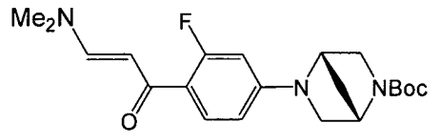
Etapa 1: (1S,4S)-5-(4-Acetil-3-fluorofenil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo



A una solución de 2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de (1S,4S)-terc-butilo (0,2 g, 1 mmol) en 4 ml de HMPA se le añadieron 1-(2,4-difluorofenil)etanona (0,151 ml, 1,2 mmol) y carbonato potásico (0,552 g, 4 mmol). Esta solución se calentó a 70 ºC durante 36 horas en un baño de aceite. Después, la mezcla se enfrió a temperatura ambiente, se diluyó con 100 ml de éter y se lavó tres veces con agua. Después, la fase acuosa se lavó con éter y las fases orgánicas se combinaron. Las fases de éter combinadas se secaron sobre sulfato sódico y se concentraron, produciendo un residuo que se purificó por cromatografía sobre gel de sílice (12:88, ^{i}PrOH:Hexanos), dando

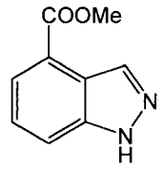
0,290 g (87 %) de (1S,4S)-5-(4-acetil-3-fluorofenil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo en forma de un sólido de color blanco. EM: 335,2 [M+H].

Etapa 2: (1S,4S)-5-{4-[(2E)-3-(dimetilamino)prop-2-enoil]-3-fluorofenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo



Una solución de (1S,4S)-5-(4-acetil-3-fluorofenil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo (0,42 g, 1,26 mmol) y *terc*-butoxibis(dimetilamino)metano (0,8 ml, 3,8 mmol) en 3 ml de THF se calentó a 100 °C durante una noche en un tubo cerrado herméticamente. La mezcla de reacción se concentró y después se diluyó con 1 ml de agua, precipitando el producto deseado. La fase acuosa se decantó y el residuo se lavó con agua. El residuo se disolvió en EtOAc, se lavó con agua, se secó sobre $NaSO_4$ y se filtró. El filtrado se evaporó, dando 0,455 g (93 %) de (1S,4S)-5-{4-[(2E)-3-(dimetilamino)prop-2-enoil]-3-fluorofenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo en forma de un sólido de color amarillo. EM: 390,2 [M+H].

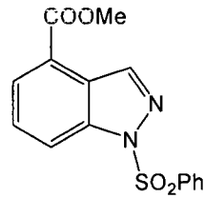
Etapa 3: 1H-indazol-4-carboxilato de metilo



A una solución fría (0-5 °C) de benzoato de metil-3-amino-2-metilo (16,6 ml, 19,0 g, 0,12 mol) en cloroformo (200 ml) se le añadió gota a gota anhídrido

acético (24,8 ml, 0,26 mol) seguido de agitación durante 5 minutos. La mezcla resultante se dejó calentar a temperatura ambiente, se agitó durante 1 hora, después se añadieron acetato potásico (3,35 g, 0,034 mol) y nitrito de isoamilo (33,0 ml, 0,25 mol) y se calentó a reflujo durante 20 horas. La mezcla se enfrió a temperatura ambiente y el disolvente se evaporó, produciendo un sólido de color pardo. Al sólido se le añadió agua, seguido de evaporación, produciendo un residuo sólido. El residuo se trató con ácido clorhídrico concentrado y la mezcla resultante se calentó a 50 °C durante 2 horas. Después de enfriar con un baño de hielo, la solución se basificó a pH 14 con una solución al 50 % de hidróxido potásico. El sólido resultante se recogió por filtración, se lavó con agua y se secó, produciendo 17,8 g de 1H-indazol-4-carboxilato de metilo en forma de un sólido de color beige. EM: 177,0 [M+H].

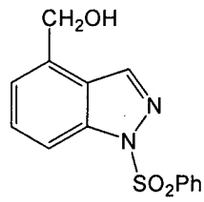
Etapa 4: 1-(fenilsulfonil)-1H-indazol-4-carboxilato de metilo



A una suspensión fría (0-5 °C) de hidruro sódico (0,6 g, 15,0 mmol) en DMF (20 ml) se le añadió en porciones 1H-indazol-4-carboxilato de metilo (2,4 g, 13,62 mmol) [D.Batt, et al. J. Med. Chem., 2000, 43, 41-58] durante un periodo de 5 minutos y la mezcla resultante se agitó a 5 °C durante 15 minutos. Después, se añadió gota a gota una solución de cloruro de bencenosulfonilo (1,9 ml, 15,0 mmol) y la mezcla resultante se agitó a 5 °C durante 30 minutos y después a temperatura ambiente durante 3 horas. La mezcla se vertió en hielo y el sólido se recogió por filtración, se lavó con agua y se secó, produciendo 3,91 g (91 %) de 1-(fenilsulfonil)-1H-indazol-4-carboxilato de metilo en forma de

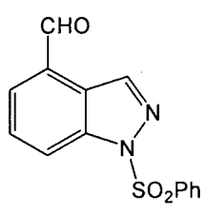
un sólido de color beige. EM: 317,0 [M+H].

Etapa 5: [1-(fenilsulfonil)-1H-indazol-4-il]metanol



A una suspensión de 1-(fenilsulfonil)-1H-indazol-4-carboxilato de metilo (3,11 g, 9,83 mmol) en una mezcla de THF (30 ml) y tolueno (15 ml) se le añadió borohidruro de litio en forma de una solución 2,0 M en THF (2,7 ml, 5,5 mmol) y la mezcla resultante se agitó y se calentó a 70 °C durante 30 minutos. Se añadió en porciones más cantidad de solución 2,0 M de borohidruro de litio (2,0 ml, 4,0 mmol) durante un periodo de 2,5 horas hasta que se consumió todo el éster de partida. Después, la mezcla se enfrió y se vertió en agua enfriada con hielo y las dos fases resultantes se separaron. La fase acuosa se extrajo con acetato de etilo. Las fases orgánicas combinadas se secaron sobre sulfato sódico anhidro, se filtraron y se concentraron al vacío. El aceite en bruto se purificó por cromatografía sobre gel de sílice (3:1 de hexano/acetato de etilo, después 3:2 de hexano/acetato de etilo), produciendo 2,0 g (71 %) de [1-(fenilsulfonil)-1H-indazol-4-il]metanol en forma de un sólido de color blanco. EM: 289,1 [M+H].

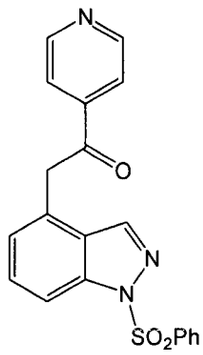
Etapa 6: 1-(fenilsulfonil)-1H-indazol-4-carbaldehído



Una mezcla de [1-(fenilsulfonil)-1H-indazol-4-il]metanol (13,0 g, 45,08

mmol) y peryodinano de Dess-Martin (22,9 g, 54,0 mmol) en diclorometano (420 ml) se agitó a temperatura ambiente durante 1 hora. La reacción se interrumpió por agitación durante 20 minutos con una solución saturada de tiosulfato sódico (100 ml) y una solución saturada de bicarbonato sódico (75 ml). Las dos fases se separaron y la fase acuosa se extrajo con cloruro de metileno. La fase orgánica combinada se secó sobre sulfato sódico anhidro, se filtró y se concentró al vacío. El sólido en bruto resultante se disolvió en cloruro de metileno y se pasó a través de un lecho de gel de sílice, produciendo 12,65 g (98 %) de 1-(fenilsulfonil)-1H-indazol-4-carbaldehído en forma de un sólido de color blanco. EM: 287,1 [M+H].

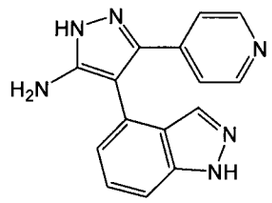
Etapa 7: 2-[1-(fenilsulfonil)-1H-indazol-4-il]-1-piridin-4-iletanona



Una mezcla de 1-(fenilsulfonil)-1H-indazol-4-carboxaldehído (12,33 g, 43,07 mmol), (fenilamino)(piridin-4-il)metilfosfonato de difenilo (17,6 g, 42,27 mmol, preparado de acuerdo con el procedimiento de Tet. Letters 39, 1717-1720, 1988), carbonato de cesio (16,44 g, 50,46 mmol), tetrahidrofurano (246 ml) y alcohol isopropílico (82 ml) se calentó a 45 °C durante 3,5 horas. La mezcla de color amarillo se enfrió a temperatura ambiente, se vertió en una solución enfriada con hielo de HCl 3 N (250 ml) y se agitó a temperatura ambiente durante 18 horas. La solución amarilla se extrajo con éter (2 x 200 ml)

y el extracto de éter se extrajo de nuevo con HCl al 10 % (2 x 100 ml). Los extractos de HCl combinados se enfriaron a 0-5 °C y se neutralizaron a pH 7-8 usando NaOH 2,5 N. El sólido se recogió por filtración, se lavó con agua enfriada con hielo y se secó, produciendo 15,5 g (97 %) de 2-(1-(fenilsulfonil)-1H-indazol-4-il)-1-(piridin-4-il)etanona en forma de un sólido de color beige. EM: 378,0 [M+H].

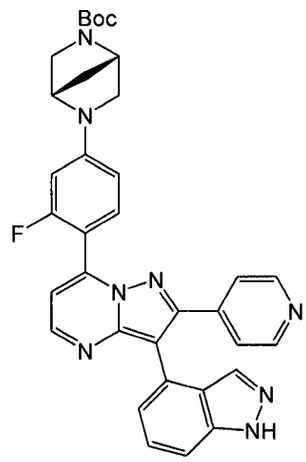
Etapa 8: 4-(1H-indazol-4-il)-3-piridin-4-il-1H-pirazol-5-amina



A una solución fría (0-5 °C) de dimetilformamida (13,0 ml, 254,3 mmol) se le añadió gota a gota una solución de oxicloruro de fósforo (9,9 ml, 106,2 mmol) y la mezcla resultante se agitó durante 20 min. A esta mezcla se le añadió gota a gota una solución de 2-(1-(fenilsulfonil)-1H-indazol-4-il)-1-(piridin-4-il)etanona (8,0 g, 21,2 mmol) en cloroformo (80 ml), se calentó a 80 °C y se agitó durante 18 horas. La reacción se enfrió a temperatura ambiente y se interrumpió con una solución saturada enfriada con hielo de bicarbonato sódico (500 ml). Después de la extracción con metanol al 5 % en diclorometano (4 x 150 ml), la fase orgánica se secó sobre sulfato sódico anhidro, se filtró y el filtrado se evaporó, produciendo un semi-sólido. La mezcla en bruto se disolvió en dimetilformamida (26 ml) seguido de la adición de clorhidrato de hidroxilamina (1,77 g, 25,45 mmol) y se agitó a temperatura ambiente durante 2,5 horas. Después de enfriar a 0 °C, se añadió oxicloruro de fósforo (3,0 ml,

32,2 mmol) y la mezcla se agitó durante una noche a temperatura ambiente. La reacción se interrumpió con una solución saturada enfriada con hielo de bicarbonato sódico. El sólido se recogió por filtración, se lavó con una pequeña cantidad de agua enfriada con hielo y se secó. El sólido en bruto 3-cloro-2-(1H-indazol-4-il)-3-(piridin-4-il)acrilonitrilo se disolvió en etanol (80 ml) seguido de la adición de hidrazina monohidrato (3,0 ml, 95,6 mmol) y se calentó a reflujo durante 2,5 h. Después de enfriar a temperatura ambiente, el disolvente se retiró por evaporación. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice, eluyendo con metanol en diclorometano (gradiente al 2-12 %), dando 4,7 g (rendimiento del 80 %) de 4-(1H-indazol-4-il)-3-(piridin-4-il)-1H-pirazol-5-amina en forma de un sólido de color beige. EM: 277,1 [M+H].

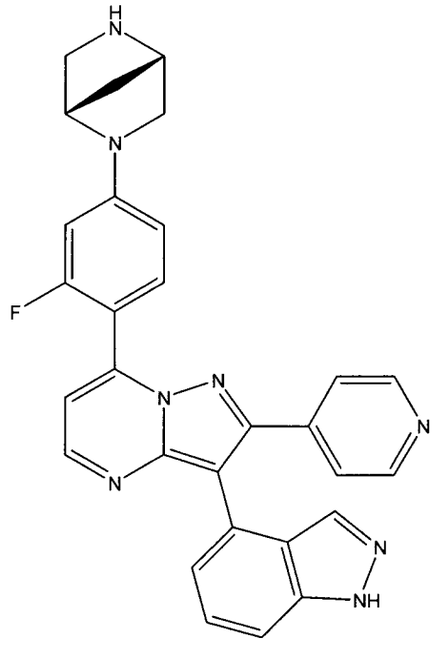
Etapa 9: (1S,4S)-5-{3-fluoro-4-[3-(1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]fenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo



Una mezcla de (1S,4S)-5-{4-[(2E)-3-(dimetilamino)prop-2-enoil]-3-fluorofenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo (2,3 g, 5,9

mmol), 4-(1H-indazol-4-il)-3-(piridin-4-il)-1H-pirazol-5-amina (1,59 g, 5,75 mmol) y ácido trifluoroacético (4,4 ml, 57,5 mmol) en 25 ml de etanol se agitó a temperatura ambiente durante una noche. La mezcla de reacción se evaporó, se enfrió y se agitó con una solución saturada de bicarbonato sódico. El sólido se recogió por filtración, se lavó con agua y se secó. El sólido en bruto se purificó por cromatografía sobre gel de sílice (^{i}PrOH al 3-6 %/CH_2Cl_2). La purificación adicional se consiguió por recristalización en EtOH caliente o EtOH/hexano, produciendo 2,43 g (70 %) de (1S,4S)-5-{3-fluoro-4-[3-(1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]fenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo en forma de un sólido de color amarillo. EM: 603,2 [M+H].

Ejemplo 93: 7-{4-[(1S,4S)-2,5-diazabiciclo[2.2.1]hept-2-il]-2-fluorofenil}-3-(1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina



Se disolvió (1S,4S)-5-{3-fluoro-4-[3-(1H-indazol-4-il)-2-piridin-4-

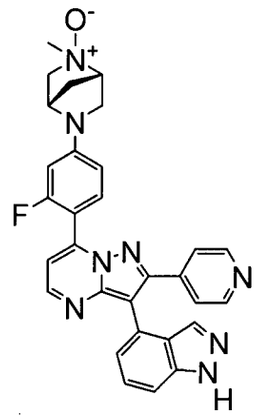
ilpirazolo[1,5-a]pirimidin-7-il]fenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo (2,43 g, 4,0 mmol) en 60 ml de metanol, después se añadieron 30 ml de ácido clorhídrico concentrado y la mezcla resultante se agitó a temperatura ambiente durante 3 horas. El sólido precipitado se recogió por filtración y después se lavó con una pequeña cantidad de metanol. El filtrado se evaporó a sequedad y el residuo se recogió en una cantidad mínima de metanol. El sólido resultante se recogió por filtración, se lavó con una cantidad mínima de metanol y los sólidos se combinaron. Al material en bruto se le añadió una solución saturada enfriada con hielo de bicarbonato sódico. Después de la filtración, el sólido en bruto se purificó por una columna corta de gel de sílice (80:18:2, cloruro de metileno:metanol:hidróxido de amonio), dando 1,9 g (95 %) de 7-{4-[(1S,4S)-2,5-diazabiciclo[2.2.1]hept-2-il]-2-fluorofenil}-3-(1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina en forma de un sólido de color amarillo. EM: 503,3 [M+H].

Ejemplo 94: 7-{2-Fluoro-4-[(1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina

Una mezcla de 7-{4-[(1S,4S)-2,5-diazabiciclo[2.2.1]hept-2-il]-2-fluorofenil}-3-(1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina (1,9 g, 3,78 mmol), HCHO al 37 % (1,0 ml, 13,3 mmol), $NaBH(OAc)_3$ (2,12 g,10,04 mmol) y 6 gotas de ácido acético en 35 ml de DMF se agitó a temperatura ambiente durante 3 horas. La DMF se evaporó a sequedad y al residuo se le añadieron 80 ml de una solución 7 N de metanol en amoniaco, se agitó durante 2 horas y el disolvente se evaporó a sequedad. Al residuo resultante se le añadió una solución saturada de bicarbonato sódico. El sólido se recogió por filtración, se lavó con agua y se secó. El sólido en bruto se purificó por cromatografía

ultrarrápida (80:20, CH_2Cl_2/metanol), dando 1,7 g (87 %) de un sólido de color amarillo. Este sólido se recristalizó en etanol caliente, produciendo 1,4 g (72 %) de 7-{2-fluoro-4-[(1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina en forma de un sólido de color amarillo. EM: 279,6 [M+ACN+2H].

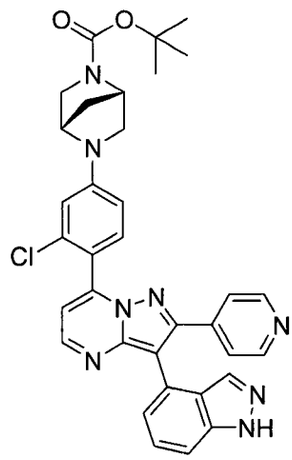
Ejemplo 95: 7-{2-fluoro-4-[(1S,4S)-5-metil-5-oxido-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina



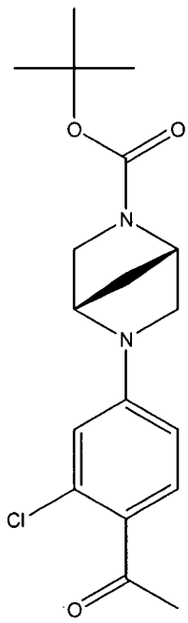
Una mezcla de 7-{2-fluoro-4-[(1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina (0,23 g, 0,45 mmol) y ácido 3-cloroperbenzoico (0,09 g, 0,40 mmol) en cloruro de metileno se agitó a temperatura ambiente durante 3 horas. El disolvente se evaporó y el residuo se agitó con una solución saturada de bicarbonato sódico. El sólido resultante se recogió por filtración, se lavó con agua y se secó. El sólido en bruto se purificó por cromatografía sobre gel de sílice, eluyendo con metanol al 20 % en cloruro de metileno, y después con una mezcla de metanol al 10 % e hidróxido de amonio al 1 % en cloruro de metileno, produciendo 0,121 g (51 %) de 7-{2-fluoro-4-[(1S,4S)-5-metil-5-oxido-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-

(1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina en forma de un sólido de color amarillo. EM: 287,7 [M+ACN+2H].

Ejemplo 96: Éster terc-butílico del ácido (1S,4S)-5-{3-cloro-4-[3-(1H-indazol-4-il)-2-piridin-4-il-pirazolo[1,5-a]pirimidin-7-il]-fenil}-2,5-diaza-biciclo[2.2.1]heptano-2-carboxílico

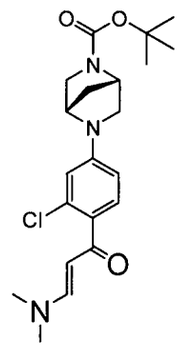


Etapa 1: (1S,4S)-5-(4-acetil-3-clorofenil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo



A una solución de 2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de (1S,4S)-terc-butilo (4,13 g, 20,86 mmol) en 20 ml de DMF se le añadieron 2'-cloro-4'-fluoroacetofenona (3,0 g, 17,4 mmol) y carbonato potásico (7,2 g, 52,14 mmol). Esta mezcla se calentó a 100 ºC durante 16 horas, se enfrió a temperatura ambiente y se diluyó con 200 ml de cloruro de metileno. La fase orgánica se secó y se concentró, produciendo un residuo que se purificó por cromatografía sobre gel de sílice (eluyendo con un gradiente de 15:85 a 30:70 de EtOAc/hexano), produciendo 4,02 g (66 %) de (1S,4S)-5-(4-acetil-3-clorofenil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo en forma de un sólido de color beige. EM 351,1 [M+H].

Etapa 2: 5-(4-((E)-3-(dimetilamino)acriloil)-3-clorofenil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de (1S,4S)-terc-butilo



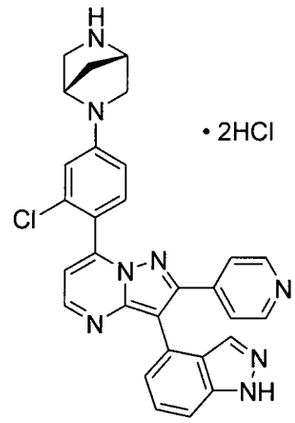
Una mezcla de 5-(4-acetil-3-clorofenil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de (1S,4S)-terc-butilo (2,457 g, 7,00 mmol) y 5,00 ml de C-terc-butoxi-N,N,N',N'-tetrametilmetanodiamina se calentó a 100 ºC durante 3 horas. Después, la mezcla se concentró al vacío y el residuo gomoso se digirió con 75 ml de éter dietílico. La solución se lavó con 75 ml de agua y 75 ml de una solución saturada de NaCl, se secó sobre sulfato de magnesio anhidro, se filtró y el disolvente se retiró al vacío, dando 2,679 g (97 %) de 5-(4-((E)-3-

(dimetilamino)acriloil)-3-clorofenil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de (1S,4S)-terc-butilo en forma de una espuma de color amarillo clara que se usó sin purificación. EM: 406,3 [M+H].

Etapa 3: Ester terc-butílico del ácido (1S,4S)-5-{3-cloro-4-[3-(1H-indazol-4-il)-2-piridin-4-il-pirazolo[1,5-a]pirimidin-7-il]-fenil}-2,5-diaza-biciclo[2.2.1]heptano-2-carboxílico

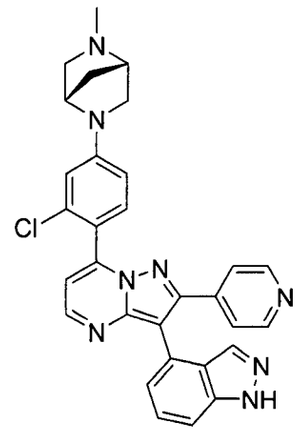
A una solución de 5-(4-((E)-3-(dimetilamino)acriloil)-3-clorofenil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de (1S,4S)-*terc*-butilo (2,638 g, 6,50 mmol) y 4-(1H-indazol-4-il)-3-(piridin-4-il)-1H-pirazol-5-amina (1,877 g, 6,79 mmol) en 30 ml de metanol se le añadieron 5 ml de ácido trifluoroacético y la solución resultante se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 108 horas. La mezcla se repartió entre 200 ml de diclorometano y 200 ml de una solución saturada de bicarbonato sódico. La fase orgánica se separó y la fase acuosa se extrajo con 100 ml más de diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato de magnesio anhidro, se filtraron y el disolvente se retiró al vacío. La espuma de color amarillo/pardo resultante se purificó por cromatografía sobre gel de sílice, proporcionando éster terc-butílico del ácido 3,374 g (84 %) de (1S,4S)-5-{3-cloro-4-[3-(1H-indazol-4-il)-2-piridin-4-il-pirazolo[1,5-a]pirimidin-7-il]-fenil}-2,5-diaza-biciclo[2.2.1]heptano-2-carboxílico, en forma de una espuma de color amarillo. EM: 619,3 [M+H].

Ejemplo 97: Sal bis-clorhidrato de 7-[2-cloro-4-((1S,4S)-2,5-diaza-biciclo[2.2.1]hept-2-il)-fenil]-3-(1H-indazol-4-il)-2-piridin-4-il-pirazolo[1,5-a]pirimidina



A una solución de éster terc-butílico del ácido (1S,4S)-5-{3-cloro-4-[3-(1H-indazol-4-il)-2-piridin-4-il-pirazolo[1,5-a]pirimidin-7-il]-fenil}-2,5-diaza-biciclo[2.2.1]heptano-2-carboxílico (3,370 g, 5,44 mmol) en 50 ml de metanol se le añadieron 25 ml de una solución de ácido clorhídrico concentrado durante 2-3 minutos. La solución de color rojo oscuro resultante se agitó a temperatura ambiente durante 30 minutos. Los disolventes se retiraron al vacío y el residuo se digirió con 50 ml de metanol. Los cristales resultantes se filtraron y se aclararon con metanol recién preparado. El producto húmedo se transfirió rápidamente a un desecador y se secó a alto vacío durante una noche, proporcionando 2,638 g (82 %) de sal bis-clorhidrato de 7-[2-cloro-4-((1S,4S)-2,5-diaza-biciclo[2.2.1]hept-2-il)-fenil]-3-(1H-indazol-4-il)-2-piridin-4-il-pirazolo[1,5-a]pirimidina en forma de cristales de color amarillo/naranja. EM: 280,6 [M+CH_3CN+2H].

Ejemplo 98: 7-[2-Cloro-4-((1S,4S)-5-metil-2,5-diaza-biciclo[2.2.1]hept-2-il)-fenil]-3-(1H-indazol-4-il)-2-piridin-4-il-pirazolo[1,5-a]pirimidina

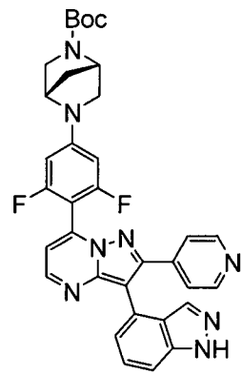


Etapa 1: Se digirió sal bis-clorhidrato de 7-[2-cloro-4-((1S,4S)-2,5-diaza-biciclo[2.2.1]hept-2-il)-fenil]-3-(1H-indazol-4-il)-2-piridin-4-il-pirazolo[1,5-a]pirimidina (2,800 g, 4,73 mmol) con 50 ml de una solución semi-saturada de bicarbonato sódico teniendo cuidado de evitar la formación incontrolada de espuma. El sólido resultante se filtró, se lavó con varias porciones de agua y se secó al vacío, dando 2,287 g (93 %) de la base libre de 7-[2-cloro-4-((1S,4S)-2,5-diaza-biciclo[2.2.1]hept-2-il)-fenil]-3-(1H-indazol-4-il)-2-piridin-4-il-pirazolo[1,5-a]pirimidina en forma de un sólido de color amarillo.

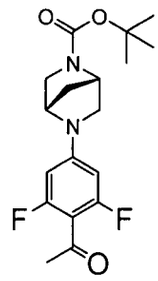
Etapa 2: A una solución de 7-[2-Cloro-4-((1S,4S)-2,5-diaza-biciclo[2.2.1]hept-2-il)-fenil]-3-(1H-indazol-4-il)-2-piridin-4-il-pirazolo[1,5-a]pirimidina (2,283 g, 4,40 mmol) en 20 ml de dimetilformamida se le añadió una solución acuosa al 37 % de formaldehído (1,10 ml, 14,77 mmol) seguido de 3 gotas de ácido acético y borohidruro sódico (2,797 g, 13,15 mmol). La mezcla se calentó ligeramente con una pistola de calor y se diluyó con 20 ml más de dimetilformamida para facilitar la disolución. Después de la retirada de algún material insoluble, la mezcla se agitó 2,5 horas a temperatura ambiente. Después, se concentró a sequedad por evaporación rotatoria y el residuo se digirió con 20 ml de una solución 7 N de amoniaco metanólico. La mezcla

resultante se agitó durante 15 horas a temperatura ambiente. Después, se filtró para retirar pequeñas cantidades de material insoluble y el filtrado se concentró al vacío. El residuo se digirió con 50 ml de diclorometano y se filtró. El sólido se lavó con varias porciones adicionales de diclorometano. El filtrado y los lavados combinados se concentraron al vacío, dando un sólido de color amarillo que se purificó por cromatografía sobre gel de sílice, dando 1,756 g de un polvo de color amarillo. Este material se repartió entre 150 ml de diclorometano y 150 ml de una solución semi-saturada de bicarbonato sódico. La fase orgánica se separó y la fase acuosa se extrajo con 50 ml de diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato de magnesio anhidro, se filtraron y se concentraron al vacío, dando 1,746 g de 7-[2-cloro-4-((1S,4S)-5-metil-2,5-diaza-biciclo[2.2.1]hept-2-il)-fenil]-3-(1H-indazol-4-il)-2-piridin-4-il-pirazolo[1,5-a]pirimidina en forma de un polvo de color amarillo. EM: 533,1 [M+H].

Ejemplo 99: (1S,4S)-5-{3,5-difluoro-4-[3-(1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]fenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo

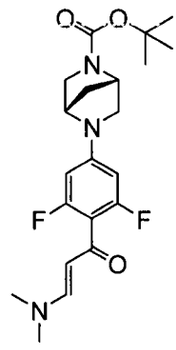


Etapa 1: 5-(4-Acetil-3,5-difluorofenil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de (1S,4S)-*terc*-butilo



A una solución de 1-(2,4,6-trifluorofenil)etanona en 30 ml de hexametilfosforamida (3,9 g, 22,5 mmol) se le añadieron 2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de (1S,4S)-terc-butilo (3,0 g, 15 mmol) y carbonato potásico (6,2 g, 45 mmol). Esta solución se agitó a temperatura ambiente durante 4 días. La mezcla se diluyó con 200 ml de éter dietílico y se lavó con 200 ml de agua. La solución acuosa se extrajo dos veces con éter dietílico. La fase orgánica combinada se lavó tres veces con agua, después se secó y se concentró. El residuo se purificó por cromatografía sobre gel de sílice (isopropanol, hexanos), dando 3,3 g (rendimiento del 62 %) de 5-(4-acetil-3,5-difluorofenil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de (1S,4S)-*terc*-butilo. EM: 353,1 [M+H].

Etapa 2: 5-(4-((E)-3-(dimetilamino)acriloil)-3,5-difluorofenil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de (1S,4S)-terc-butilo



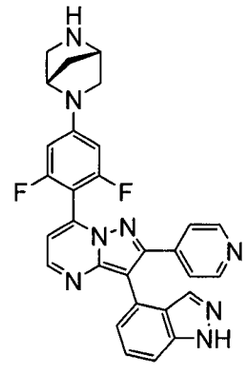
Una mezcla de 5-(4-acetil-3,5-difluorofenil)-2,5-

diazabiciclo[2.2.1]heptano-2-carboxilato de (1S,4S)-*terc*-butilo (3,3 g, 9,4 mmol) y 30 ml de 1,1-dimetoxi-N,N-dimetilmetanamina se calentaron a reflujo durante 35 horas. La mezcla de reacción se concentró y el residuo se purificó por cromatografía sobre gel de sílice (isopropanol, diclorometano), dando 3,8 (99 %) de 5-(4-((E)-3-(dimetilamino)acriloil)-3,5-difluorofenil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de (1S,4S)-*terc*-butilo. EM: 408,3 [M+H].

Etapa 3: (1S,4S)-5-{3,5-Difluoro-4-[3-(1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]fenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo

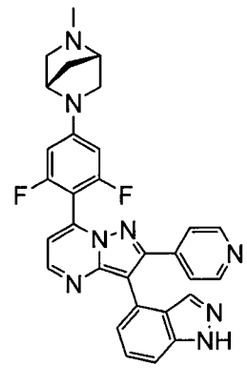
A una solución de ácido 2,2,2-trifluoroacético (0,54 ml) en 18 ml de metanol se le añadieron 5-(4-((E)-3-(dimetilamino)acriloil)-3,5-difluorofenil)-2,5-diazabiciclo-[2.2.1]heptano-2-carboxilato de (1S,4S)-terc-butilo (1,1 g, 2,6 mmol) y 4-(1H-indazol-4-il)-3-(piridin-4-il)-1H-pirazol-5-amina (0,72 g, 2,6 mmol). Esta solución se agitó a temperatura ambiente durante 3 días. La mezcla se basificó con amoniaco metanólico, se adsorbió sobre gel de sílice y se purificó por cromatografía sobre gel de sílice (isopropanol, diclorometano), dando 1,4 g (rendimiento del 87 %) de (1S,4S)-5-{3,5-difluoro-4-[3-(1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]fenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo. EM: 621,3 [M+H].

Ejemplo 100: 7-(4-((1S,4S)-2,5-diazabiciclo[2.2.1]heptan-2-il)-2,6-difluorofenil)-3-(1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina



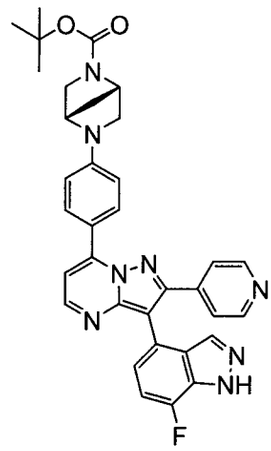
Una solución de 5-(4-(3-(1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-3,5-difluorofenil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de (1S,4S)-*terc*-butilo (1,4 g, 2,3 mmol) en HCl 6 N/metanol (19 ml HCl concentrado y 19 ml de metanol) se agitó durante 1 hora. La mezcla se concentró, se basificó con amoniaco metanólico, se adsorbió sobre gel de sílice y se purificó con cromatografía sobre gel de sílice (amoniaco, metanol, diclorometano), dando 1,1 g (rendimiento del 93 %) de 7-(4-((1S,4S)-2,5-diazabiciclo[2.2.1]heptan-2-il)-2,6-difluorofenil)-3-(1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina. EM: 521,3 [M+H].

Ejemplo 101: 7-{2,6-difluoro-4-[(1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina

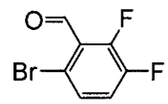


A una solución de 7-(4-((1S,4S)-2,5-diazabiciclo[2.2.1]heptan-2-il)-2,6-difluorofenil)-3-(1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina (1,1 g, 2,1 mmol) en 30 ml de DMF se le añadieron formaldehído (0,47 ml, 6,3 mmol) y triacetoxihidroborato sódico (1,3 g, 6,3 mmol). Esta solución se agitó a temperatura ambiente durante 2 horas y después se concentró. El residuo se agitó con 15 ml de amoniaco metanólico 7 N durante una noche. La solución se concentró y se purificó con cromatografía sobre gel de sílice (metanol, diclorometano), dando 0,95 g (rendimiento del 84 %) de 7-(2,6-difluoro-4-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-3-(1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina. EM: 535,4 [M+H].

Ejemplo 102: (1S,4S)-5-{4-[3-(7-Fluoro-1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]fenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo



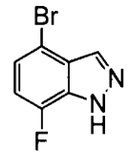
Etapa 1: 6-Bromo-2,3-difluoro-benzaldehído



A un matraz seco, en una atmósfera de nitrógeno, se le añadieron 9,24

ml de 2,2,6,6-tetrametilpiperidina (0,054 mol, 1,05 equiv.) y 103,5 ml de tetrahidrofurano (THF), y después se enfrió a –78 °C. Se añadieron gota a gota 21,7 ml de n-butil litio (0,054 mol, 1,05 equiv.), seguido de 5,86 ml de 1-bromo-3,4-difluorobenceno (0,052 mol, 1,0 equiv.) en 6 ml de THF. La mezcla resultante se agitó a –78 °C durante 2 horas y se añadieron 4,21 ml de N,N-dimetilformamida (DMF) (0,054 mol, 1,05 equiv.). La mezcla se dejó calentar a –20 °C y después se inactivó con 44 ml de HCl 1 N añadidos gota a gota. Después, esta solución se extrajo con éter dietílico y la fase orgánica se lavó tres veces con HCl 1 N, seguido de un lavado con salmuera. Después de secar la fase orgánica sobre sulfato de magnesio ($MgSO_4$), se concentró al vacío, produciendo 11,12 g de 6-bromo-2,3-difluoro-benzaldehído en forma de un aceite de color pardo que se usó sin purificación en la siguiente reacción.

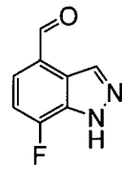
Etapa 2: 4-Bromo-7-fluoro-1H-indazol



Una porción de 11,2 g de 6-bromo-2,3-difluoro-benzaldehído se disolvió en 51 ml de dimetoxietano. A esto se le añadieron 51 ml de hidrazina anhidra, seguido de calentamiento a reflujo durante 2,5 horas; la reacción se supervisó por cromatografía de capa fina (TLC). El dimetoxietano se retiró por evaporación y el residuo restante se enfrió en un baño de hielo. Se añadió hielo y el sólido de color blanco resultante se retiró por filtración y se lavó con agua fría. Después, el sólido se calentó en diclorometano y se filtró. El filtrado se evaporó a sequedad, se calentó en diclorometano y se filtró de nuevo. En total, se recuperaron 6,19 g de 4-bromo-7-fluoro-1H-indazol en forma de un sólido de

color blanco con un rendimiento del 32 %. EM: 215,0, 217,0 [M+H].

Etapa 3: 7-Fluoro-1H-indazol-4-carbaldehído



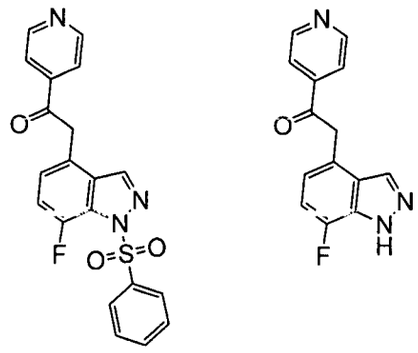
A 0,614 g de hidruro sódico (0,015 mol, 1,1 equiv.) en un matraz seco, en una atmósfera de nitrógeno, se le añadieron 46 ml de THF. La mezcla se enfrió a 0 °C en un baño de hielo. A esta mezcla se le añadieron 3 g de 4-bromo-7-fluoro-1H-indazol (0,014 mol, 1,0 equiv.), seguido de agitación a 0 °C durante 5 minutos. La mezcla de color rosa resultante se calentó a temperatura ambiente y se agitó durante 15 minutos más, después de lo cual la reacción se volvió de color pardo. Después, se enfrió a –78 °C y se añadieron lentamente 23 ml de t-butil litio 1,7 M en pentano (0,039 mol, 2,8 equiv.) mientras se agitaba a –78 °C durante 10 minutos. A esta mezcla se le añadieron gota a gota 2,16 ml de dimetilformamida en 7,5 ml de tetrahidrofurano. La mezcla se agitó durante 5 minutos a –78 °C y después se calentó a temperatura ambiente. Después de agitar durante 30 minutos más, la mezcla del producto se inactivó con ácido clorhídrico 2 M (HCl) y se extrajo con acetato de etilo. La fase orgánica se secó sobre $MgSO_4$ y se evaporó a sequedad. Se obtuvo un rendimiento cuantitativo (2,51 g) de 7-fluoro-1H-indazol-4-carbaldehído en forma de un sólido de color rosa que contenía una pequeña cantidad de DMF. EM: 165,2 [M+H].

Etapa 4: 1-Bencenosulfonil-7-fluoro-1H-indazol-4-carbaldehído

Una porción de 2,29 g de 7-fluoro-1H-indazol-4-carbaldehído (0,014 mol, 1,0 equiv.) se disolvió en 100 ml de THF. A esto se le añadieron 0,614 g de

NaH (0,015 mol, 1,1 equiv.), seguido de 20 minutos de agitación. A la mezcla de reacción se le añadieron 3,6 ml de cloruro de bencenosulfonilo (0,028 mol, 2,0 equiv.) y la reacción se agitó durante otra hora. La reacción se interrumpió con H_2O y se extrajo con diclorometano. La fase orgánica se secó sobre $MgSO_4$ y se evaporó a sequedad, produciendo un sólido húmedo de color naranja, que después se lavó con éter dietílico, produciendo 3,54 g de 1-bencenosulfonil-7-fluoro-1H-indazol-4-carbaldehído en forma de un sólido de color naranja claro con un rendimiento del 83 %. EM: 305,2 [M+H]. Los procedimientos para las siguientes 3 etapas se basan en ejemplos desvelados en la solicitud pendiente junto con la presente, Solicitud Provisional de Estados Unidos Nº 61/067.843.

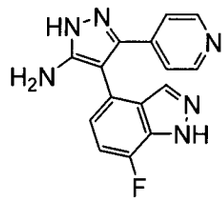
Etapa 5: 2-(1-bencenosulfonil-7-fluoro-1H-indazol-4-il)-1-piridin-4-il-etanona (CAT1788145) y 2-(7-fluoro-1H-indazol-4-il)-1-piridin-4-il-etanona



Por el procedimiento del Ejemplo 44, etapa 6, se hizo reaccionar 1-bencenosulfonil-7-fluoro-1H-indazol-4-carbaldehído con difenil(fenilamino)(piridin-4-il)metilfosfonato, proporcionando una mezcla 4:1 de 2-(1-bencenosulfonil-7-fluoro-1H-indazol-4-il)-1-piridin-4-il-etanona y 2-(7-fluoro-1H-indazol-4-il)-1-piridin-4-il-etanona. Esta mezcla se usó posteriormente sin purificación. Productos: 2-(1-bencenosulfonil-7-fluoro-1H-indazol-4-il)-1-piridin-

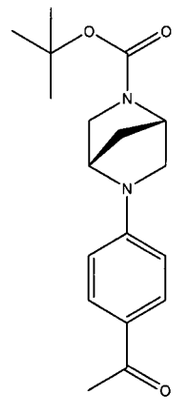
4-il-etanona EM: 396,1 [M+H] y 2-(7-fluoro-1H-indazol-4-il)-1-piridin-4-il-etanona 256,3 [M+H].

Etapa 6: 4-(7-Fluoro-1H-indazol-4-il)-5-piridin-4-il-2H-pirazol-3-ilamina



Siguiendo el procedimiento del Ejemplo 44, etapa 7, la mezcla 4:1 de 2-(1-bencenosulfonil-7-fluoro-1H-indazol-4-il)-1-piridin-4-il-etanona y 2-(7-fluoro-1H-indazol-4-il)-1-piridin-4-il-etanona se convirtió en 4-(7-fluoro-1H-indazol-4-il)-5-piridin-4-il-2H-pirazol-3-ilamina. EM: 295,2 [M+H].

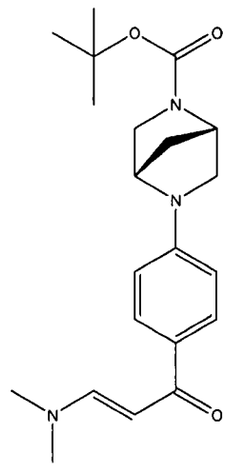
Etapa 7: (1S,4S)-5-(4-acetilfenil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo



Siguiendo el procedimiento del Ejemplo 44, Etapa 1, se hizo reaccionar 2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de (1S,4S)-*terc*-butilo con 1-(4-fluorofenil)etanona, proporcionando (1S,4S)-5-(4-acetilfenil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo en forma de un sólido de color blanquecino. EM: 317,2 [M+H].

Etapa 8: Éster terc-butílico del ácido 5-[4-(3-dimetilamino-acriloil)-fenil]-

2,5-diaza-biciclo[2.2.1]heptano-2-carboxílico



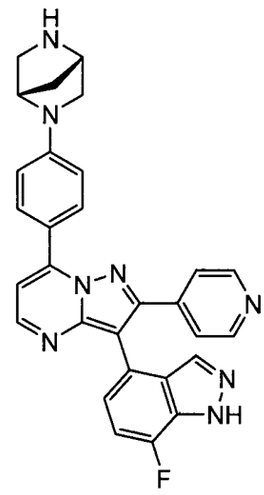
Siguiendo el procedimiento del Ejemplo 92, Etapa 2, se hizo reaccionar (1S,4S)-5-(4-acetilfenil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo con *terc*-butoxibis(dimetilamino)metano, éster terc-butílico del ácido proporcionando 5-[4-(3-dimetilamino-acriloil)-fenil]-2,5-diaza-biciclo[2.2.1]heptano-2-carboxílico en forma de un sólido de color amarillo pálido. EM: 372,3 [M+H]. El procedimiento para la siguiente etapa se basa en un ejemplo desvelado en una solicitud pendiente junto con la presente, Solicitud Provisional de Estados Unidos Nº 61/067,843.

Etapa 9: (1S,4S)-5-{4-[3-(7-Fluoro-1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]fenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo

Siguiendo el procedimiento del Ejemplo 98, Etapa 4, 4-(7-fluoro-1H-indazol-4-il)-5-piridin-4-il-2H-pirazol-3-ilamina (0,38 g, 1,3 mmol) y éster terc-butílico del ácido 5-[4-(3-dimetilamino-acriloil)-fenil]-2,5-diaza-biciclo[2.2.1]heptano-2-carboxílico (0,53 g, 1,4 mmol) proporcionaron una mezcla 3,7:1 de los regioisómeros éster terc-butílico del ácido 5-{4-[3-(7-fluoro-

1H-indazol-4-il)-2-piridin-4-il-pirazolo[1,5-a]pirimidin-7-il]-fenil}-2,5-diaza-biciclo[2.2.1]-heptano-2-carboxílico y éster terc-butílico del ácido 5-{4-[3-(7-fluoro-1H-indazol-4-il)-2-piridin-4-il-pirazolo[1,5-a]pirimidin-5-il]-fenil}-2,5-diaza-biciclo[2.2.1]heptano-2-carboxílico. Estos isómeros se separaron por cromatografía ultrarrápida usando un gradiente de MeOH del 1 % al 3 %/CH_2Cl_2, proporcionando (1S,4S)-5-{4-[3-(7-fluoro-1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]fenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo en forma de un sólido de color amarillo. EM: 603,3 [M+H].

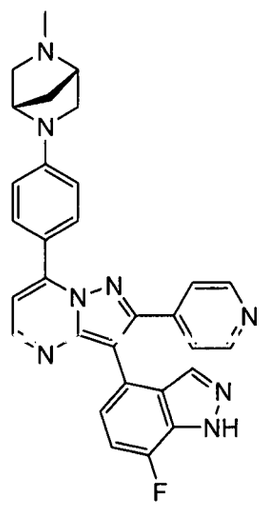
Ejemplo 103: 7-[4-(2,5-Diaza-biciclo[2.2.1]hept-2-il)-fenil]-3-(7-fluoro-1H-indazol-4-il)-2-piridin-4-il-pirazolo[1,5-a]pirimidina



Una porción de (1S,4S)-5-{4-[3-(7-fluoro-1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]fenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo (0,32 g, 5,2 mmol) se disolvió en 10,8 ml de HCl 4 N (HCl concentrado diluido con metanol) seguido de espectrometría de masas hasta que la reacción se completó. La mezcla se concentró al vacío y se purificó por cromatografía ultrarrápida usando 9:1:0,1 de MeOH/CH_2Cl_2/hidróxido de amonio, proporcionando 0,24 g de 7-[4-(2,5-diaza-biciclo[2.2.1]hept-2-il)-fenil]-

3-(7-fluoro-1H-indazol-4-il)-2-piridin-4-il-pirazolo[1,5-a]pirimidina en forma de un sólido de color amarillo (rendimiento del 92 %). EM: 503,3 [M+H].

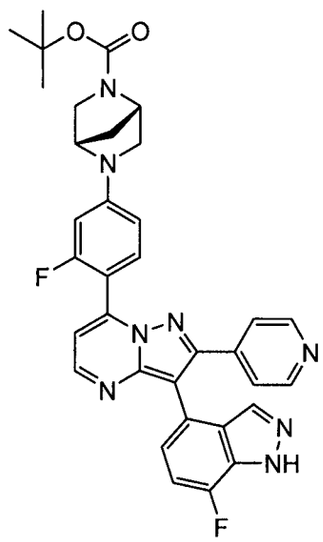
Ejemplo 104: clorhidrato de 3-(7-fluoro-1H-indazol-4-il)-7-{4-[(1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina



Una porción de 0,22 g de 7-[4-(2,5-diaza-biciclo[2.2.1]hept-2-il)-fenil]-3-(7-fluoro-1H-indazol-4-il)-2-piridin-4-il-pirazolo[1,5-a]pirimidina se disolvió en 7,8 ml de DMF y se añadieron 0,16 ml de una solución de formaldehído al 37 % en H_2O (2,2 mmol, 5,0 equiv.), seguido de 0,05 ml de ácido acético (0,9 mmol, 2,0 equiv.). Esta mezcla se agitó durante 15 minutos, después se añadieron 0,46 g de triacetoxiborohidruro sódico ($Na(OAc)_3BH$) (2,2 mmol, 5,0 equiv.) y la reacción se agitó durante una hora. La mezcla del producto se inactivó con 5 ml de amoniaco 7 N en metanol y se agitó durante 30 minutos más. Después, la reacción se concentró al vacío y se purificó por cromatografía ultrarrápida usando 9:1:0,1 de MeOH/CH_2Cl_2/hidróxido de amonio. Después, el sólido de color amarillo se disolvió en diclorometano y se lavó con bicarbonato sódico saturado, se secó sobre $MgSO_4$ y se evaporó a sequedad, produciendo 0,22 g de un sólido de color amarillo. Después, este sólido se disolvió en 5 ml de

metanol y se enfrió en un baño de hielo. A esto se le añadieron 0,34 ml de HCl metanólico 3 N y la mezcla se agitó a 0 °C durante 15 minutos. La mezcla del producto se concentró al vacío, produciendo 0,2 g de sal clorhidrato de 3-(7-fluoro-1H-indazol-4-il)-7-[4-(5-metil-2,5-diaza-biciclo[2.2.1]hept-2-il)-fenil]-2-piridin-4-il-pirazolo[1,5-a]pirimidina en forma de un sólido de color naranja-rojo (rendimiento del 83 %). EM: 517,3 [M+H].

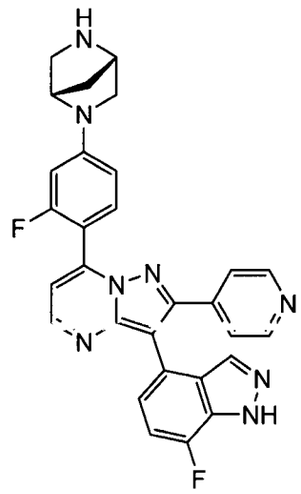
Ejemplo 105: (1S,4S)-5-{3-Fluoro-4-[3-(7-fluoro-1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]fenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo



Una porción de 2,31 g de éster terc-butílico del ácido 5-[4-(3-dimetilamino-acriloil)-3-fluoro-fenil]-2,5-diaza-biciclo[2.2.1]heptano-2-carboxílico (1,1 equiv, 5,9 mmol) se disolvió en 37 ml de metanol. A esto se le añadieron 1,59 g de 4-(7-fluoro-1H-indazol-4-il)-5-piridin-4-il-2H-pirazol-3-ilamina (1,0 equiv, 5,4 mmol), seguido de 1,1 ml de ácido trifluoroacético y la reacción se agitó a temperatura ambiente durante 16 horas. La reacción se concentró al vacío, se neutralizó con bicarbonato sódico acuoso saturado ($NaHCO_3$) y se

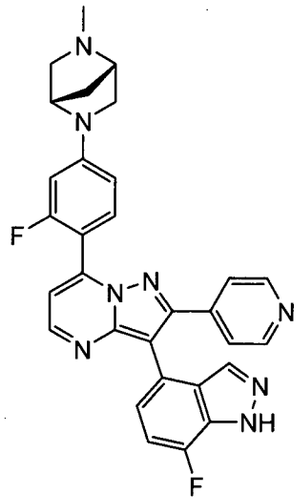
filtró. El sólido se lavó con agua y se secó al vacío. La purificación se realizó por cromatografía ultrarrápida sobre sílice, eluyendo con metanol al 5 %-10 %/acetato de etilo, produciendo 2,37 g de éster terc-butílico del ácido 5-{3-fluoro-4-[3-(7-fluoro-1H-indazol-4-il)-2-piridin-4-il-pirazolo[1,5-a]pirimidin-7-il]-fenil}-2,5-diaza-biciclo[2.2.1]heptano-2-carboxílico en forma de un sólido de color amarillo (rendimiento del 70,7 %). EM: 621,3 [M+H].

Ejemplo 106: 7-{4-[(1S,4S)-2,5-diazabiciclo[2.2.1]hept-2-il]-2-fluorofenil}-3-(7-fluoro-1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina



Siguiendo el procedimiento del Ejemplo 103, éster terc-butílico del ácido 5-{3-fluoro-4-[3-(7-fluoro-1H-indazol-4-il)-2-piridin-4-il-pirazolo[1,5-a]pirimidin-7-il]-fenil}-2,5-diaza-biciclo[2.2.1]heptano-2-carboxílico proporcionó 7-[4-(2,5-diaza-biciclo[2.2.1]hept-2-il)-2-fluoro-fenil]-3-(7-fluoro-1H-indazol-4-il)-2-piridin-4-il-pirazolo[1,5-a]pirimidina. EM: 521,2 [M+H]; 261,2 [M+2H].

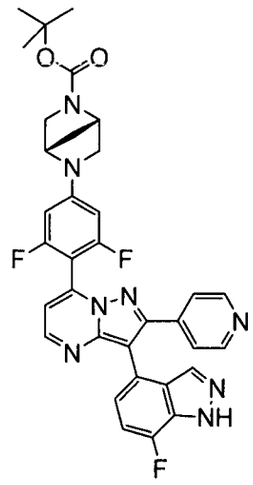
Ejemplo 107: 3-(7-fluoro-1H-indazol-4-il)-7-{2-fluoro-4-[(1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina



Una porción de 1,44 g de 7-[4-(2,5-diaza-biciclo[2.2.1]hept-2-il)-2-fluoro-fenil]-3-(7-fluoro-1H-indazol-4-il)-2-piridin-4-il-pirazolo[1,5-a]pirimidina (2,8 mmol, 1,0 equiv.) se disolvió en 50 ml de DMF y se añadió 1 ml de una solución de formaldehído acuoso al 37 % (13,8 mmol, 5,0 equiv.). A esta mezcla se le añadieron 0,32 ml de ácido acético (5,5 mmol, 2,0 equiv.)) y la solución se agitó durante 15 minutos. Se añadió una porción de 2,93 g de $Na(OAc)_3BH$ (13,8 mmol, 5,0 equiv.) y la reacción se agitó durante una hora. La mezcla del producto se inactivó con 30 ml de amoniaco 7 N en MeOH y se agitó durante 30 minutos más. Después, la reacción se repartió entre agua y acetato de etilo y la fase acuosa se extrajo de nuevo con acetato de etilo. Las fases orgánicas se combinaron, se secaron sobre $MgSO_4$ y se concentraron al vacío, dando un aceite de color amarillo. Después de la adición de agua a este aceite, precipitó un sólido. El sólido resultante se filtró y se secó, proporcionando 1,3 g de 3-(7-fluoro-1H-indazol-4-il)-7-[2-fluoro-4-(5-metil-2,5-diaza-biciclo[2.2.1]hept-2-il)-fenil]-2-piridin-4-il-pirazolo[1,5-a]pirimidina en forma de un sólido de color amarillo (rendimiento del 88 %). EM: 535,2 [M+H].

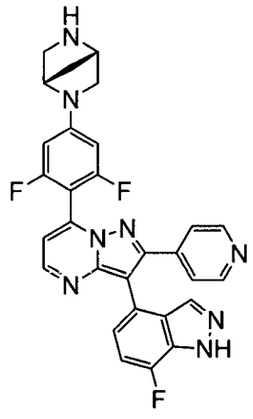
Ejemplo 108: (1S,4S)-5-{3,5-Difluoro-4-[3-(7-fluoro-1H-indazol-4-il)-2-

piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]fenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo



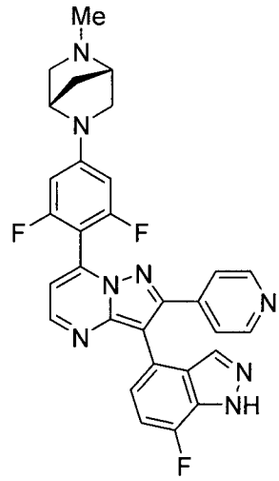
Siguiendo el procedimiento del Ejemplo 100, Etapa 3, se preparó 5-(3,5-difluoro-4-(3-(7-fluoro-1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)fenil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de (1S,4S)-terc-butilo a partir de 4-(7-fluoro-1H-indazol-4-il)-3-(piridin-4-il)-1H-pirazol-5-amina y 5-(4-((E)-3-(dimetilamino)acriloil)-3,5-difluorofenil)-2,5-diazabiciclo[2.2.1]-heptano-2-carboxilato de (1S,4S)-terc-butilo. EM: 639,2 [M+H].

Ejemplo 109: 7-{4-[(1S,4S)-2,5-Diazabiciclo[2.2.1]hept-2-il]-2,6-difluorofenil}-3-(7-fluoro-1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina



Siguiendo el procedimiento del Ejemplo 102, se preparó 7-(4-((1S,4S)-2,5-diazabiciclo[2.2.1]heptan-2-il)-2,6-difluorofenil)-3-(7-fluoro-1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina a partir de 5-(3,5-difluoro-4-(3-(7-fluoro-1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)fenil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de (1S,4S)-*terc*-butilo. EM: 539,3 [M+H].

Ejemplo 110: 7-{2,6-Difluoro-4-[(1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(7-fluoro-1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina



Siguiendo el procedimiento del Ejemplo 101, se preparó 7-(2,6-difluoro-4-((1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]heptan-2-il)fenil)-3-(7-fluoro-1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina a partir de 7-(4-((1S,4S)-2,5-diazabiciclo[2.2.1]heptan-2-il)-2,6-difluorofenil)-3-(7-fluoro-1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina. EM: 553,2 [M+H].

Los Ejemplos 111-210 se resumen en la Tabla 1.

Ejemplo	Nombre del Compuesto	EM, IEN (m/z)
111	3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-5-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo	494
112	2-{3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]oct-8-il}etanol	466,3
113	3-(1*H*-indazol-4-il)-7-(8-isopropil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	464,3
114	3-(1*H*-indazol-4-il)-7-[8-(metilsulfonil)-8-azabiciclo[3.2.1]oct-3-il]-2-piridin-4-ilpirazolo[1,5-a]pirimidina	500,3
115	3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxamida	465,2
116	2-{3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]oct-8-il}-*N*,*N*-dimetil-2-oxoetanamina	507,3
117	{3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]oct-8-il}acetonitrilo	461,2
118	*N*-etil-3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxamida	493,2
119	7-(8-acetil-8-azabiciclo[3.2.1]oct-3-il)-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	464,2

Ejemplo	Nombre del Compuesto	EM, IEN (m/z)
120	3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-*N*,*N*-dimetil-8-azabiciclo[3.2.1]octano-8-carboxamida	493,2
121	(1*S*,4*S*)-5-{[3-(4-cloro-3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]metil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo	547,2;
122	(1*S*,4*S*)-5-{4-[3-(7-fluoro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-5-il]fenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo	603,2
123	(1*S*,4*S*)-5-{3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]fenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo	585,3
124	7-{3-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	485,2
125	(1*S*,4*S*)-5-{4-[3-(7-cloro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]fenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo	619,2
126	3-(1*H*-indazol-4-il)-7-{3-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina	499,2
127	3-(7-cloro-1*H*-indazol-4-il)-7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina	519,3

Ejemplo	Nombre del Compuesto	EM, IEN (m/z)
128	(2*S*)-2-({3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]oct-8-il}carbonil)pirrolidin-1-carboxilato de *terc*-butilo	619,3;
129	3-(1*H*-indazol-4-il)-7-(8-L-prolil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	519,3
130	1-{3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]oct-8-il}propan-2-ona	478,2
131	3-[3-(7-fluoro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-5-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo	512,3
132	7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-2-fluorofenil}-3-(3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	493,2
133	3-(7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-2-fluorofenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol	479,2
134	3-(7-{2-fluoro-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol	493,2
135	7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-2-metilfenil}-3-(7-fluoro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	517,2

Ejemplo	Nombre del Compuesto	EM, IEN (m/z)
136	3-(7-fluoro-1*H*-indazol-4-il)-7-{2-metil-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina	531,2
137	7-(8-azabiciclo[3.2.1]oct-3-il)-3-(7-fluoro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	440,2
138	{3-[3-(7-fluoro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]oct-8-il}acetonitrilo	479,1
139	3-(7-cloro-1*H*-indazol-4-il)-5-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina	519,0
140	3-(1*H*-indazol-4-il)-7-[6-(8-metil-3,8-diazabiciclo[3.2.1]oct-3-il)piridin-3-il]-2-piridin-4-ilpirazolo[1,5-a]pirimidina	514,3
141	3-(7-cloro-1*H*-indazol-4-il)-7-{4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina	533,3;
142	7-(1,4-dioxaespiro[4.5]dec-8-il)-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	453,3;
143	3-(1*H*-indazol-4-il)-7-{4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.2]oct-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina	513,2
144	7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.2]oct-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	499,2

Ejemplo	Nombre del Compuesto	EM, IEN (m/z)
145	7-{2-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-4,6-difluorofenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	521,7
146	5-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-2-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-*N*,*N*-dimetilanilina	528,3
147	7-{2,4-difluoro-6-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	535,2
148	2-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-*N*,*N*-dimetil-5-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]anilina	542,3
149	7-{*cis*-4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]ciclohexil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	491,5
150	3-(1*H*-indazol-4-il)-7-[*cis*-4-(3-oxa-8-azabiciclo[3.2.1]oct-8-il)ciclohexil]-2-piridin-4-ilpirazolo[1,5-a]pirimidina	506,5
151	3-(1*H*-indazol-4-il)-7-[*trans*-4-(3-oxa-8-azabiciclo[3.2.1]oct-8-il)ciclohexil]-2-piridin-4-ilpirazolo[1,5-a]pirimidina	506,5

Ejemplo	Nombre del Compuesto	EM, IEN (m/z)
152	3-(1*H*-indazol-4-il)-7-[*cis*-4-(8-oxa-3-azabiciclo[3.2.1]oct-3-il)ciclohexil]-2-piridin-4-ilpirazolo[1,5-a]pirimidina	506,2
153	3-(1*H*-indazol-4-il)-7-[*trans*-4-(8-oxa-3-azabiciclo[3.2.1]oct-3-il)ciclohexil]-2-piridin-4-ilpirazolo[1,5-a]pirimidina	506,2
154	3-(1*H*-indazol-4-il)-7-{*cis*-4-[(1*S*,4*S*)-2-oxa-5-azabiciclo[2.2.1]hept-5-il]ciclohexil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina	492,5
155	3-(1*H*-indazol-4-il)-7-{*trans*-4-[(1*S*,4*S*)-2-oxa-5-azabiciclo[2.2.1]hept-5-il]ciclohexil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina	492,4
156	7-{*trans*-4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]ciclohexil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	491,5
157	7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-3-(trifluorometil)fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	553,2
158	7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-1-naftil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	535,2
159	3-(1*H*-indazol-4-il)-7-{4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]-3-(trifluorometil)fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina	567,2

Ejemplo	Nombre del Compuesto	EM, IEN (m/z)
160	3-(1*H*-indazol-4-il)-7-{4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]-1-naftil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina	549,2
161	7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-3,5-difluorofenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	521,2
162	7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-2,3-difluorofenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	521,2
163	7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-2,5-difluorofenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	521,5
164	7-{3,5-difluoro-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	535,2
165	7-{2,3-difluoro-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	535,2
166	7-{2,5-difluoro-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	535,2

Ejemplo	Nombre del Compuesto	EM, IEN (m/z)
167	7-{4-[(1*S*,4*S*)-5-etil-2,5-diazabiciclo[2.2.1]hept-2-il]-2,6-difluorofenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	549,3
168	7-{2,6-difluoro-4-[(1*S*,4*S*)-5-isobutil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	577,3
169	7-{2,6-difluoro-4-[(1*S*,4*S*)-5-isopropil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	563,2
170	7-{4-[(1*S*,4*S*)-5-ciclobutil-2,5-diazabiciclo[2.2.1]hept-2-il]-2,6-difluorofenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	575,2
171	7-(1,4-dioxaespiro[4.5]dec-8-il)-3-(7-fluoro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	471,2
172	7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.2]oct-2-il]-2-fluorofenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	517,2
173	7-{2-fluoro-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.2]oct-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	531,2
174	3-(1*H*-indazol-4-il)-2-piridin-4-il-7-{2,3,5,6-tetrafluoro-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}pirazolo[1,5-a]pirimidina	571,2

Ejemplo	Nombre del Compuesto	EM, IEN (m/z)
175	(1*S*,4*S*)-5-{3-cloro-4-[3-(7-fluoro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]fenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo	637,3
176	7-{*cis*-4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]ciclohexil}-3-(7-fluoro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	509,2
177	3-(7-fluoro-1*H*-indazol-4-il)-7-{*cis*-4-[(1*S*,4*S*)-2-oxa-5-azabiciclo[2.2.1]hept-5-il]ciclohexil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina	510,3
178	3-(7-fluoro-1*H*-indazol-4-il)-7-{*trans*-4-[(1*S*,4*S*)-2-oxa-5-azabiciclo[2.2.1]hept-5-il]ciclohexil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina	510,3
179	3-(7-fluoro-1*H*-indazol-4-il)-7-[*cis*-4-(8-oxa-3-azabiciclo[3.2.1]oct-3-il)ciclohexil]-2-piridin-4-ilpirazolo[1,5-a]pirimidina	524,3
180	3-(7-fluoro-1*H*-indazol-4-il)-7-[*trans*-4-(8-oxa-3-azabiciclo[3.2.1]oct-3-il)ciclohexil]-2-piridin-4-ilpirazolo[1,5-a]pirimidina	524,3
181	3-(7-fluoro-1*H*-indazol-4-il)-7-[*cis*-4-(3-oxa-8-azabiciclo[3.2.1]oct-8-il)ciclohexil]-2-piridin-4-ilpirazolo[1,5-a]pirimidina	524,3

Ejemplo	Nombre del Compuesto	EM, IEN (m/z)
182	3-(7-fluoro-1*H*-indazol-4-il)-7-[*trans*-4-(3-oxa-8-azabiciclo[3.2.1]oct-8-il)ciclohexil]-2-piridin-4-ilpirazolo[1,5-a]pirimidina	524,3
183	7-{*trans*-4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]ciclohexil}-3-(7-fluoro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	509,2
184	7-{2-cloro-4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(7-fluoro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	289,6
185	7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-3-fluorofenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	503,2
186	7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-2-(trifluorometil)fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	553,2
187	7-{2-bromo-4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	563,1
188	7-{3-fluoro-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	517,2

Ejemplo	Nombre del Compuesto	EM, IEN (m/z)
189	3-(1*H*-indazol-4-il)-7-{4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]-2-(trifluorometil)fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina	567,2
190	7-{2-bromo-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	577,1
191	7-(1,4-dioxaespiro[4.5]dec-7-en-8-il)-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	451,2
192	7-{2,6-difluoro-4-[(1*S*,4*S*)-5-metil-5-oxido-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	551,3
193	3-(1*H*-indazol-4-il)-7-{5-[(1*S*,4*S*)-2-oxa-5-azabiciclo[2.2.1]hept-5-ilmetil]furan-3-il}-2-piridin-4-ilpirazolo[1,5-a]pirimidina	490,1
194	(1*S*,4*S*)-5-({4-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]furan-2-il}metil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo	589,1
195	7-{5-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-ilmetil]furan-3-il}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	489,2
196	(1*S*,4*S*)-5-({5-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]tiofen-2-il}metil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo	605,2

Ejemplo	Nombre del Compuesto	EM, IEN (m/z)
197	3-(1*H*-indazol-4-il)-7-{5-[(1*S*,4*S*)-2-oxa-5-azabiciclo[2.2.1]hept-5-ilmetil]tiofen-2-il}-2-piridin-4-ilpirazolo[1,5-a]pirimidina	506,1
198	7-{5-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-ilmetil]tiofen-2-il}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	505,1
199	(3-endo)-3-[3-(1*H*-indazol-4-il)-6-metil-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo	508,2
200	3-(1*H*-indazol-4-il)-7-[6-(8-oxa-3-azabiciclo[3.2.1]oct-3-il)piridin-3-il]-2-piridin-4-ilpirazolo[1,5-a]pirimidina	501,2
201	3-(1*H*-indazol-4-il)-7-{6-[(1*S*,4*S*)-2-oxa-5-azabiciclo[2.2.1]hept-5-il]piridin-3-il}-2-piridin-4-ilpirazolo[1,5-a]pirimidina	487,2
202	(1*S*,4*S*)-5-{3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]bencil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo	599,3
203	(1*S*,4*S*)-5-{4-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]bencil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo	599,3
204	3-(1*H*-indazol-4-il)-7-{4-[(1*S*,4*S*)-2-oxa-5-azabiciclo[2.2.1]hept-5-ilmetil]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina	500,2

Ejemplo	Nombre del Compuesto	EM, IEN (m/z)
205	7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-ilmetil]-2-fluorofenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	517,2
206	7-{2-fluoro-4-[(1*S*,4*S*)-2-oxa-5-azabiciclo[2.2.1]hept-5-ilmetil]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	518,2
207	7-{2-fluoro-4-[(1*R*,4*R*)-2-oxa-5-azabiciclo[2.2.1]hept-5-ilmetil]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	518,2
208	7-{3-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-ilmetil]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	499,2
209	7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-ilmetil]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina	499,3
210	9-{3-fluoro-4-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]bencil}-3,7-dioxa-9-azabiciclo[3.3.1]nonano	543,3

PROCEDIMIENTOS DE ENSAYO BIOLÓGICOS Y FARMACOLÓGICOS CONVENCIONALES

La evaluación de los compuestos representativos de la presente invención en procedimientos de ensayo farmacológicos convencionales indican que los compuestos de la presente invención poseen actividad anticancerígena significativa y son inhibidores de Raf quinasa. Basándose en la actividad

mostrada en los procedimientos de ensayo farmacológico convencionales, los compuestos de la presente invención son por lo tanto útiles como agentes antineoplásicos. En particular, estos compuestos son útiles en el tratamiento, inhibiendo el crecimiento de, o erradicando neoplasmas tales como los de mama, riñón, vejiga, tiroides, boca, laringe, esófago, estómago, colon, ovario, pulmón, páncreas, hígado, próstata y piel. Los compuestos de la invención son útiles como agentes anti-inflamatorios y poseen actividad frente la inflamación asociada con las Raf quinasas.

ENSAYO PARA INHIBIDORES DE RAF QUINASA

Los compuestos de fórmula A se ensayaron como inhibidores de Raf Quinasa para B-Raf quinasa, B-Raf quinasa mutante y C-Raf quinasa, que están asociadas con la inhibición del crecimiento de células tumorales que contienen formas oncogénicas de Receptores de Tirosina Quinasas, K-Ras y Raf quinasas.

B-RAF QUINASA:

Reactivos: B-Raf humana recombinante marcada con Flag/GST producida en células de insecto Sf9, Mek-1-GST humana no activa (proteína recombinante producida en *E. coli*); y un Ab policlonal específico de fosfo-MEK1 de la Tecnología de Señalización Celular (Nº de cat.: 9121).

ENSAYO PARA INHIBIDORES DE B-RAF QUINASA

Procedimiento de ensayo de B-Raf1 Quinasa: se usó B-Raf-1 para fosforilar GST-MEK1. La fosforilación de MEK1 se mide mediante un anticuerpo fosfo-específico (de la Tecnología de Señalización Celular, Nº de cat.: 9121) que detecta la fosforilación de dos restos de serina en las posiciones 217 y 221 sobre MEK1.

Se usó el siguiente protocolo de ensayo quinasa de acuerdo con la invención:

Soluciones madre de ensayo de B-Raf

1. Tampón de Dilución de Ensayo (ADB): MOPS 20 mM, pH 7,2, ß-glicerol fosfato 25 mM, EGTA 5mM, ortovanadato sódico 1 mM, ditiotreitol 1 mM, Triton X-100 al 0,01 %.

2. Cocktel de Magnesio/ATP: solución ADB (sin Triton X-100) mas ATP frío 200 μM y cloruro de magnesio 40 mM.

4. Quinasa Activa: B-Raf activa: usada a 0,2 nM por punto de ensayo.

5. GST-MEK1 no-activa: usada a una concentración final de 2,8 nM.

6. TBST-Tris (50 mM, pH 7,5), NaCl (150 mM), Tween-20 (0,05 %).

7. Ab anti-GST (GE)

8. Ab anti pMEK (arriba)

9. Ab anti-conejo/conjugado con Europio (Wallac).

PROCEDIMIENTO DE ENSAYO B-RAF:

1. Añadir 20 μl de ADB que contiene B-Raf y Mek por ensayo (es decir por pocillo de una placa de 96 pocillos)

2. Añadir 25 μl de ATP 0,2 mM y cloruro de magnesio 40 mM en el cóctel Magnesio/ATP.

3. Incubar durante 45 minutos a TA con agitación ocasional.

4. Transferir esta mezcla a una placa de 96 pocillos revestida con Ab anti-GST (placas Nunc inmunoabsorbentes revestidas durante una noche con un-GST. Lavar antes del uso la placa tres veces con TBS-T reciente.

5. Incubar durante una noche a 30°C en un ambiente frio.

6. Lavar 3 veces con TBST, añadir Anti-Fosfo MEK1 (1:1000, la dilución

depende del lote)

7. Incubar durante 60 minutos a TA en un incubador de agitación.

8. Lavar 3 veces con TBST, añadir Ab anti-conejo/conjugado con Europio (Wallac) (1:500, la dilución depende del lote)

9. Incubar durante 30 minutos a TA en un agitador de plataforma.

10. Lavar la placa 3 x con TBS-T-

11. Añadir 100 µl de Solución de Potenciación Wallac Delfia y agitar durante 10 minutos.

12. Leer las places en un lector de placa modelo Wallac Victor.

13. Recoger los datos y analizar para puntos únicos y determinaciones CI_{50} como describen Mallon R., y col. (2001) Anal. Biochem. 294:48.

ENSAYO PARA INHIBIDORES DE C-RAF QUINASA

Se ensayó en un ensayo de cascada Raf-MEK-MAP quinasa como se ha descrito anteriormente (Mallon R., y col. (2001) Anal. Biochem. 294:48), excepto que la C-Raf quinasa se adquirió de Upstate Lake Placid NY y se usó una concentración de 0,215 nM por punto de ensayo.

ENSAYO PARA MUTANTES DE INHIBIDORES B-RAF QUINASA

Se ensayó en un ensayo de cascada Raf-MEK-MAP quinasa como se ha descrito anteriormente (Mallon R., y col. (2001) Anal. Biochem. 294:48), excepto que se usaron mutantes B-Raf quinasa (V600E).

ANÁLISIS DE LOS RESULTADOS

Las determinaciones CI_{50} de B-Raf se realizaron en los compuestos de fórmula A a partir de ensayos de un solo punto con una inhibición > al 80 %. El ensayo de un solo punto: % de inhibición a 10 mg/ml (% de inhibición = 1 – muestra tratada con compuesto de fórmula A/muestra control no tratada). El %

de inhibición se determinó para cada concentración de compuesto. Las determinaciones CI_{50} – típicamente el ensayo B-Raf se realizaron a las concentraciones del compuesto a partir de 1 μM a 3 nM ó 0,1 μM a 3 pm en diluciones semilogarítmicas.

Los compuestos seleccionados de fórmula A mostraron valores CI_{50} de Raf quinasa que varían de 1 μM a 0,1 nM, indicando que los compuestos son inhibidores eficaces de Raf quinasas, incluyendo B-Raf quinasa, B-Raf quinasa mutante y C-Raf quinasa. Estos datos se resumen en la Tabla 2.

Tabla 2. Datos CI_{50} de B-Raf para compuestos de Fórmula A

Ejemplo CI_{50} Media (μM)

Ejemplo	CI_{50} Media (uM)
1	0,002
2	0,002
3	0,001
4	>1
5	0,006
6	0,057
7	0,087
8	0,001
9	0,004
10	0,054
11	0,002
12	0,0004
13	0,0003
14	0,002

Ejemplo	CI_{50} Media (uM)
15	0,01
16	0,009
17	0,044
18	0,0006
19	0,071
20	0,835
21	>1
22	>1
23	>1
24	NE
25	0,001
26	0,01
27	<0,0003
28	0,016
29	0,0005
30	<0,003
31	0,0018
32	0,0087
33	<0,0003
34	0,0023
35	0,0015
36	0,0082
37	0,021

Ejemplo	CI_{50} Media (uM)
38	0,0005
39	0,0005
40	0,0007
41	<0,0003
42	0,0004
43	0,134
44	0,0006
45	<0,0003
46	0,0032
47	0,0008
48	>1,0
49	0,255
50	>1,0
51	0,0008
52	<0,0003
53	<0,0003
54	0,15
55	NE
56	<0,0003
57	<0,0003
58	<0,0003
59	<0,0003
60	<0,0003

Ejemplo	CI_{50} Media (uM)
61	<0,0003
62	<0,0003
63	<0,0003
64	0,003
65	0,302
66	0,329
67	>1,0
68	0,058
69	NE
70	NE
71	NE
72a	0,566
72b	0,417
73	0,002
74	NE
75	0,0003
76	0,004
77	0,017
78	0,0007
79	0,004
80	0,048
81	0,0004
82	0,002

Ejemplo	CI_{50} Media (uM)
83	>1,0
84	>1,0
85	0,036
86	0,27
87	0,032
88	>1,0
89	NE
90	0,046
91	0,162
92	NE
93	<0,0003
94	0,0001
95	0,00059
96	NE
97	<0,0003
98	<0,0003
99	0,0016
100	<0,0002
101	<0,0001
102	0,00204
103	<0,0003
104	0,00024
105	NE

Ejemplo	CI_{50} Media (uM)
106	<0,0003
107	<0,0003
108	NE
109	<0,0003
110	<0,0001
111	No Ensayado
112	0,0228
113	0,067
114	0,0049
115	0,0091
116	0,0618
117	0,0028
118	0,0067
119	0,0091
120	0,0064
121	>0,1
122	0,0191
123	No Ensayado
124	0,0376
125	0,0449
126	0,0612
127	0,0313
128	0,0394

Ejemplo	CI_{50} Media (uM)
129	0,0021
130	0,0759
131	0,0010
132	0,0004
133	<0,0003
134	<0,0003
135	<0,0003
136	<0,0003
137	0,0038
138	0,0004
139	0,0012
140	0,0012
141	0,0023
142	0,0022
143	0,0007
144	0,0006
145	0,0744
146	0,0063
147	>0,1
148	0,0073
149	0,0032
150	0,0399
151	0,0064

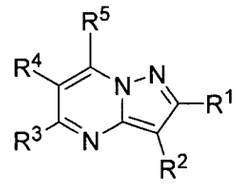
Ejemplo	CI_{50} Media (uM)
152	0,0064
153	0,0037
154	0,0114
155	0,0035
156	0,0006
157	0,0012
158	0,0209
159	0,002
160	0,0253
161	0,0027
162	0,0005
163	<0,0003
164	0,0096
165	0,0006
166	0,0004
167	<0,0003
168	<0,0003
169	<0,0003
170	<0,0003
171	No Ensayado
172	0,0003
173	0,0004
174	0,0004

Ejemplo	CI_{50} Media (uM)
175	0,001
176	0,001
177	0,004
178	0,0067
179	0,0086
180	0,0018
181	0,0021
182	0,0013
183	<0,0003
184	<0,0003
185	0,0017
186	0,0011
187	<0,0003
188	0,0019
189	0,0014
190	<0,0003
191	0,0561
192	0,0004
193	0,0188
194	0,0091
195	0,013
196	0,0115
197	0,0057

Habiendo descrito la invención como antecede, se declara como propiedad lo contenido en las siguientes

REIVINDICACIONES

1. Un compuesto de fórmula A:



A

y sales farmacéuticamente aceptables del mismo;

en la que

R^1 es un anillo heterocíclico de 5-7 miembros o un anillo heteroarilo, comprendiendo dicho anillo 1-3 heteroátomos seleccionados entre N, O o S, y estando dicho anillo opcionalmente sustituido con uno a cuatro sustituyentes seleccionados entre -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$, $-R^8NR^7C(O)NR^7R^7$, $-YR^8R^{10}$, $-YR^8NR^7R^7$ y $-YR^{10}$;

R^2 se selecciona entre un anillo arilo, un anillo arilo bicíclico de 9-14 miembros, un anillo heteroarilo de 5-7 miembros y un anillo heteroarilo bicíclico de 9-14 miembros, comprendiendo dicho anillo heteroarilo 1-3 heteroátomos

seleccionados entre N, O y S, estando dicho anillo opcionalmente sustituido con uno a cuatro sustituyentes seleccionados entre -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$, $-R^8NR^7C(O)NR^7R^7$, $-OPO(OR^7)_2$, $-YR^8R^{10}$, $-YR^8NR^7R^7$ y $-YR^{10}$;

cada uno de R^3, R^4 y R^5 se selecciona independientemente entre R^6 unido a carbono, $-X-W-R^6$, H, J, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-NR^7C(O)R^7$, -CN, alquilo de 1-6 átomos de carbono, alquilo ramificado de 1-8 átomos de carbono, anillo cicloalquilo de 3-10 carbonos, anillo arilo, anillo heterocíclico de 5-7 miembros y anillo heteroarilo de 5-10 miembros, comprendiendo dicho anillo heterocíclico o anillo heteroarilo 1-3 heteroátomos seleccionados entre N, O y S, estando dicho alquilo de 1-6 átomos de carbono, alquilo ramificado de 1-8 átomos de carbono, anillo arilo, anillo heterocíclico de 5-7 miembros y anillo heteroarilo de 5-10 miembros opcionalmente sustituidos con uno a cuatro sustituyentes seleccionados entre -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$ $-R^8NR^7C(O)NR^7R^7$ e YR^{10}, en los que al menos uno de R^3, R^4 y R^5 comprende R^6;

R^6 es un anillo heterocíclico, bicíclico, puenteado, de 6-14 miembros o un anillo heterocíclico, espiro, bicíclico, estando dicho anillo opcionalmente sustituido con uno o más sustituyentes seleccionados entre -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$ o $-R^8NR^7C(O)NR^7R^7$ e YR^{10};

R^7 es H o se selecciona independientemente entre alquilo de 1-6 átomos de carbono, alquilo ramificado de 1-8 átomos de carbono, alquenilo de 2-6 átomos de carbono, alquinilo de 2-6 átomos de carbono, anillo arilo y un anillo heteroarilo de 5-10 miembros, opcionalmente sustituido con uno a cuatro sustituyentes seleccionados entre -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, -R, -OR, $-S(O)_mR$, -NRR, $-NRS(O)_mR$, $-OR^9OR$, $-OR^9NRR$, $-N(R)R^9OR$, $-N(R)R^9NRR$, -NRC(O)R, -C(O)R, -C(O)OR, -C(O)NRR, -OC(O)R, -OC(O)OR, -OC(O)NRR, NRC(O)R, -NRC(O)OR, -NRC(O)NRR, $-R^8OR$, $-R^8NRR$, $-R^8S(O)_mR$, $-R^8C(O)R$, $-R^8C(O)OR$, $-R^8C(O)NRR$, $-R^8OC(O)R$, $-R^8OC(O)OR$, $-R^8OC(O)NRR$, $-R^8NRC(O)R$, $-R^8NRC(O)OR$, $-R^8NRC(O)NRR$ y ZR^{10}, en los que R se selecciona entre alquilo de 1-6 átomos de carbono, alquilo ramificado de 1-8 átomos de carbono, alquenilo de 2-6 átomos de carbono, alquinilo de 2-6 átomos de carbono, cicloalquilo de 3-10 átomos de carbono, arilo de 6-10 átomos de carbono y heteroarilo de 6-10 átomos, comprendiendo el heteroarilo 1-3 heteroátomos seleccionados entre N, O y S;

R^8 es un grupo divalente seleccionado independientemente entre alquilo de 1-6

átomos de carbono, alquenilo de 2-6 átomos de carbono, alquinilo de 2-6 átomos de carbono, arilo, heteroarilo, cicloalquilo y cicloheteroalquilo;

R^9 es independientemente un grupo alquilo divalente de 2-6 átomos de carbono;

R^{10} se selecciona independientemente entre anillo cicloalquilo de 3-10 carbonos, anillo bicicloalquilo de 3-10 carbonos, anillo arilo, anillo heterocíclico, anillo heteroarilo y un anillo heteroarilo condensado con uno a tres anillos arilo o heteroarilo, comprendiendo cada anillo heterocíclico o anillo heteroarilo 1-3 heteroátomos seleccionados entre N, O y S, cada uno opcionalmente sustituido con uno a cuatro sustituyentes seleccionados entre –H, -arilo, $-CH_2$-arilo, -NH-arilo, -O-arilo, $-S(O)_m$-arilo, -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$-, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $-NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$ y $–R^8NR^7C(O)NR^7R^7$;

J es flúor, cloro, bromo o yodo;

m es un número entero de 0-2;

Y es un grupo divalente seleccionado independientemente entre un enlace, alquilo de 1-6 átomos de carbono, alquenilo de 2-6 átomos de carbono, alquinilo de 2-6 átomos de carbono, O y $-NR^7$;

X se selecciona entre un grupo alquilo divalente de 1-6 átomos de carbono, alquenilo de 2-6 átomos de carbono, alquinilo de 2-6 átomos de carbono, anillo cicloalquilo de 3-10 carbonos, anillo bicicloalquilo de 3-10 carbonos, anillo arilo,

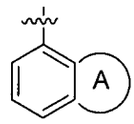
anillo heterocíclico y un anillo heteroarilo, comprendiendo cada anillo heterocíclico o anillo heteroarilo 1-3 heteroátomos seleccionados entre N, O o S; opcionalmente sustituido con uno a cuatro sustituyentes seleccionados entre –H, -arilo, -CH_2-arilo, -NH-arilo, -O-arilo, -$S(O)_m$-arilo, -J, -NO_2, -CN, -N_3, -CHO, -CF_3, -OCF_3, -R^7, -OR^7, -$S(O)_mR^7$, -NR^7R^7, -$NR^7S(O)_mR^7$, -OR^9OR^7, -$OR^9NR^7R^7$, -$N(R^7)R^9OR^7$, -$N(R^7)R^9NR^7R^7$, -$NR^7C(O)R^7$, -$C(O)R^7$, -$C(O)OR^7$, -$C(O)NR^7R^7$, -$OC(O)R^7$-, -$OC(O)OR^7$, -$OC(O)NR^7R^7$, -$NR^7C(O)R^7$, -$NR^7C(O)OR^7$, -$NR^7C(O)NR^7R^7$, -R^8OR^7, $R^8NR^7R^7$, -$R^8S(O)_mR^7$, -$R^8C(O)R^7$, -$R^8C(O)OR^7$, -$R^8C(O)NR^7R^7$, -$R^8C(O)R^7$, -$R^8C(O)OR^7$, -$R^8C(O)NR^7R^7$, -$R^8OC(O)R^7$, -$R^8OC(O)OR^7$, -$R^8OC(O)NR^7R^7$, -$R^8NR^7C(O)R^7$, -$R^8NR^7C(O)OR^7$ y –$R^8NR^7C(O)NR^7R^7$;

W se selecciona entre un enlace, Z, -OZ-, -ZO-, -$S(O)_mZ$-, -$S(O)_2NR^7Z$-, -$NR^7S(O)_mZ$ -, -NR^7Z-, -ZNR^7-, -C(O)Z-; -C(O)OZ-, -$C(O)NR^7Z$-, -$NR^7C(O)Z$-, -$NR^7C(O)NR^7Z$-, -OC(O)Z-, -$NR^7C(O)OZ$- y -OC(O) NR^7Z-; y

Z es un enlace o un alquilo divalente de 1-6 átomos de carbono.

2. El compuesto de la reivindicación 1, en el que R^1 es 4-piridinilo o 4-morfolinilo, opcionalmente sustituido con uno a cuatro sustituyentes seleccionados entre -J, -NO_2, -CN, -N_3, -CHO, -CF_3, -OCF_3, -R^7, -OR^7, -$S(O)_mR^7$, -NR^7R^7, -$NR^7S(O)_mR^7$, -OR^9OR^7, -$OR^9NR^7R^7$, -$N(R^7)R^9OR^7$, -$N(R^7)R^9NR^7R^7$, -$NR^7C(O)R^7$, -$C(O)R^7$, -$C(O)OR^7$, -$C(O)NR^7R^7$, -$OC(O)R^7$, -$OC(O)OR^7$, -$OC(O)NR^7R^7$, $NR^7C(O)R^7$, -$NR^7C(O)OR^7$, -$NR^7C(O)NR^7R^7$, -R^8OR^7, -$R^8NR^7R^7$, -$R^8S(O)_mR^7$, -$R^8C(O)R^7$, -$R^8C(O)OR^7$, -$R^8C(O)NR^7R^7$, -$R^8OC(O)R^7$, -$R^8OC(O)OR^7$, -$R^8OC(O)NR^7R^7$, -$R^8NR^7C(O)R^7$, -$R^8NR^7C(O)OR^7$, -$R^8NR^7C(O)NR^7R^7$, -$OPO(OR^7)_2$, -YR^8R^{10}, -$YR^8NR^7R^7$ y -YR^{10}.

3. El compuesto de la reivindicación 2, en el que R^2 es un anillo arilo o un anillo bicíclico de fórmula

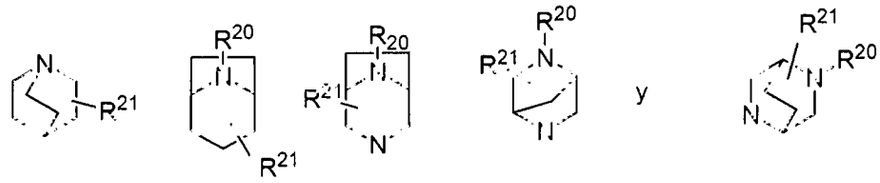


en la que  se refiere a un anillo heteroarilo de 5-7 miembros que comprende 1-3 heteroátomos seleccionados entre N, O y S, estando dicho anillo opcionalmente sustituido con uno a cuatro sustituyentes seleccionados entre -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$, $-R^8NR^7C(O)NR^7R^7$, $-YR^8R^{10}$, $-YR^8NR^7R^7$ y $-YR^{10}$.

4. El compuesto de la reivindicación 2, en el que R^2 es un anillo fenilo o un anillo indazolilo, opcionalmente sustituido con uno a cuatro sustituyentes seleccionados entre -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$, $-R^8NR^7C(O)NR^7R^7$, $-YR^8R^{10}$, $-YR^8NR^7R^7$ y $-YR^{10}$.

5. El compuesto de la reivindicación 2, en el que R^2 se selecciona entre fenilo sustituido con halógeno, fenilo sustituido con alquil C_1-C_6-sulfonamido, fenilo sustituido con carbamato, fenilcarbamato sustituido con alcoxi C_1-C_6, benzonitrilo, benzonitrilo sustituido con hidroxilo, benzonitrilo sustituido con alcoxi C_1-C_6, hidroxifenilo, hidroxifenilo sustituido con alquilo C_1-C_6, hidroxifenilo sustituido con halógeno, alcoxi C_1-C_6-fenilo, alcoxi C_1-C_6-fenilo sustituido con halógeno, hidroxipiridinilo, alcoxi C_1-C_6-piridinilo, aminofenilo, aminofenilo sustituido con halógeno, aminofenilo sustituido con hidroxilo, fenilo sustituido con formamida, fenilformamida sustituida con hidroxilo, fenilformamida sustituida con alcoxi C_1-C_6, aminofenilo sustituido con alcoxi C_1-C_6, fenilo sustituido con urea, benzamido, benzamido sustituido con alquilo C_1-C_6, benzamido sustituido con halógeno, indazolilo, indazolilo sustituido con alquilo C_1-C_6, indazolilo sustituido con halógeno, haloindazolilo sustituido con alquilo C_1-C_6, perfluoroindazolilo sustituido con alquilo C_1-C_6, benzamidazolilo, benzamidazolilo sustituido con halógeno, dihidro-pirrolodinilo, dihidro-pirrolodinilo sustituido, dihidro-indolilo, dihidro-indolilo sustituido y fenilo sustituido con oxadiazolilo.

6. El compuesto de la reivindicación 2, en el que R^6 es un anillo heterocíclico, bicíclico, puenteado, seleccionado entre:



opcionalmente sustituidos en el nitrógeno con R^{20} y opcionalmente sustituidos en uno o más carbonos del anillo heterocíclico, bicíclico, puenteado con R^{21}, en

los que

R^{20} se selecciona entre H, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-C(O)R^7$, $-S(O)_mR^7$, alquilo de 1-6 átomos de carbono, alquilo ramificado de 1-8 átomos de carbono, anillo cicloalquilo de 3-10 carbonos, anillo arilo, anillo heterocíclico de 5-7 miembros y anillo heteroarilo de 5-10 miembros, comprendiendo cada anillo heterocíclico o anillo heteroarilo 1-3 heteroátomos seleccionados entre N, O o S, cada uno del alquilo de 1-6 átomos de carbono, alquilo ramificado de 1-8 átomos de carbono, anillo arilo, anillo heterocíclico y anillo heteroarilo opcionalmente sustituido con uno a cuatro sustituyentes seleccionados entre -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$ o $-R^8NR^7C(O)NR^7R^7$ e YR^{10}; y

R^{21} se selecciona entre H, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$ o $-R^8NR^7C(O)NR^7R^7$ e YR^{10}.

7. El compuesto de la reivindicación 4, en el que R^5 es R^6.

8. El compuesto de la reivindicación 4, en el que R^5 es X-W-R^6, X es arilo o heteroarilo y W es un enlace.

9. El compuesto de la reivindicación 4, en el que R^5 es X-W-R^6, X es arilo o heteroarilo y W es ZN R^7 o NR^7Z.

10. Un compuesto de la reivindicación 4 en el que R^5 es un anillo espiroheterocíclico bicíclico que comprende 1-3 heteroátomos seleccionados entre N, O y S, opcionalmente sustituido con uno a cuatro sustituyentes seleccionados entre -J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, $-R^7$, $-OR^7$, $-S(O)_mR^7$, $-NR^7R^7$, $-NR^7S(O)_mR^7$, $-OR^9OR^7$, $-OR^9NR^7R^7$, $-N(R^7)R^9OR^7$, $-N(R^7)R^9NR^7R^7$, $-NR^7C(O)R^7$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)NR^7R^7$, $-OC(O)R^7$, $-OC(O)OR^7$, $-OC(O)NR^7R^7$, $NR^7C(O)R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)NR^7R^7$, $-R^8OR^7$, $-R^8NR^7R^7$, $-R^8S(O)_mR^7$, $-R^8C(O)R^7$, $-R^8C(O)OR^7$, $-R^8C(O)NR^7R^7$, $-R^8OC(O)R^7$, $-R^8OC(O)OR^7$, $-R^8OC(O)NR^7R^7$, $-R^8NR^7C(O)R^7$, $-R^8NR^7C(O)OR^7$, $-R^8NR^7C(O)NR^7R^7$ e YR^{10}.

11. Un compuesto seleccionado entre 3-(7-{6-[(1-azabiciclo[2.2.2]oct-4-ilmetil)amino]piridin-3-il}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol, 3-(7-{6-[(3*S*)-1-azabiciclo[2.2.2]oct-3-ilamino]piridin-3-il}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol, 3-(7-{6-[(3*R*)-1-azabiciclo[2.2.2]oct-3-ilamino]piridin-3-il}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol, (3*R*)-*N*-{4-[3-(3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]piridin-2-il}quinuclidin-3-amina, (3*R*)-*N*-{5-[3-(4-cloro-3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]piridin-2-il}quinuclidin-3-amina, 3-{7-[(1-azabiciclo[2.2.2]oct-4-ilmetil)amino]-2-piridin-4-

ilpirazolo[1,5-a]pirimidin-3-il}fenol, 3-[3-(3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, 3-[3-(3-hidroxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]-octano-8-carboxilato de etilo, 3-[7-(8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]fenol, 3-[3-(4-cloro-3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, 3-[3-(4-cloro-3-hidroxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, 5-[7-(8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]-2-clorofenol, 5-[7-(8-acetil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]-2-clorofenol, 2-cloro-5-{7-[8-(metilsulfonil)-8-azabiciclo[3.2.1]oct-3-il]-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il}fenol, acetato de 5-[7-(8-acetil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]-2-clorofenilo, 7-(8-azabiciclo[3.2.1]oct-3-il)-3-(4-cloro-3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(4-cloro-3-metoxifenil)-7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 2-cloro-5-[7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]fenol, 7-(8-azabiciclo[3.2.1]oct-3-il)-3-(3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-3-(2-metoxipiridin-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 4-[7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]piridin-2-ol, 4-[7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]anilina, 1-{4-[7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]fenil}urea, 3-(3-metoxifenil)-7-[4-(8-metil-3,8-diazabiciclo[3.2.1]oct-3-il)fenil]-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-{7-[4-(8-metil-3,8-diazabiciclo[3.2.1]oct-3-il)fenil]-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il}fenol, 3-(4-cloro-3-metoxifenil)-7-[4-(8-

metil-3,8-diazabiciclo[3.2.1]oct-3-il)fenil]-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 2-cloro-5-{7-[4-(8-metil-3,8-diazabiciclo[3.2.1]oct-3-il)fenil]-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il}fenol, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol, 3-(7-{4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol, 3-(4-cloro-3-metoxifenil)-7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(4-fluoro-3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 5-(7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)-2-fluorofenol, 3-(1*H*-indazol-4-il)-7-{6-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]piridin-3-il}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-7-{4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(3-metoxifenil)-7-{4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]-hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(4-fluoro-3-metoxifenil)-7-{4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 5-(7-{4-[(1*S*,4*S*)-5-etil-2,5-diazabiciclo[2.2.1]-hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)-2-fluorofenol, 5-(7-{4-[(1*S*,4*S*)-5-acetil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)-2-fluorofenol, 7-{6-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]piridin-3-il}-3-(7-metil-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(7-cloro-1*H*-indazol-4-il)-7-{6-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]piridin-3-il}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(7-fluoro-1*H*-indazol-4-il)-7-{6-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]piridin-3-il}-2-piridin-4-ilpirazolo[1,5-

a]pirimidina, 3-(7-{6-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]piridin-3-il}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)benzamida, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-2-metilfenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-7-{2-metil-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-4-fluorofenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-fluoro-2-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, (1*S*,4*S*)-5-{2-[3-(4-cloro-3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-5-fluorofenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo, 3-(4-cloro-3-metoxifenil)-7-{2-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-4-fluorofenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(4-cloro-3-metoxifenil)-7-{4-fluoro-2-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo-[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-2-fluorofenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2-fluoro-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 2-fluoro-5-(7-{4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol, 3-(4-fluoro-3-metoxifenil)-7-{2-metil-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 2-fluoro-5-(7-{2-metil-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol, 3-(7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-2-metilfenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol, 3-(7-{2-metil-4-[(1*S*,4*S*)-5-metil-2,5-

diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol, 3-(7-{2-cloro-4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol, 3-(7-{2-cloro-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol, 7-{2-cloro-4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2-cloro-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-[3-(3-hidroxi-4-metilfenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, 5-[7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]-2-fluorofenol, 3-[3-(2,3-difluorofenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, 3-(3-{3-[(metilsulfonil)amino]-fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, {4-[7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]fenil}carbamato de metilo, 4-[7-(8-etil-8-azabiciclo[3.2.1]-oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]-2-hidroxibenzonitrilo, {4-[7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]-2-metoxifenil}carbamato de terc-butilo, 4-[7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]-2-metoxianilina, 2-amino-5-[7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]fenol, *N*-{4-[7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]-2-hidroxifenil}formamida, *N*-{4-[7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]-2-metoxifenil}formamida, 3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, 7-(8-

azabiciclo[3.2.1]oct-3-il)-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo-[1,5-a]pirimidina, 3-[3-(7-cloro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, 3-{2-piridin-4-il-3-[7-(trifluorometil)-1*H*-indazol-4-il]pirazolo[1,5-a]pirimidin-7-il}-8-azabiciclo[3.2.1]-octano-8-carboxilato de etilo, 7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-3-(7-metil-1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-[3-(7-metil-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, 3-(7-cloro-1*H*-indazol-4-il)-7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-il-3-[7-(trifluorometil)-1*H*-indazol-4-il]pirazolo[1,5-a]pirimidina, 3-[3-(7-fluoro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, 3-(7-cloro-6-fluoro-1*H*-indazol-4-il)-7-(8-etil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-[3-(2-oxo-2,3-dihidro-1*H*-benzoimidazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]-octano-8-carboxilato de etilo, 3-[3-(1*H*-indol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, 3-[3-(1*H*-indol-6-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, 3-[3-(2-oxo-2,3-dihidro-1*H*-pirrolo[2,3-b]piridin-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, 7-(8-etil-8-azabiciclo-[3.2.1]oct-3-il)-3-(1*H*-indol-6-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-[3-(2-oxo-2,3-dihidro-1*H*-indol-6-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, 2-cloro-5-[7-(2,2-dimetil-1,3-dioxolan-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il]fenol, 7-(8-Etil-8-azabiciclo[3.2.1]-octan-3-il)-3-(1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina, 3-(3-(3-(1,3,4-Oxadiazol-2-

il)fenil)-2-(piridin-4-il)pirazolo[1,5-a]pirimidin-7-il)-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, (1S,4S)-5-{3-Fluoro-4-[3-(1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]fenil}-2,5-diazabiciclo-[2.2.1]heptano-2-carboxilato de *terc*-butilo, 7-{4-[(1S,4S)-2,5-diazabiciclo[2.2.1]hept-2-il]-2-fluorofenil}-3-(1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2-Fluoro-4-[(1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2-fluoro-4-[(1S,4S)-5-metil-5-oxido-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1H-indazol-4-il)-2-piridin-4-ilpirazolo-[1,5-a]pirimidina, Éster terc-butílico del ácido (1S,4S)-5-{3-cloro-4-[3-(1H-indazol-4-il)-2-piridin-4-il-pirazolo[1,5-a]pirimidin-7-il]-fenil}-2,5-diaza-biciclo[2.2.1]heptano-2-carboxílico, Sal bis-clorhidrato de 7-[2-cloro-4-((1S,4S)-2,5-diaza-biciclo[2.2.1]hept-2-il)-fenil]-3-(1H-indazol-4-il)-2-piridin-4-il-pirazolo[1,5-a]pirimidina, 7-[2-Cloro-4-((1S,4S)-5-metil-2,5-diaza-biciclo[2.2.1]hept-2-il)-fenil]-3-(1H-indazol-4-il)-2-piridin-4-il-pirazolo[1,5-a]pirimidina, (1S,4S)-5-{3,5-difluoro-4-[3-(1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]fenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo, 7-(4-((1S,4S)-2,5-diazabiciclo[2.2.1]-heptan-2-il)-2,6-difluorofenil)-3-(1H-indazol-4-il)-2-(piridin-4-il)pirazolo[1,5-a]pirimidina, 7-{2,6-difluoro-4-[(1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, (1S,4S)-5-{4-[3-(7-Fluoro-1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]fenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo, 7-[4-(2,5-Diaza-biciclo[2.2.1]hept-2-il)-fenil]-3-(7-fluoro-1H-indazol-4-il)-2-piridin-4-il-pirazolo[1,5-a]pirimidina, clorhidrato de 3-(7-fluoro-1H-indazol-4-il)-7-{4-[(1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, (1S,4S)-5-{3-Fluoro-4-[3-(7-fluoro-1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]fenil}-2,5-

diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo, 7-{4-[(1S,4S)-2,5-diazabiciclo[2.2.1]hept-2-il]-2-fluorofenil}-3-(7-fluoro-1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(7-fluoro-1H-indazol-4-il)-7-{2-fluoro-4-[(1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, (1S,4S)-5-{3,5-difluoro-4-[3-(7-fluoro-1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]fenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo, 7-{4-[(1S,4S)-2,5-Diazabiciclo[2.2.1]hept-2-il]-2,6-difluorofenil}-3-(7-fluoro-1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2,6-Difluoro-4-[(1S,4S)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(7-fluoro-1H-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-5-il]-8-azabiciclo[3.2.1]-octano-8-carboxilato de etilo, 2-{3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]oct-8-il}etanol, 3-(1*H*-indazol-4-il)-7-(8-isopropil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-7-[8-(metilsulfonil)-8-azabiciclo[3.2.1]oct-3-il]-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxamida, 2-{3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]oct-8-il}-*N*,*N*-dimetil-2-oxoetanamina, {3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]oct-8-il}acetonitrilo, *N*-etil-3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxamida, 7-(8-acetil-8-azabiciclo[3.2.1]oct-3-il)-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-*N*,*N*-dimetil-8-azabiciclo[3.2.1]octano-8-carboxamida, (1*S*,4*S*)-5-{[3-(4-cloro-3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]metil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo,

(1*S*,4*S*)-5-{4-[3-(7-fluoro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-5-il]fenil}-2,5-diazabiciclo-[2.2.1]heptano-2-carboxilato de *terc*-butilo, (1*S*,4*S*)-5-{3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]fenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo, 7-{3-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, (1*S*,4*S*)-5-{4-[3-(7-cloro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]fenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo, 3-(1*H*-indazol-4-il)-7-{3-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(7-cloro-1*H*-indazol-4-il)-7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, (2*S*)-2-({3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]oct-8-il}carbonil)pirrolidin-1-carboxilato de *terc*-butilo, 3-(1*H*-indazol-4-il)-7-(8-L-prolil-8-azabiciclo[3.2.1]oct-3-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 1-{3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]oct-8-il}propan-2-ona, 3-[3-(7-fluoro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-5-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-2-fluorofenil}-3-(3-metoxifenil)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-2-fluorofenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol, 3-(7-{2-fluoro-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidin-3-il)fenol, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-2-metilfenil}-3-(7-fluoro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(7-fluoro-1*H*-indazol-4-il)-7-{2-metil-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo-[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-(8-azabiciclo[3.2.1]oct-3-il)-3-(7-fluoro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, {3-[3-(7-fluoro-1*H*-indazol-

4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]oct-8-il}acetonitrilo, 3-(7-cloro-1*H*-indazol-4-il)-5-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-7-[6-(8-metil-3,8-diazabiciclo[3.2.1]oct-3-il)piridin-3-il]-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(7-cloro-1*H*-indazol-4-il)-7-{4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-(1,4-dioxaespiro[4.5]dec-8-il)-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-7-{4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.2]oct-2-il]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo-[2.2.2]oct-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-4,6-difluorofenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 5-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-2-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-*N*,*N*-dimetilanilina, 7-{2,4-difluoro-6-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 2-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-*N*,*N*-dimetil-5-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]anilina, 7-{*cis*-4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]ciclohexil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-7-[*cis*-4-(3-oxa-8-azabiciclo[3.2.1]oct-8-il)ciclohexil]-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-7-[*trans*-4-(3-oxa-8-azabiciclo[3.2.1]-oct-8-il)ciclohexil]-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-7-[*cis*-4-(8-oxa-3-azabiciclo[3.2.1]oct-3-il)ciclohexil]-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-7-[*trans*-4-(8-oxa-3-azabiciclo[3.2.1]oct-3-il)ciclohexil]-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-7-{*cis*-4-[(1*S*,4*S*)-2-oxa-5-azabiciclo[2.2.1]hept-5-il]ciclohexil}-2-

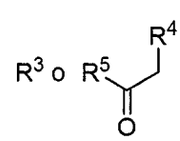
piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-7-{*trans*-4-[(1*S*,4*S*)-2-oxa-5-azabiciclo[2.2.1]hept-5-il]ciclohexil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{*trans*-4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]ciclohexil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-3-(trifluorometil)fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-1-naftil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-7-{4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]-3-(trifluorometil)fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-7-{4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]-1-naftil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-3,5-difluorofenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-2,3-difluorofenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-2,5-difluorofenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{3,5-difluoro-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2,3-difluoro-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2,5-difluoro-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-[(1*S*,4*S*)-5-etil-2,5-diazabiciclo[2.2.1]-hept-2-il]-2,6-difluorofenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2,6-difluoro-4-[(1*S*,4*S*)-5-isobutil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2,6-difluoro-4-[(1*S*,4*S*)-5-isopropil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-[(1*S*,4*S*)-5-ciclobutil-2,5-

diazabiciclo[2.2.1]hept-2-il]-2,6-difluorofenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-(1,4-dioxaespiro[4.5]dec-8-il)-3-(7-fluoro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.2]oct-2-il]-2-fluorofenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2-fluoro-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.2]oct-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-2-piridin-4-il-7-{2,3,5,6-tetrafluoro-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}pirazolo[1,5-a]pirimidina, (1*S*,4*S*)-5-{3-cloro-4-[3-(7-fluoro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]fenil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo, 7-{*cis*-4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]ciclohexil}-3-(7-fluoro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(7-fluoro-1*H*-indazol-4-il)-7-{*cis*-4-[(1*S*,4*S*)-2-oxa-5-azabiciclo[2.2.1]hept-5-il]ciclohexil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(7-fluoro-1*H*-indazol-4-il)-7-{*trans*-4-[(1*S*,4*S*)-2-oxa-5-azabiciclo[2.2.1]hept-5-il]ciclohexil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(7-fluoro-1*H*-indazol-4-il)-7-[*cis*-4-(8-oxa-3-azabiciclo[3.2.1]oct-3-il)ciclohexil]-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(7-fluoro-1*H*-indazol-4-il)-7-[*trans*-4-(8-oxa-3-azabiciclo[3.2.1]oct-3-il)ciclohexil]-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(7-fluoro-1*H*-indazol-4-il)-7-[*cis*-4-(3-oxa-8-azabiciclo[3.2.1]oct-8-il)ciclohexil]-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(7-fluoro-1*H*-indazol-4-il)-7-[*trans*-4-(3-oxa-8-azabiciclo[3.2.1]oct-8-il)ciclohexil]-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{*trans*-4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]ciclohexil}-3-(7-fluoro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2-cloro-4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]-hept-2-il]fenil}-3-(7-fluoro-1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-3-

fluorofenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]-2-(trifluorometil)fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2-bromo-4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{3-fluoro-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-7-{4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]-2-(trifluorometil)fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2-bromo-4-[(1*S*,4*S*)-5-metil-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-(1,4-dioxaespiro[4.5]dec-7-en-8-il)-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2,6-difluoro-4-[(1*S*,4*S*)-5-metil-5-oxido-2,5-diazabiciclo[2.2.1]hept-2-il]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-7-{5-[(1*S*,4*S*)-2-oxa-5-azabiciclo[2.2.1]hept-5-ilmetil]furan-3-il}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, (1*S*,4*S*)-5-({4-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]furan-2-il}metil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo, 7-{5-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-ilmetil]furan-3-il}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, (1*S*,4*S*)-5-({5-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]tiofen-2-il}metil)-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo, 3-(1*H*-indazol-4-il)-7-{5-[(1*S*,4*S*)-2-oxa-5-azabiciclo[2.2.1]hept-5-ilmetil]tiofen-2-il}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{5-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-ilmetil]tiofen-2-il}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, (3-endo)-3-[3-(1*H*-indazol-4-il)-6-metil-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]-8-azabiciclo[3.2.1]octano-8-carboxilato de etilo, 3-(1*H*-indazol-4-il)-7-[6-(8-oxa-3-azabiciclo[3.2.1]oct-3-il)piridin-3-il]-2-

piridin-4-ilpirazolo[1,5-a]pirimidina, 3-(1*H*-indazol-4-il)-7-{6-[(1*S*,4*S*)-2-oxa-5-azabiciclo-[2.2.1]hept-5-il]piridin-3-il}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, (1*S*,4*S*)-5-{3-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]bencil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de *terc*-butilo, (1*S*,4*S*)-5-{4-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]bencil}-2,5-diazabiciclo[2.2.1]-heptano-2-carboxilato de *terc*-butilo, 3-(1*H*-indazol-4-il)-7-{4-[(1*S*,4*S*)-2-oxa-5-azabiciclo[2.2.1]-hept-5-ilmetil]fenil}-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-ilmetil]-2-fluorofenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2-fluoro-4-[(1*S*,4*S*)-2-oxa-5-azabiciclo[2.2.1]hept-5-ilmetil]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{2-fluoro-4-[(1*R*,4*R*)-2-oxa-5-azabiciclo[2.2.1]hept-5-ilmetil]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{3-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-ilmetil]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 7-{4-[(1*S*,4*S*)-2,5-diazabiciclo[2.2.1]hept-2-ilmetil]fenil}-3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidina, 9-{3-fluoro-4-[3-(1*H*-indazol-4-il)-2-piridin-4-ilpirazolo[1,5-a]pirimidin-7-il]bencil}-3,7-dioxa-9-azabiciclo[3.3.1]nonano y sales farmacéuticamente aceptables de los mismos.

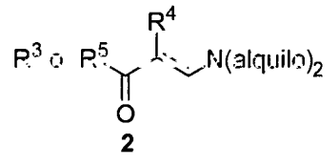
12. Un procedimiento para preparar un compuesto de la reivindicación 1, que comprende las etapas de: (a) hacer reaccionar una cetona sustituida de fórmula 1



1

con un acetal de N,N-dialquilformamida o un acetal de N,N-dialquilacetamida

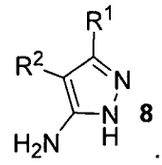
para proporcionar un compuesto de enaminona de fórmula 2



2

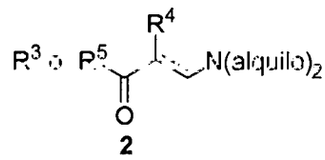
; y

(b) hacer reaccionar el compuesto de enaminona de fórmula 2 con un 3-aminopirazol sustituido de fórmula 8



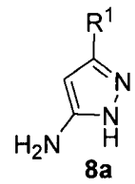
8

13. Un procedimiento para preparar un compuesto de la reivindicación 1, que comprende las etapas de: (a) hacer reaccionar un compuesto de enaminona de fórmula 2



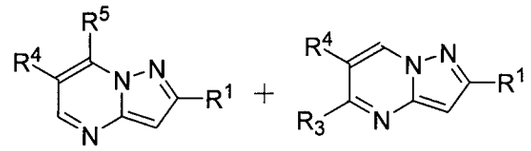
2

con un aminopirazol de fórmula 8a



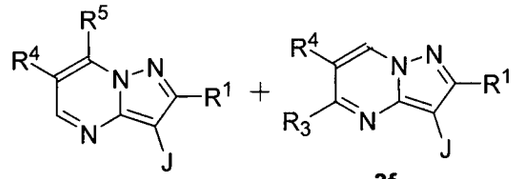
8a

para proporcionar compuestos de fórmula 3c y 3d



3c **3d** ;

(b) halogenar uno o los dos compuestos de fórmula 3c y 3d para proporcionar uno o los dos compuestos de fórmula 3e y 3f



3e **3f** ; y

(c) someter uno o los dos compuestos de fórmula 3e y 3f a un acoplamiento de Suzuki catalizado con paladio usando ácidos aril o heteroarilborónicos o ésteres boronato correspondientes.

14. El procedimiento de acuerdo con la reivindicación 13, que comprende una etapa adicional de separación de compuestos de fórmula 3c y 3d antes de la etapa (b).

15. El procedimiento de acuerdo con la reivindicación 13, que comprende una etapa adicional de separación de compuestos de fórmula 3e y 3f antes de la etapa (c).

16. El procedimiento de acuerdo con la reivindicación 13, que comprende una etapa adicional de separación de compuestos después de la etapa (c).

17. Una composición farmacéutica que comprende un compuesto de

acuerdo con cualquiera de las reivindicaciones 1-10 y un vehículo farmacéuticamente aceptable.

18. Una composición farmacéutica que comprende un compuesto de acuerdo con cualquiera de las reivindicaciones 1-10 en combinación con otras composiciones farmacéuticas inhibidoras de quinasa o agentes quimioterapéuticos y un vehículo farmacéuticamente aceptable.

19. Una composición farmacéutica de acuerdo con las reivindicaciones 16 ó 17, que es capaz de inhibir la actividad Raf quinasa.

20. Un procedimiento de tratamiento de una enfermedad asociada con la inhibición de la actividad Raf quinasa en un mamífero que comprende administrar al mamífero una cantidad farmacéuticamente eficaz de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1-10.

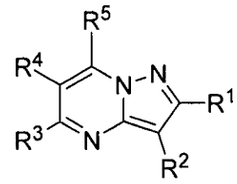
21. El procedimiento de la reivindicación 20, en el que la enfermedad está asociada con una afección dependiente de B-Raf quinasa, una afección de B-Raf quinasa mutante o una afección dependiente de C-Raf quinasa.

22. El procedimiento de la reivindicación 20, en el que la enfermedad comprende inflamación o cáncer.

23. El procedimiento de la reivindicación 22, en el que el cáncer se selecciona entre cáncer de mama, riñón, vejiga, tiroides, boca, laringe, esófago,

Resumen

Se describen compuestos de fórmula A:



A

y sales farmacéuticamente aceptables de los mismos, que inhiben selectivamente la actividad Raf quinasa y son útiles para tratar trastornos mediados por Raf quinasas.

PATENT COOPERATION TREATY PCT/US2009/035422

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

MAZZAPESE, Joseph M.
Wyeth LLC
Patent Law Department
Five Giralda Farms
Madison, New Jersey 07940
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*
04 February 2010 (04.02.2010)

Applicant's or agent's file reference
AM103005

IMPORTANT NOTIFICATION

International application No.
PCT/US2009/035422

International filing date *(day/month/year)*
27 February 2009 (27.02.2009)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address:
WYETH
Five Giralda Farms
Madison, NJ 07940
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address:
WYETH LLC
Five Giralda Farms
Madison, NJ 07940
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:
☐ Notifications by e-mail authorized

3. Further observations, if necessary:
The above change is to be recorded also in respect of the agent, as indicated in the addressee box at the top of this form.

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 82 70

Authorized officer
Blanc Veronique
e-mail PT08.PCT@WIPO.INT
Telephone No. +41 22 338 74 08

Form PCT/IB/306 (January 2009) 1/ECNBG0UA18

Julie Decca
5-18

ATENT COOPERATION TREAT

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

To:
WYETH
Attn. Mazzarese, Joseph M.
Patent Law Department
Five Giralda Farms
Madison, New Jersey 07940-0874
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*	08/05/2009
Applicant's or agent's file reference: AM103005	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No.: PCT/US2009/035433	International filing date *(day/month/year)* 27/02/2009
Applicant: WYETH	

1. [X] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46).

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

RECEIVED
MAY 12 2009

RECEIVED
MAY 22 2009

Name and mailing address of the International Searching Authority: European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer: Chantal Gottar / SHEILA McBRIDE

Form PCT/ISA/220 (October 2005) *(See notes on accompanying sheet)*

CARL RIVER

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims,description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 20, 31, 32, 34, 35, 37 to 45 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1–10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1*bis*(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43*bis*.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.

ATENT COOPERATION TREAT

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
AM103005		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2009/035422	27/02/2009	29/02/2008
Applicant		
WYETH		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 19. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

national application No
.CT/US2009/035422

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D491/20 A61K31/519 A61P35/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/109093 A (WYETH CORP [US]; GOPALSAMY ARIAMALA [US]; CISZEWSKI GREGORY M [US]; SH) 27 September 2007 (2007-09-27) paragraphs [0116] - [0143]; claim 1	1-25
X	WO 2004/052315 A (MERCK & CO INC [US]; FRALEY MARK E [US]) 24 June 2004 (2004-06-24) cited in the application claim 1	1-25
A	US 2004/157838 A1 (GRIFFITH DAVID A [US]) 12 August 2004 (2004-08-12)	1-25

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 April 2009	08/05/2009

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, Fax: (+31-70) 340-3016	Seelmann, Ingo

2

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2009/035422

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007109093 A	27-09-2007	AU 2007227557 A1	27-09-2007
		CA 2643968 A1	27-09-2007
		CN 101405289 A	08-04-2009
		EP 1996594 A2	03-12-2008
WO 2004052315 A	24-06-2004	AU 2003299651 A1	30-06-2004
US 2004157838 A1	12-08-2004	NONE	

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2009/035422	27.02.2009	29.02.2008

International Patent Classification (IPC) or both national classification and IPC
INV. C07D491/20 A61K31/519 A61P35/00

Applicant
WYETH

1. This opinion contains indications relating to the following items:

- ☑ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☑ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Seelmann, Ingo Telephone No. +49 89 2399-7490

Form PCT/ISA/237 (Cover Sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2009/035422

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ on paper

   ☐ in electronic form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in electronic form.

   ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-25
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-25
Industrial applicability (IA)	Yes:	Claims	1-25
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Claims 20-25 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

1. PRIOR ART

Reference is made to the following documents:

D1: WO 2007/109093 A
D2: WO 2004/052315 A
D3: US 2004/157838 A1

2. NOVELTY

The subject-matter of the claims is considered to be novel (Article 33(2) PCT). D1 and D2 disclose pyrazolo[1,5-A]pyrimidines. The essential structural difference between the claimed compounds and those of D1 and D2 resides in the bridged or spiro-condensed ring system R6 linked to the pyrazolo[1,5-A]pyrimidine of the presently claimed compounds (cf. application page 140, line 8-9). At least in D1 such ringsystems are nevertheless encompassed - although not explicitly mentioned - in the definition of "heterocyclic ring" (cf. paragraph 96), a novel selection can however be acknowledged. D3 discloses such bridged or spiro-condensed ring systems linked to a pyrazolo[1,5-A]pyrimidine (cf. Table 3), however, R0 and R1 (corresponding to R1 and R2 of the application) are in all examples Phenyl, therefore novelty vis-a-vis D3 can be acknowledged.

3. INVENTIVE STEP

The subject-matter of the claims cannot be considered as involving an inventive step (Article 33(3) PCT).

The documents D1 and D2 can both be regarded as being the closest prior art to the subject-matter of claim 1. D1 discloses pyrazolo[1,5-A]pyrimidines as RAF inhibitors, D2 discloses pyrazolo[1,5-A]pyrimidines as tyrosine kinases in general. Both documents relate

i.a. to the treatment of cancer and inflammation. The structural difference to the present compounds is as outlined above. The problem to be solved by the present invention cannot be seen in the provision of further pyrazolo[1,5-A]pyrimidines as RAF inhibitors or tyrosine kinase inhibitors, because the proposed solution would be seen as obvious. In view of the extremely close structural relationship to the compounds of D1 and D2 it is considered that the man skilled in the art would regard the new compounds of this application as being obvious alternatives to the known compounds. (E.g. the heterocyclic ring in R5 of the generic formula in claim 1 of D1 encompasses both bridged and spiro ring systems, although they are not explicitly mentioned, the definitions of the linking group between the bridged or spiro ring and the pyrazolo[1,5-A]pyrimidine are also overlapping, X in the application can be aryl and W overlaps with NW' of D1). Therefore, the problem underlying the present application should be seen in the provision of new derivatives having unexpected properties over those of the closest prior art compounds (D1/D2). In the absence of comparative test results or other appropriate information it is not possible to decide whether such a problem has been solved or not. In the case where comparative tests are envisaged in order to support an inventive step, these must be carried out between the compounds of the present application having the maximum structural similarity with the compounds of the closest prior art, such that the effect is shown to have its origins in the distinguishing feature of the claimed invention.

If the compounds of claim 11 fall within the scope of claim 1, claim 9 should be reformulated as a dependent claim.

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-104173- -00000-0000

Fecha: 2010-08-24 16:42:32 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 218

PATENTE DE INVENCIÓN ☐ **MODELO DE UTILIDAD** ☐ **Art 33 Decisión 486/00**

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☑ **MODELO DE UTILIDAD PCT** ☐ **Art.33 Decisión 486/00, Circular Única**

- ☑ Indicación que se solicita una PCT
- ☑ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☑ Dibujos de ser estos pertinentes
- ☑ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☑ Incompleta ☐

DISEÑO INDUSTRIAL ☐ **(Art. 119 Decisión 486/00)**

- ☐ Indicación que se solicita Diseño industrial
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ **(Art. 92 Decisión 486/00)**

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
WYETH LLC

REFERENCIA	Radicación No.	10 104173
	Solicitud internacional	PCT/US2009/035422
	Fecha inicio fase nacional	29/09/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	14051

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 38 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
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 29 OCT. 2010.
adpa11

Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
OLARTE GARCIA CARLOS REINALDO
Apoderado(a) y/o Representante de
WYETH LLC

REFERENCIA	Radicación No.	10 104173
	Solicitud internacional	PCT/US2009/035422
	Fecha inicio fase nacional	29/09/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	№ 14052

Teniendo en cuenta que el capítulo reivindicatorio presentado excede de diez 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 título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

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