Industria y Comercio

SUPERINTENDENCIA

PCT

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-131169- -00000-0000
Fecha: 2010-10-22 13:47:05 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 382

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 10-131169

54. **TÍTULO** COMPUESTOS DE QUINUCLIDINA COMO LIGANDOS DEL RECEPTOR NICOTINICO DE ACETILCOLINA ALFA-7

51. **CLASIFICACIÓN INTERNACIONAL**

71. **SOLICITANTE** BRISTOL-MYERS SQUIBB COMPANY

DOMICILIO ESTADOS UNIDOS DE AMERICA

74. **APODERADO** ALVARO CORREA ORDOÑEZ

22. **BOGOTÁ, D.C.,** OCTUBRE 22, 2010

(FORMA P-10)

23-11-2010

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-131169- -00000-0000
Fecha: 2010-10-22 13:47:05 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 382

ión

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

(1) SOLICITUD DE :

[X] Patente de Invención [ ] Patente de Modelo de Utilidad
[X] Capítulo I. [ ] Capítulo II.

(2) SOLICITANTE (71)

Nombre: BRISTOL-MYERS SQUIBB COMPANY
Dirección: Route 206 and Province Line Road Princeton, NJ 08543-4000, Estados Unidos de América.
Nacionalidad o Domicilio: Estados Unidos de América
Lugar de Constitución: Estados Unidos de América
Teléfono: Fax:
E-Mail

IDENTIFICACION
C.C. [ ] NIT [ ]
C.E. [ ] Otro [ ]
Cual
Número

(3) REPRESENTANTE O APODERADO

Nombre: ALVARO CORREA ORDOÑEZ
Dirección: Avenida 82 No. 10-62 Piso 6
Teléfono: 6341500 Fax: 3762211
E-Mail: Alvaro.Correa@bakermckenzie.com

IDENTIFICACION
C.C. [X] NIT [ ]
C.E. [ ] Otro [ ]
Cual
Número 79.143.366 Usaquén TP 20281

En caso de haber presentado poder general para asuntos que se adelanten ante la Delegatura de propiedad Industrial, sírvase indicar el número de radicación (del poder).

(4) INVENTOR (ES) (72)

Nombre: COOK II, James, H.; MCDONALD, Ivar, M.; KING, Dalton; OLSON, Richard, E.; WANG, Nenghui; IWUAGWU, Christiana, I.; ZUSI, F., Christopher; MACOR, John, E.
Dirección: 5 Research Parkway Wallingford, CT 06492 (US).
Nacionalidad o Domicilio: Estados Unidos de América

(5) PCT (85)

Solicitud Internacional No. PCT/US2009/041076 Fecha Abril 20, 2009
Publicación Internacional No. WO 2009/131926 Fecha Octubre 29, 2009

(6) Título (54) COMPUESTOS DE QUINUCLIDINA COMO LIGANDOS DEL RECEPTOR NICOTÍNICO DE ACETILCOLINA ALFA-7

(7) Clasificación Internacional (51) *C07D 498/20* (2006.01); **A61K 31/439** (2006.01); *A61P 25/28* (2006.01)

(8) Prioridad SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Abril 23, 2008	61/047,211
US	Abril 14, 2009	12/423,299

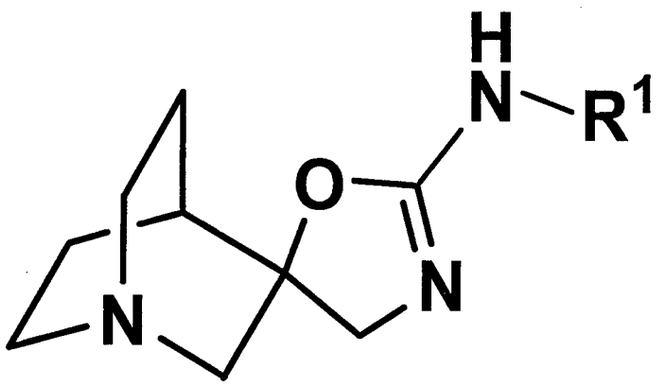
(9) Comprobante de pago No. 10-82,204; 10-75,987; 10-86,578, 10-86517 **Fecha** Sept. 30, 2010; Sept. 13, 2010, Oct. 13, 2010.

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

(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
- [ ] 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
- [X] 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: Extractos

(11) **FIGURA CARATERISTICA**



(12) Solicito la concesión de la patente.

NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA:

C.C. 79.143.366 de Usaquén T.P. 20.281

Instrucciones para la presentación de los anexos, ver reverso de esta página

2010/019 3

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-131169- -00000-0000
Fecha: 2010-10-22 13:47:05 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 382

RECIBO OFICIAL DE CAJA : 10 - 82,204
FECHA : SEPTIEMBRE 30 DE 2010

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	139003675	30/09/2010	79,775,000.00

***** 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._____

41

2010/018

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 10 - 75,987
FECHA : SEPTIEMBRE 13 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-131169- -00000-0000
Fecha: 2010-10-22 13:47:05 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 382

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	150579483	13/09/2010	161,459,900.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVCIOS ADMINISTRATIVOS	8,000.00
		TOTAL : $	8,000.00

SON: OCHO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

2010/020 5

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 86,578
FECHA : OCTUBRE 13 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-131169- -00000-0000
Fecha: 2010-10-22 13:47:05 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 382

***** C O N S I G N A C [illegible] *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	353168045	12/10/2010	94,250,000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	26,000.00
			TOTAL : $	26,000.00

SON: VEINTISEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

2010/020

6

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 10 - 86,517
FECHA : OCTUBRE 13 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-131169- -00000-0000
Fecha: 2010-10-22 13:47:05 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 382

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	353168045	12/10/2010	94,250,000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVCIOS ADMINISTRATIVOS		70,000.00
		TOTAL :	$	70,000.00

SON: SETENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

POD-4002

TRADUCCIÓN OFICIAL N° 0507071 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

PODER OTORGADO POR BRISTOL-MYERS SQUIBB COMPANY

APOSTILLA

1. PAÍS: ESTADOS UNIDOS DE AMÉRICA

2. ESTE DOCUMENTO PÚBLICO HA SIDO FIRMADO POR:
SALLY B. HANSEN

3. QUIEN ACTÚA EN CALIDAD DE NOTARIO PÚBLICO DE NUEVA JERSEY

4. LLEVA EL SELLO DE:
SALLY B. HANSEN, NOTARIO

CERTIFICADO

5. EN TRENTON, NUEVA JERSEY

6. EL 28 DE JUNIO DE 2007

7. POR BRADLEY ABELOW, TESORERO DE NUEVA JERSEY

8. N° A295716

9. SELLO (APARECE ADHERIDO SELLO DORADO)

10. FIRMA (FIRMADO) BRADLEY ABELOW

Texto en inglés y en español mediante el cual **BRISTOL-MYERS SQUIBB COMPANY** domiciliada en Nueva York, Nueva York, otorga poder a **ALVARO CORREA ORDOÑEZ y/o OLGA GEORGETTE OTERO y/o RICARDO METKE y/o JUAN PABLO CONCHA**

Dado y suscrito el 30 de mayo de 2007

(Firmado) Anastasia P. Winslow, Senior Patent Counsel (Abogado de Patentes Senior)

AUTENTIFICACIÓN DE COPIA DE ORIGINAL
COMO NOTARIO ENCARGADO DEL CIRCULO DE BOGOTA, D.C.
CERTIFICO QUE PREVIO EL COTEJO RESPECTIVO LA
PRESENTE COPIA CONCUERDA CON EL ORIGINAL TENIDO A LA VISTA.
21 OCT 2010
Eduardo Durán Gómez
NOTARIO 38 DE BOGOTA, D.C.

JAIME A. GARAVITO B
TRADUCTOR E INTÉRPRETE OFICIAL
Res. 034 de enero 11 de 1983
MINISTERIO DE JUSTICIA

TRADUCCIÓN OFICIAL N° 0507071 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

CERTIFICACIÓN NOTARIAL

Texto en inglés y en español mediante el cual el suscrito Notario certifica el 30 de mayo de 2007 la existencia legal de la sociedad **BRISTOL-MYERS SQUIBB COMPANY** así como las funciones y firma de su representante autorizado Anastasia P. Winslow, Senior Patent Counsel (Abogado de Patentes Senior) para lo cual se basó en los documentos relacionados en inglés en el punto 6 de la certificación los cuales se traducen aquí al español, a saber:

Certificación suscrita por el Vicepresidente Senior y el Asesor Legal de Bristol-Myers Squibb Company el 7 de abril de 2007.

Certificado de Constitución Enmendado y Replanteado de Bristol-Myers Squibb Company fechado mayo 24, 2005.

[Firmado] SALLY B. HANSEN, Notario Público

[Sello en tinta que dice: "SALLY B. HANSEN. Notario Público de Nueva Jersey. Mi comisión vence el 6 de junio de 2010"]

[Aparece sello realzado]

La anterior es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

Jaime Armando Garavito Burgos
c.c. N° 19.130.702 de Bogotá
Traductor e Intérprete Oficial según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia

BOGDM5 # 82106

AUTENTICACION DE COPIA DE ORIGINAL
COMO NOTARIO [illegible] Y OCHO DEL CIRCULO DE BOGOTA, D.C.
CERTIFICO QUE PREVIO EL COTEJO RESPECTIVO LA
PRESENTE COPIA CONCIDE CON EL ORIGINAL TENIDO A LA VISTA
21 OCT 2010
Eduardo Durán Gómez
NOTARIO 38 DE BOGOTA, D.C.

JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Res. 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
SALLY B HANSEN

3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY

4. BEARS THE SEAL/STAMP OF:
SALLY B HANSEN, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY

6. THE 28TH DAY OF JUNE 2007

7. BY: Bradley Abelow, NEW JERSEY TREASURER

8. NO. A295716

9. SEAL/STAMP:

10. SIGNATURE

Bradley Abelow

AUTENTICACION DE COPIA DE ORIGINAL
COMO NOTARIO CUARENTA Y OCHO DEL CIRCULO DE BOGOTA, D.C.
CERTIFICO QUE PREVIO EL COTEJO RESPECTIVO LA
PRESENTE COPIA CONCUERDA CON EL ORIGINAL TENIDO A LA VISTA
21 OCT 2010
Eduardo Durán Gómez
NOTARIO 38 DE BOGOTA, D.C.

BAKER & MCKENZIE

Raisbeck, Lara, Rodriguez & Rueda
Av. 82 No. 10 - 62 6th Floor
Bogota, Colombia

NIT: 860.066.840-3
Tel: +57 1 634 1500
Fax: +57 1 376 2211
www.bakernet.com

POWER OF ATTORNEY

The undersigned.

BRISTOL-MYERS SQUIBB COMPANY

domiciled in

Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 United States of America

declares that it hereby grants to

ALVARO CORREA-ORDOÑEZ and/or
OLGA GEORGETTE OTERO and/or
RICARDO METKE and/or
JUAN PABLO CONCHA

with domicile at Av. 82 No. 10 – 62, 6Th floor, of Bogotá D. C., Colombia, a full and sufficient power of attorney to obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models, industrial designs, integrated circuits, layout-designs and vegetal varieties; the registration of trademarks, denominations of origin, commercial names, trade emblems, slogans and domain names; its renewal, assignments, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b)Processes of protection to the consumer, unfair competition, oppositions, cancellations, nullity, precautionary injunctions, infringement, granting of licenses, writ mandamus, the protection of trade secrets, and in general the civil, penal, an administrative processes relating to those rights. And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

I hereby ratify all actions previously taken on behalf of this company by the aforementioned attorneys with respect to the mentioned matters.

Done and subscribed in

On the 30 day of May of 2007

Signature of the person issuing the Power

Anastasia P. Winslow
Senior Patent Counsel

PODER DE ABOGADO

La abajo firmada,

BRISTOL-MYERS SQUIBB COMPANY

domiciliada en

Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 Estados Unidos de América

declara por el presente que otorga a

ALVARO CORREA-ORDOÑEZ y/o
OLGA GEORGETTE OTERO y/o
RICARDO METKE y/o
JUAN PABLO CONCHA

con domicilio en la Av. 82 No. 10 – 62 Piso 6 en Bogotá D. C., Colombia, poder especial amplio y suficiente, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera autoridades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, diseños industriales, esquemas de trazado de circuitos integrados y variedades vegetales; el registro de marcas, denominaciones de origen, nombres comerciales, enseñas, lemas comerciales y nombres de dominio; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Los procesos para la protección del consumidor, competencia desleal, oposiciones, cancelaciones, nulidades, medidas cautelares, infracciones, concesión de licencias, la tutela, la protección de secretos industriales, y en general procesos civiles, penales, administrativos relacionados con estos derechos. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del caso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

Igualmente, ratifico todo lo actuado hasta el momento en los mismos asuntos, por cualquiera de los mencionados apoderados en representación de ésta sociedad.

Dado y firmado en

A los 30 días del mes de mayo de 2007

Firma de la persona que firma el Poder

AUTENTICACION DE COPIA DE ORIGINAL
COMO NOTARIO TREINTA Y [illegible] CIRCULO DE BOGOTA, D.C.
CERTIFICO QUE PREVIO COTEJO RESPECTIVO LA
PRESENTE COPIA COINCIDE CON EL ORIGINAL TENIDO A LA VISTA
21 OCT 2010
Eduardo Duran Gomez
NOTARIO 38 DE BOGOTA, D.C.

NOTARIAL CERTIFICATION

On this 30 day of May 2007, the undersigned Notary

CERTIFIES

1. That Name of the person issuing the power
Anastasia P. Winslow
of legal age and domiciled in
Princeton, NJ USA
Address, city, state, country
set his hand on the foregoing document.

2. That the grantor is to me personally known and that he/she has legal capacity to execute the instrument.

3. That the grantor has executed the foregoing document as
Senior Patent Counsel
Position of the person issuing the Power
of the judicial person **BRISTOL-MYERS SQUIBB COMPANY**

4. That the judicial person **BRISTOL-MYERS SQUIBB COMPANY**
having its home office in
Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 United States of America
is duly organized, has present legal existence and that the purposes for which the power of attorney is granted are within the scope of its corporate purposes.

5. That the grantor has in fact the referred to authority and that his/her representation is legal.

6. That I have based certifications 3, 4 and 5 above on the following authentic documents for such purpose exhibited to me and which I mention specifically, giving their dates and their origin or source:
(Please indicate here the documents such as the articles of incorporation, by laws or resolution from the Board of Directors and their dates, on which the notary relied to grant the certification)
- Certification executed by Sr. Vice President and General Counsel of Bristol-Myers Squibb Company on April 7, 2007
- Amended and Restated Certificate of Incorporation of Bristol-Myers Squibb Company dated May 24, 2005

Notary Public
Sally B. Hansen
SALLY B. HANSEN
Notary Public of New Jersey
My Commission Expires June 6, 2010

CERTIFICACION NOTARIAL

A los 30 días del mes de mayo de 2007, el suscrito Notario

DA FE

1 Que Anastasia P. Winslow
mayor y domiciliado en Princeton, NJ Estados Unidos de América
suscribió de su puño y letra el documento que antecede.

2. Que conozco al otorgante y que éste tiene capacidad legal para el otorgamiento.

3 Que el otorgante ha suscrito el referido documento en su carácter de
Abogados de Patentes Senior
de la persona jurídica **BRISTOL-MYERS SQUIBB COMPANY**

4 Que la persona jurídica **BRISTOL-MYERS SQUIBB COMPANY**
con sede en
Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 Estados Unidos de América
está legalmente constituida, que tiene existencia legal actual y que el acto para el cual se otorga el poder está comprendido entre los que constituyen su objeto social.

5 Que el otorgante tiene efectivamente la representación que ostenta y que ésta es legítima.

6. Que he basado las certificaciones 3, 4 y 5 anteriores en los siguientes documentos auténticos que al efecto se me exhibieron y que menciono específicamente con expresión de sus fechas y de su origen o procedencia:
- Certificación suscrita por el Vicepresidente Senior y el Asesor Legal de Bristol-Myers Squibb Company el 7 de abril de 2007.
- Certificado de Constitución Enmendado y Replanteado de Bristol-Myers Squibb Company fechado el 4 de mayo de 2005.

El Notario Público

AUTENTICACION DE COPIA DE ORIGINAL
CENTRO NOTARIO TREINTA Y OCHO DEL CIRCULO DE BOGOTA D.C.
CERTIFICO QUE PREVIO EL COTEJO RESPECTIVO LA PRESENTE COPIA CORRESPONDE CON EL ORIGINAL PRESENTADO
21 OCT 2010
Eduardo Durán Gómez
NOTARIO 38 DE BOGOTA, D.C.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 October 2009 (29.10.2009)

PCT

(10) International Publication Number
WO 2009/131926 A1

(51) International Patent Classification:
C07D 498/20 (2006.01) *A61P 25/28* (2006.01)
A61K 31/439 (2006.01)

(21) International Application Number:
PCT/US2009/041076

(22) International Filing Date:
20 April 2009 (20.04.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

61/047,211	23 April 2008 (23.04.2008)	US
12/423,299	14 April 2009 (14.04.2009)	US

(71) Applicant *(for all designated States except US)*: **BRISTOL-MYERS SQUIBB COMPANY** [US/US]; Route 206 and Province Line Road, Princeton, NJ 08543-4000 (US).

(72) Inventors; and

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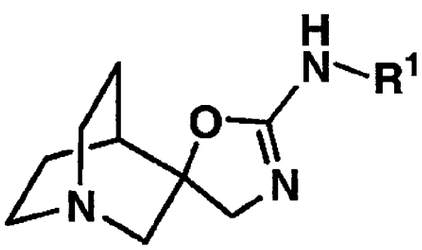
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM,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

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(54) Title: QUINUCLIDINE COMPOUNDS AS ALPHA-7 NICOTINIC ACETYLCHOLINE RECEPTOR LIGANDS



(I)

(57) Abstract: The disclosure provides compounds of formula I, including their salts, as well as compositions and methods of using the compounds. The compounds are ligands for the nicotinic α 7 receptor and may be useful for the treatment of various disorders of the central nervous system, especially affective and neurodegenerative disorders.

WO 2009/131926 A1

QUINUCLIDINE COMPOUNDS AS ALPHA-7 NICOTINIC ACETYLCHOLINE RECEPTOR LIGANDS

CROSS-REFERENCE TO RELATED APPLCIATIONS

This patent application claims the benefit of U.S. non-provisional patent application no. 12/423,299 filed April 14, 2009 and U.S. provisional patent application no. 61/047,211 filed April 23, 2008.

BACKGROUND OF THE INVENTION

The disclosure generally relates to compounds of formula I, including their salts, as well as compositions and methods of using the compounds. The compounds are ligands for the nicotinic α7 receptor and may be useful for the treatment of various disorders of the central nervous system, especially affective and neurodegenerative disorders.

Schizophrenia is a serious mental disorder, affecting approximately 1% of the population. Its progressive course results in major impairment of mental and social functioning and often leads to the development of other pathologies. Susceptibility often runs in families, with both genetic and environmental factors thought to be important. The direct and indirect costs of the disease are estimated in the tens of billion dollars annually in the U.S. alone.

Patients with schizophrenia have an elevated risk of suicide (approximately a 10% lifetime risk). They have a 2.5 fold increase in all-cause mortality, resulting in a 20% lowered life expectancy. The onset of illness can result in cascade of unhealthy lifestyle factors and behaviors that elevate the risk of various conditions and consequently the risk of death.

The onset of schizophrenia is most often in late adolescence or early adulthood, and episodes recur throughout life. The disease is characterized by the expression of three distinct symptom domains: positive, negative and cognitive. Psychotic or positive symptoms include delusions, hallucinations, thought disorder and paranoia. Negative symptoms include negative affect, social withdrawal, and anhedonia. Cognitive dysfunction includes deficits in attention, working memory and executive function. The pathophysiology of schizophrenia is not well understood, however, most experts believe it is a multi-factorial disorder in which

biological, genetic and environmental factors play a role. Most current therapies target the dopaminergic system and have resulted in the suggestion that an excess of dopaminergic neurotransmission underlies at least some aspects of schizophrenia. This theory received further support from findings that drugs which increase the levels of dopamine cause psychoses similar to the positive symptoms of the disease. Also, post mortem analysis of brains from schizophrenic patients indicate increased numbers of D2 dopamine receptors. Although newer antipsychotic agents, known as atypical antipsychotics, which are active at several additional neurotransmitter receptors, have been introduced in the past decade, these agents still share efficacy against the D2 dopamine receptor. All currently-used agents also have major limitations. Although positive symptoms are generally reduced in a majority of patients, these drugs do little to relieve the negative symptoms and cognitive deficits that are common and often most debilitating. In addition, antipsychotic agents have a number of unwanted and limiting side effects.

Nicotine is among the few agents which have a positive effect on cognitive function. Many schizophrenics smoke; the rate in patients is 2-4 times that of the general population, and up to 90% in schizophrenics who have been institutionalized do smoke. This smoking habit has been characterized as a form of self-medication.

Alzheimer's disease is a progressive neurodegenerative disorder, resulting in the general loss of cognitive functions. The incidence increases with age, to the degree that 25-50% of all individuals over 85 are estimated to suffer from some degree of dementia. A diagnosis of Alzheimer's implies that the remaining life expectancy is reduced by half, compared to normal adults.

Clinical signs of Alzheimer's disease are progressive cognitive deterioration, decreased ability to perform the activities of daily living and neuropsychiatric symptoms or behavioral changes. In the advanced stages of the disease, deterioration of musculature and mobility may lead to inability to feed oneself, and eventually to the patient becoming bedridden. Language becomes severely disorganized, and then is lost altogether. Patients are not able to perform even simple tasks independently and require constant supervision. The cost of institutional care makes up nearly 70% of the cost of the disease. Therefore, therapies which increase cognitive function and delay institutionalization are greatly needed.

Nicotinic acetylcholine receptors (nAChR's) are pentameric ligand-gated ion channels which are widely expressed through the central and peripheral nervous system. These channels are fast-desensitizing calcium channels which, when open, increase the intracellular concentration of the Ca^{++} ion. Although there are 12 individual receptors, the most abundant nicotinic receptors in the brain are α4β2 and α7. The α4β2 complex has been identified as the "high affinity" nicotine site. The homo-pentameric α7 receptor selectively binds the natural product, α-bungarotoxin, which has allowed its relatively facile localization and measurement. The α7 receptor is primarily expressed in the cortex, hippocampus and subcortical limbic regions and commonly occurs pre-synaptically. The localization of a7 nAChRs in areas involved with learning and memory has led to studies using both knockout mice and pharmacological manipulation. It is involved in sensory gating, memory, and neuronal plasticity. Compounds which selectively bind to the α7 receptor have been shown to improve learning and memory functions in normal and aged animals, reverse scopolamine-induced memory deficits, reverse pharmacologically-induced gating deficits, and to possess some anxiolytic properties. The α7 receptor has also been shown to be involved in the reduction of inflammation via the vagus nerve.

Alzheimer's disease has been shown in several studies to be accompanied by a reduction in nicotinic receptors in the cortex and hippocampus. Nicotine injections or nicotine skin patches have been reported to significantly improve attention, memory and learning in Alzheimer's disease patients. While there is a progressive loss of nicotinic receptors during the course of Alzheimer's disease, the α7 neurons are relatively spared, compared to the more abundant α4 receptors. Recently, the administration of selective nicotinic α7 agonists has been shown to increase cognitive functioning in Alzheimer's patients when dosed as long as 8 weeks.

The following references provide general reviews of the nicotinic receptor system and α7 receptors and ligands: Picciotto and Zoli, *J. Neurobio.* (2002) **53**:641-655; Brening, *et al*, *Ann. Reports in Med. Chem.* (2005) **40**:3-16; Dani and Bertrand, *Ann. Rev. Pharm. Tox.* (2007) **47**:699-729; Olincy and Stevens, *Biochem. Pharmacol.* (2007) **74**:1192-1201; Broad, *et al*, *Drugs Future* (2007) **32** (2):161-70; de Jonge and Ulloa, *Brit. J. Pharmacol.* (2007) **151**:915-929; Romanelli, *et al*, *ChemMedChem* (2007) **2**(6):746-767.

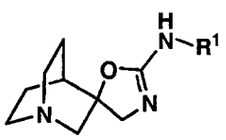
Ligands for the nicotinic α7 receptor have been disclosed. See EP 452,101, EP 337,547, WO 2003/092580, WO 2004/000,469, US patent application publication 2007004715, and C.J. Swain, *et al.*, *J. Med. Chem.*, (1992) **35**:1019-1031.

The invention provides technical advantages, for example, the compounds are novel and are effective against hepatitis C. Additionally, the compounds provide advantages for pharmaceutical uses, for example, with regard to one or more of their mechanism of action, binding, inhibition efficacy, target selectivity, solubility, safety profiles, or bioavailability.

DESCRIPTION OF THE INVENTION

The invention encompasses compounds formula I, including pharmaceutically acceptable salts, and compositions and methods of treatment using these compounds. The compounds may be useful for the treatment of various disorders of the central nervous system:

One aspect of the invention is a compound of formula I, or a stereoisomer thereof,



I

wherein:

R^1 is selected from the group consisting of isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, triazinyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, naphthyridinyl, indazolyl, indolyl, 2-indolonyl, benzisoxazolyl, benzoisothiazolyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, furopyridinyl, thienopyridinyl, thienopyrimidinyl, isothiazolopyridinyl, thiazolopyridinyl, thiazolopyridinonyl, thiazolopyrazinyl, thiazolopyrimidinyl, triazolopyridinyl, triazolopyrazinyl,

pyrrolotriazinyl, 5,6-dihydrobenzo[h]quinazolinyl, 5H-chromeno[4,3-d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[d]pyrimidinyl, 5,6,7,8-tetrahydroquinazolinyl, 7,8-dihydroquinazolin-5(6H)-onyl, and tetrahydrobenzothiazolyl, and is substituted with 0-3 substituents independently selected from the group consisting of C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}haloalkoxy, C_{3-7}cycloalkoxy, C_{1-4}alkylthio, phenoxy, benzyloxy, halo, hydroxy, cyano, C_{1-4}alkylsulfonyl, NR^2R^3, pyrrolidinonyl, methylenedioxy, furyl, thienyl, triazolyl, pyrimidinyl, naphthyl, C_{1-4}alkylamido, $CONR^2R^3$, pyridyl, phenyl, and benzyl, and where pyridyl, phenyl and benzyl are substituted with 0-2 substituents independently selected from the group consisting of halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, and NR^2R^3;

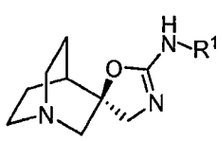
R^2 is hydrogen, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, or C_{1-4}aminoalkyl;

R^3 is hydrogen, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, or C_{1-4}aminoalkyl;

or R_2 and R_3 taken together with the nitrogen atom to which they are attached is axetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, N-(C_{1-4}alkyl)piperazinyl, morpholinyl, or homopiperidinyl;

or a pharmaceutically acceptable salt thereof.

Another aspect of the invention is stereoisomer of formula I according to formula Ia.



Ia

Another aspect of the invention is a compound of formula I or Ia where R^1 is selected from the group consisting of dimethylisoxazolyl, (methyl)(phenyl)isoxazolyl, methylpyrazolyl, dimethylpyrazolyl, thienylpyrazolyl,

methoxyphenylpyrazolyl, thiazolyl, bromothiazolyl, cyanothiazolyl, methylthiazolyl, dimethylthiazolyl, (methyl)(phenyl)thiazolyl, isopropylthiazolyl, butylthiazolyl, benzylthiazolyl, methoxyphenylmethylthiazolyl, phenylthiazolyl, chlorophenylthiazolyl, methoxyphenylthiazolyl, (methoxyphenyl)(methyl)thiazolyl, pyridinylthiazolyl, (phenyl)(methyl)imidazolyl, methyloxadiazolyl, ethyloxadiazolyl, methylthiadiazolyl, fluorophenylthiadiazolyl, furylthiadiazolyl, (dimethylcarboxamido)(methyl)thiazolyl, (pyrrolidinylCO)thiazolyl, phenyltriazolyl, pyridinyl, bromopyridinyl, chloropyridinyl, (chloro)(fluoro)pyridinyl, (chloro)(methyl)pyridinyl, dichloropyridinyl, fluoropyridinyl, cyanopyridinyl, (cyano)(methyl)pyridinyl, (cyano)(dimethyl)pyridinyl, methoxypyridinyl, (methylpyrrolidinyl)pyridinyl, phenylpyridinyl, methoxypyridinylpyridinyl, pyridazinyl, bromopyridazinyl, chloropyridazinyl, methylpyridazinyl, methoxypyridazinyl, methylthiopyridazinyl, pyrrolidinylpyridazinyl, pyrrolidinonylpyridazinyl, phenylpyridazinyl, pyridinylpyridazinyl, methoxypyridinylpyridazinyl, pyrimidinyl, (bromo)(isopropyl)pyrimidinyl, (bromo)(dimethyl)pyrimidinyl, (bromo)(cyclopropyl)pyrimidinyl, (bromo)(methoxy)pyrimidinyl, (bromo)(phenyl)pyrimidinyl, (bromo)(pyridinyl)pyrimidinyl, chloropyrimidinyl, (chloro)(dimethyl)pyrimidinyl, (methyl)(methoxy)pyrimidinyl, methylpyrimidinyl, ethylpyrimidinyl, (methyl)(phenyl)pyrimidinyl, dimethylpyrimidinyl, butylpyrimidinyl, isopropylpyrimidinyl, cyclopropylpyrimidinyl, methoxypyrimidinyl, dimethoxypyrimidinyl, isopropoxypyrimidinyl, cyclopentoxypyrimidinyl, difluoromethoxypyrimidinyl, trifluoroethoxypyrimidinyl, phenoxypyrimidinyl, methylthiopyrimidinyl, phenylpyrimidinyl, chlorophenylpyrimidinyl, methylphenylpyrimidinyl, methoxyphenylpyrimidinyl, (phenyl)(triazolyl)pyrimidinyl, pyridinylpyrimidinyl, methoxypyridinylpyrimidinyl, methoxypyrimidinylpyrimidinyl, naphthylpyrimidinyl, pyrazinyl, bromopyrazinyl, (bromo)(methoxy)pyrazinyl, chloropyrazinyl, methylpyrazinyl, dimethylpyrazinyl, butylpyrazinyl, cyanopyrazinyl, methoxypyrazinyl, isopropoxypyrazinyl, trifluoromethylpyrazinyl, and phenylpyrazinyl, and dimethyltriazinyl; or a pharmaceutically acceptable salt thereof.

Another aspect of the invention is a compound of formula I or Ia where R^1 is selected from the group consisting of dimethylpyridinoisoxazolyl, benzoxazolyl, chlorobenzoxazolyl, fluorophenylbenzoxazolyl, ethylphenylbenzoxazolyl, dimethylaminophenylbenzoxazolyl, pyridinylbenzoxazolyl, benzothiazolyl, acetamidobenzothiazolyl, bromobenzothiazolyl, chlorobenzothiazolyl, (chloro)(methyl)benzothiazolyl, (chloro)(methoxy)benzothiazolyl, fluorobenzothiazolyl, difluorobenzothiazolyl, cyanobenzothiazolyl, methylbenzothiazolyl, dimethylbenzothiazolyl, (methyl)(methoxy)benzothiazolyl, ethylbenzothiazolyl, trifluoromethylbenzothiazolyl, hydroxybenzothiazolyl, methoxybenzothiazolyl, ethoxybenzothiazolyl, isopropoxybenzothiazolyl, trifluoromethoxybenzothiazolyl, difluoromethoxybenzothiazolyl, dimethoxybenzothiazolyl, morpholinylbenzothiazolyl, (pyrrolidinylCO)benzothiazolyl, methylsulfonylbenzothiazolyl, chlorothiazolopyridinyl, dimethylthiazolopyridinyl, benzyloxythiazolopyridinyl, difluoromethoxythiazolopyridinyl, benzotriazolyl, indolonyl, indazolyl, bromoindazolyl, chloroindazolyl, fluoroindazolyl, (methyl)(methoxy)indazolyl, methoxyindazolyl, trifluoromethylindazolyl, trifluoromethoxyindazolyl, difluoromethoxyindazolyl, benzimidazolyl, fluorobenzimidazolyl, methylbenzimidazolyl, (methyl)(methoxy)benzimidazolyl, methoxybenzimidazolyl, tetrahydrobenzothiazolyl, furopyridinyl, dimethylfuropyrimidinyl, thienopyrimidinyl, isopropylthienopyrimidinyl, dimethylthienopyrimidinyl, chlorotriazolopyridinyl, methyltriazolopyridinyl, trifluoromethyltriazolopyridinyl, methoxytriazolopyridinyl, triazolopyrazinyl, bromopyrrolotriazinyl, dimethylaminothiazolopyrimidinyl, thiazolopyazinyl, bromothiazolopyazinyl, methoxythiazolopyazinyl, methylthiothiazolopyazinyl, methoxythiazolopyrimidinyl, (methyl)(methoxy)thiazolopyrimidinyl, quinolinyl, bromoquinolinyl, fluoroquinolinyl, methylquinolinyl, (methyl)(methoxy)quinolinyl, isoquinolinyl, bromoisoquinolinyl, dichloroisoquinolinyl, methylisoquinolinyl, dimethylisoquinolinyl, quinoxalinyl, chloroquinoxalinyl, methylquinoxalinyl, methoxyquinoxalinyl, quinazolinyl, bromoquinazolinyl, naphthyridinyl, 5,6-dihydrobenzo[h]quinazolinyl, 5H-chromeno[4,3-d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[d]pyrimidinyl, 5,6,7,8-tetrahydroquinazolinyl, and 7,8-dihydroquinazolin-5(6H)-onyl; or a pharmaceutically acceptable salt thereof.

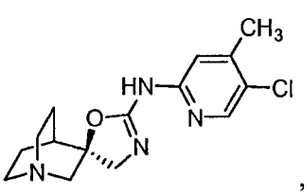
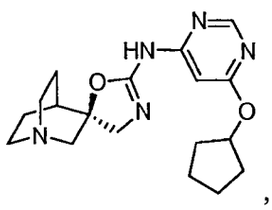
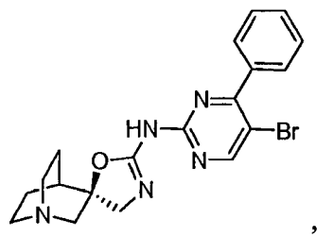
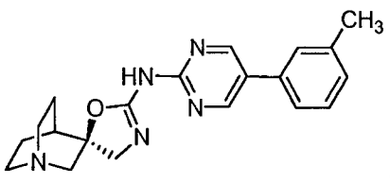
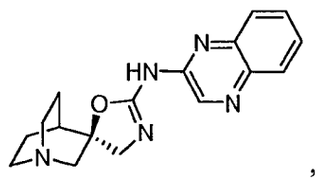
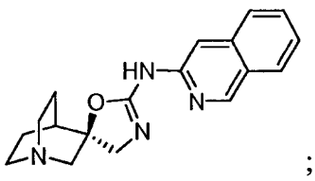
Another aspect of the invention is a compound of formula I or Ia where R^1 is selected from the group consisting of phenylthiazolyl, (chloro)(methyl)pyridinyl, (bromo)(phenyl)pyrimidinyl, methoxypyrimidinyl, difluoromethoxypyrimidinyl, difluoroethoxypyrimidinyl, cyclopentoxypyrimidinyl, (methylphenyl)pyrimidinyl, (methoxyphenyl)pyrimidinyl, bromopyrazinyl, chloropyrazinyl, methylthiopyrazinyl, methoxybenzothiazolyl, ethoxybenzothiazolyl, difluoromethoxybenzothiazolyl, thiazolopyridinonyl, trifluoromethylindazolyl, benzimidazolyl, isoquinoinyl, and quinazolinyl or a pharmaceutically acceptable salt thereof.

Another aspect of the invention is a compound or formula I or Ia where R^1 is selected from the group consisting of thiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, benzothiazolyl, thiazolopyridinyl, indazolyl, benzimidazolyl, isoquinoinyl, and quinazolinyl, and is substituted with 0-3 substituents independently selected from the group consisting of C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}haloalkoxy, C_{3-7}cycloalkoxy, C_{1-4}alkylthio, phenoxy, benzyloxy, halo, hydroxy, cyano, C_{1-4}alkylsulfonyl, NR^2R^3, pyrrolidinonyl, methylenedioxy, furyl, thienyl, triazolyl, pyrimidinyl, naphthyl, C_{1-4}alkylamido, $CONR^2R^3$, pyridyl, phenyl, and benzyl, and where pyridyl, phenyl and benzyl are substituted with 0-2 substituents independently selected from the group consisting of halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, and NR^2R^3; or a pharmaceutically acceptable salt thereof.

Another aspect of the invention is a compound or formula I or Ia where R^1 is selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, thiazolopyridinyl, and isoquinoinyl, and is substituted with 0-3 substituents independently selected from the group consisting of C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}haloalkoxy, C_{3-7}cycloalkoxy, C_{1-4}alkylthio, phenoxy, benzyloxy, halo, hydroxy, cyano, C_{1-4}alkylsulfonyl, NR^2R^3, pyrrolidinonyl, methylenedioxy, furyl, thienyl, triazolyl, pyrimidinyl, naphthyl, C_{1-4}alkylamido, $CONR^2R^3$, pyridyl, phenyl, and benzyl, and where pyridyl, phenyl and benzyl are substituted with 0-2 substituents independently selected from the group consisting of halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, and NR^2R^3; or a pharmaceutically acceptable salt thereof.

Another aspect of the invention is a compound or formula I or Ia where R^1 is selected from the group consisting of pyridinyl and isoquinoinyl, and is substituted with 0-3 substituents independently selected from the group consisting of C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}haloalkoxy, C_{3-7}cycloalkoxy, C_{1-4}alkylthio, phenoxy, benzyloxy, halo, hydroxy, cyano, C_{1-4}alkylsulfonyl, NR^2R^3, pyrrolidinonyl, methylenedioxy, furyl, thienyl, triazolyl, pyrimidinyl, naphthyl, C_{1-4}alkylamido, $CONR^2R^3$, pyridyl, phenyl, and benzyl, and where pyridyl, phenyl and benzyl are substituted with 0-2 substituents independently selected from the group consisting of halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, and NR^2R^3; or a pharmaceutically acceptable salt thereof.

Another aspect of the invention is a compound selected from the group consisting of


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or a pharmaceutically acceptable salt thereof.

Another aspect of the invention is a compound of formula I where R_1 is selected from the group consisting of thiazole, thiadiazole, isoxazole, oxazole, pyrazole, imidazole, pyridine, pyrazine, pyridazine, pyrimidine, quinoline, isoquinoline, quinoxaline, indazole, indole, 2-indolone, benzothiazole,

benzimidazole, benzoxazole, benzo(d)isothiazole, benzisoxazole, isothiazolo-[5,4-b]pyridine, (1,2,4)-triazolo[1,5-a]pyridine, thiazolo[5,4-b]pyridine and tetrahydrobenzothiazole in which each group is optionally substituted with one or two substituents selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, halogen, hydroxy, cyano, trifluoromethyl, difluoromethyl, fluoromethyl, trifluoromethoxy, difluoromethoxy, C_{1-4}alkylsulfonyl, furyl, morpholino, methylenedioxy, pyridyl, C_{1-4}alkylphenyl, halophenyl, dimethylaminophenyl, C_{1-4}alkylamido, $-CONR_2R_3$ in which R_2 and R_3 each are independently hydrogen, C_{1-4}alkyl, hydroxy C_{1-4}alkyl, amino C_{1-4}alkyl or R_2 and R_3 taken together with the atom to which they are attached are C_{3-6} cycloalkyl; phenyl, substituted phenyl, phenylmethyl, substituted phenylmethyl in which said substituted phenyl and substituted phenylmethyl are substituted with substituents independently selected from the group consisting of halogen, C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethyl and trifluromethoxy; or a pharmaceutically acceptable salt thereof.

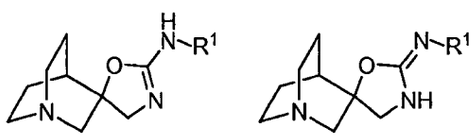
For a compound of formula I or Ia, the scope of any instance of a variable substituent, including R^1, R^2, and R^3, can be used independently with the scope of any other instance of a variable substituent. As such, the invention includes combinations of the different aspects.

Unless specified otherwise, these terms have the following meanings. "Alkyl" means a straight or branched alkyl group composed of 1 to 4 carbons. "Alkenyl" means a straight or branched alkyl group composed of 2 to 4 carbons with at least one double bond. "Alkynyl" means a straight or branched alkyl group composed of 2 to 4 carbons with at least one triple bond. "Cycloalkyl" means a monocyclic ring system composed of 3 to 7 carbons. "Haloalkyl" and "haloalkoxy" include all halogenated isomers from monohalo to perhalo. Terms with a hydrocarbon moiety (e.g. alkoxy) include straight and branched isomers for the hydrocarbon portion. Parenthetic and multiparenthetic terms are intended to clarify bonding relationships to those skilled in the art. For example, a term such as ((R)alkyl) means an alkyl substituent further substituted with the substituent R.

The invention includes all pharmaceutically acceptable salt forms of the compounds. Pharmaceutically acceptable salts are those in which the counter ions do not contribute significantly to the physiological activity or toxicity of the compounds and as such function as pharmacological equivalents. These salts can be made according to common organic techniques employing commercially available reagents. Some anionic salt forms include acetate, acistrate, besylate, bromide, chloride, citrate, fumarate, glucouronate, hydrobromide, hydrochloride, hydroiodide, iodide, lactate, maleate, mesylate, nitrate, pamoate, phosphate, succinate, sulfate, tartrate, tosylate, and xinofoate. Some cationic salt forms include ammonium, aluminum, benzathine, bismuth, calcium, choline, diethylamine, diethanolamine, lithium, magnesium, meglumine, 4-phenylcyclohexylamine, piperazine, potassium, sodium, tromethaminc, and zinc.

Some of the compounds of the invention exist in stereoisomeric forms. The invention includes all stereoisomeric forms of the compounds including enantiomers and diastereromers. Methods of making and separating stereoisomers are known in the art.

The invention includes all tautomeric forms of the compounds. An example of a tautomeric pair is shown below.



Synthetic Methods

The compounds may be made by methods known in the art including those described below and including variations within the skill of the art. Some reagents and intermediates are known in the art. Other reagents and intermediates can be made by methods known in the art using readily available materials. The variables (e.g. numbered "R" substituents) used to describe the synthesis of the compounds are intended only to illustrate how to make the compounds and are not to be confused

with variables used in the claims or in other sections of the specification. The following methods are for illustrative purposes and are not intended to limit the scope of the invention.

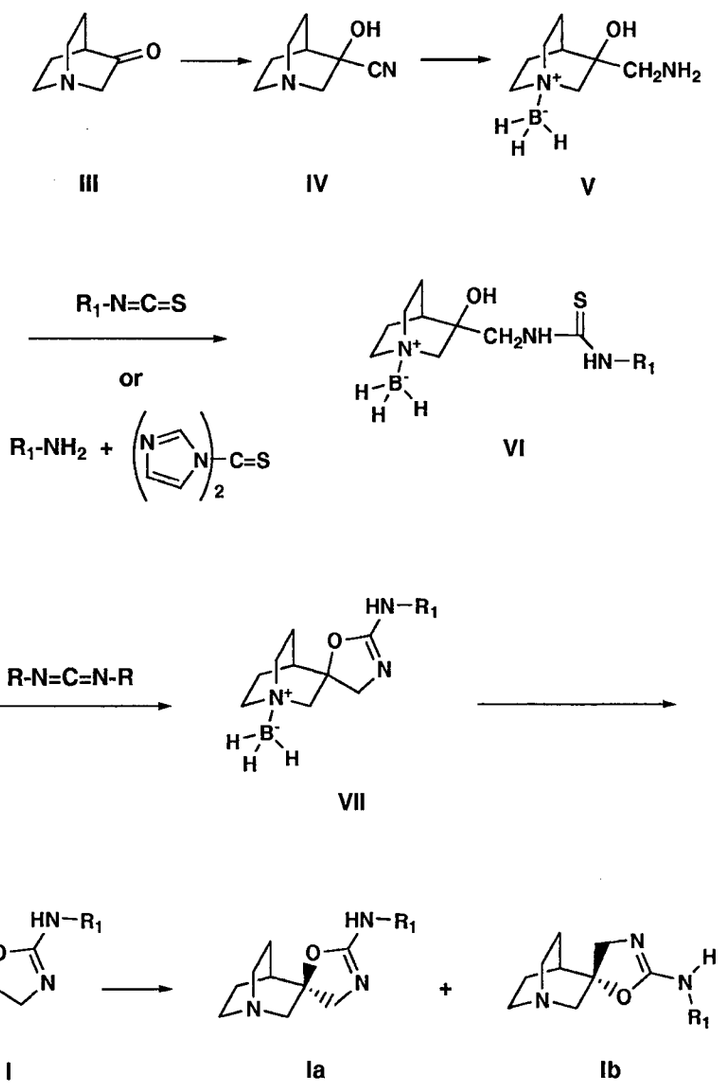
Some of the compounds may be prepared using the reactions and techniques described in this section. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents which are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used.

Abbreviations used in the schemes generally follow conventions used in the art. Chemical abbreviations used in the specification and examples are defined as follows: "NaHMDS" for sodium bis(trimethylsilyl)amide; "DMF" for N,N-dimethylformamide; "MeOH" for methanol; "NBS" for N-bromosuccinimide; "Ar" for aryl; "TFA" for trifluoroacetic acid; "LAH" for lithium aluminum hydride; "BOC", "DMSO" for dimethylsulfoxide; "h" for hours; "rt" for room temperature or retention time (context will dictate); "min" for minutes; "EtOAc" for ethyl acetate; "THF" for tetrahydrofuran; "EDTA" for ethylenediaminetetraacetic acid; "Et_2O" for diethyl ether; "DMAP" for 4-dimethylaminopyridine; "DCE" for 1,2-dichloroethane; "ACN" for acetonitrile; "DME" for 1,2-dimethoxyethane; "HOBt" for 1-hydroxybenzotriazole hydrate; "DIEA" for diisopropylethylamine, "Nf" for $CF_3(CF_2)_3SO_2$-; and "TMOF" for trimethylorthoformate.

Abbreviations as used herein, are defined as follows: "1 x" for once, "2 x" for twice, "3 x" for thrice, "°C" for degrees Celsius, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or milligrams, "L" for liter or liters, "mL" for milliliter or milliliters, "μL" for microliter or microliters, "N" for normal, "M" for molar, "mmol" for millimole or millimoles, "min" for minute or minutes, "h" for hour or hours, "rt" for room temperature, "RT" for retention time, "atm" for atmosphere, "psi" for pounds per square inch, "conc." for concentrate, "sat" or "sat'd " for saturated, "MW" for molecular weight, "mp" for melting point, "ee" for enantiomeric excess, "MS" or "Mass Spec" for mass spectrometry, "ESI" for electrospray ionization mass spectroscopy, "HR" for high resolution, "HRMS" for

high resolution mass spectrometry , "LCMS" for liquid chromatography mass spectrometry, "HPLC" for high pressure liquid chromatography, "RP HPLC" for reverse phase HPLC, "TLC" or "tlc" for thin layer chromatography, "NMR" for nuclear magnetic resonance spectroscopy, "^{1}H" for proton, "δ" for delta, "s" for singlet, "d" for doublet, "t" for triplet, "q" for quartet, "m" for multiplet, "br" for broad, "Hz" for hertz, and "α", "β", "R", "S", "E", and "Z" are stereochemical designations familiar to one skilled in the art.

Scheme 1.

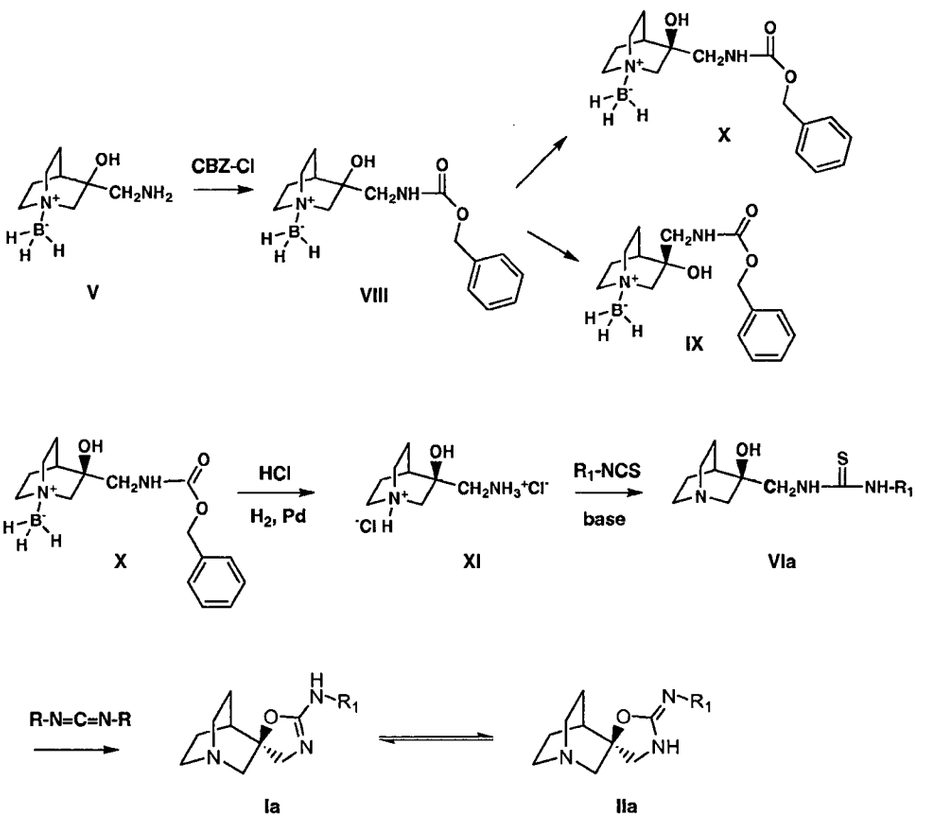


Compounds of Formula I are prepared as illustrated in Reaction Scheme 1. The ketone of Formula III (3-quinuclidone) is known, is commercially available, or may be prepared by methods known to those skilled in the art. The ketone can be converted to the corresponding cyanohydrin of Formula IV by reaction with sodium or potassium cyanide plus an acid. The compound of Formula IV can be reduced to the corresponding amino-methyl compound (borane complex) of Formula V by reaction with borane/tetrahydrofuran complex.

The compound of Formula V can be reacted with heteroaryl isothiocyanates directly in an inert solvent to give the thioureas of Formula VI. Alternatively, the heteroarylamine can be reacted with thiocarbonyl-diimidazole to give an activated species which can be used without isolation to convert the compound of Formula V to the compound of Formula VI. The heteroarylamine may be prepared by methods known to those skilled in the art.

The thiourea of Formula VI can be cyclized using, for example, di-isopropyl carbodiimide to give the oxazoline of Formula VII which may be deprotected via treatment with acid to give the racemic final product of the compound of Formula I. The compound of Formula I may be resolved into pure enantiomer compounds of Formula Ia and Formula Ib by means known in the art, for example, via chiral chromatography.

Scheme 2.



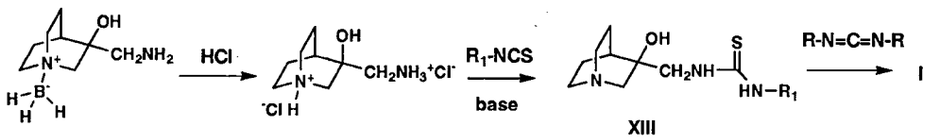
Alternatively, the free amino group of the quinuclidine of Formula V can be blocked with, for example, carbobenzyloxy-chloride ("CBZ-Cl") to give the compound of Formula VIII, as illustrated in Reaction Scheme 2.

The racemic compound of Formula VIII can be resolved into its enantiomers, Formula IX and Formula X by, for example, chiral chromatography. Either the compound of Formula IX or Formula X, and preferably the compound of Formula X, can then be carried on as shown in Reaction Scheme 2.

The borane group in the compound of Formula X can be removed, for example, by treatment with dilute hydrochloric acid, and the carbobenzyloxy group can be removed, for example, by catalytic hydrogenation to give the chiral quinuclidine amine of Formula XI. Similarly to Reaction Scheme 1, the amine salt of Formula XI can be reacted with isothiocyanates to give the thiourea of Formula VIa, which can then be reacted with dialkyl carbodiimides or mixed thioureas (as from

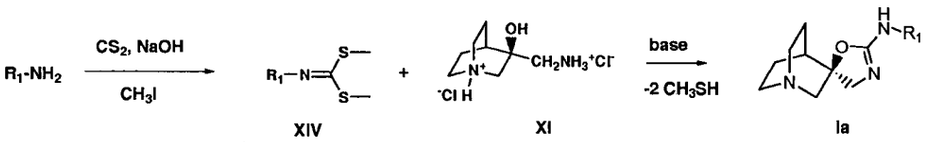
reaction with thiocarbonyl diimidazole) to give the chiral oxazoline quinuclidine compounds of Formula Ia, and its tautomer, Formula IIa.

Scheme 2a.



Alternatively, the borane group of V may be removed with hydrochloric acid to give dihydrochloride salt XII, which can be reacted in the presence of base with an isothiocyanate to give intermediate thiourea XIII, which can then be cyclized as in Reaction Schemes 1-2 to give I. XII may also be prepared by other methods, as referenced in US Patent #5,137,895 (8/11/1992).

Scheme 3.



Additionally, the (hetero)aromatic amines may be reacted with carbon disulfide, sodium hydroxide, and methyl iodide to give intermediate dimethyl carbonimidodithioates XIV. These are reacted with dihydrochloride XI in the presence of base to eliminate two moles of methanethiol and generate desired products Ia directly.

Biological methods

I) α7 Nicotinic Acetycholine Receptor Binding. Membranes were prepared for binding using HEK293 cells stably expressing the rat α7 nicotinic acetycholine receptor (rat α7 nAChR). Cells were homogenized at 4°C in hypotonic lysis buffer consisting of 10 mM Tris (pH 7.4), 5 mM EDTA and protease inhibitors and centrifuged at 32000 xg for 20 minutes. The pellet was washed once in membrane wash buffer consisting of 50 mM Tris (pH 7.4), 1 mM EDTA and protease inhibitors and centrifuged at 32000 xg for 20 minutes. This pellet was then resuspended in assay buffer consisting 50 mM KH_2PO_4 (pH 7.4 at 25°C), 1 mM EDTA, 0.005 % Triton-X 100 and 0.1% (v/v) Sigma Protease Inhibitor Cocktail. Aliquots were then frozen in dry ice/ethanol and kept at -80°C until the day of the assay.

II) A Ca^{2+} -Sensitive, Fluorescence-Based Assay α-7 for Nicotinic Acetylcholine Receptor Channel Function In Mammalian Cells ("FLIPR"). Summary: Lead compounds are evaluated for agonist activity at α-7, α3β4, α4αβ2, and α1β1δ1ε sub-types of nicotinic ACh receptor ion channels expressed in mammalian HEK 293 cells. Agonist potency and efficacy values are determined from kinetic fluorescence Ca^{2+} influx measurements made using a 384 well FLIPR (Fluorescence Image Plate Reader). The utility of fluorescent indicators for measuring changes in intracellular divalent cation concentrations, particularly Ca^{2+}, for drug discovery endeavors is well documented (Rudiger, R., *et al.*, *Nature Reviews*, 2003, **4**:579-586; Gonzalez J.E., *et al.*, *Receptors and Channels*, 2002, **8**:283-295). In this assay, channel expressing HEK cell lines seeded in 384 well assay plates are loaded with a membrane permeant fluorescent Ca^{2+} indicator dye, whose 510 nm green emission signal increases in response to elevation of intracellular Ca^{2+} concentration. The basal fluorescence from the cells is monitored in real time, followed by the acute addition of test compounds. If the compound is an agonist at any of the non-selective cation channels, the latter open and allow the movement of extracellular Ca^{2+} ions into the cell cytoplasm, where they bind to the Ca^{2+} indicator dye, and produce an increase in fluorescence output signal , which is detected by a cooled CCD imaging camera.

Materials and Methods: Reagents: The acetomethoxy (AM) ester of the Ca^{2+} indicator dye Fluo-4 was obtained from InVitrogen, (Carlsbad, CA). Acetylcholine and all buffer constituents were purchased from Sigma Chemical Company, St. Louis, MO. G418 and Minimal Essential Medium were purchased from InVitrogen Life Technologies, Carlsbad, CA. Fetal bovine serum was purchased from (InVitrogen, Carlsbad, CA).

Cell Culture: HEK-293 cells were grown in Minimal Essential Medium containing 10% (v/v) fetal bovine serum at 37° C in a 5% CO_2 incubator. HEK-293 cells stably expressing the ion channels were grown in the same medium with the addition of 500 μg/ml G418.

Ca^{2+} flux assays of Ca^{2+} channels expressed in HEK-293 cells: HEK-293 cells expressing the ion channels of interest were plated in 384 well, black-walled, clear-bottomed, poly-D-lysine coated plates at a density of ~20,000 cells/well in 20 μl of Minimal Essential Medium containing 10% (v/v) fetal bovine serum and incubated for 2 days at 29° C in a 5% CO_2 incubator. Prior to assay, cells were loaded with the Fluo-4 AM ester. Cell loading was accomplished by removing the culture medium and replacing it with 30 μl/well of the AM ester of the dye (5 μM) mixed with Hanks Balanced Salt Solution (#14175-095) containing 20mM HEPES, 2.5mM probenecid,0.5mM $CaCl_2$, 1mM MgCl2 and 10μM atropine. Dye loading was allowed to proceed for 90 minutes at room temperature at which time the dye loading solution was removed and replaced with 40 μl/well of Hanks buffer. Cells loaded with dye were loaded onto a FLIPR384 (Molecular Devices, Sunnyvale, CA). Fluo-4 dye was excited using the 488 nm line of an argon laser. Emission was filtered using a 540 +/- 30 nm bandpass filter. For evaluation of the effects of test compounds using the Ca^{2+} flux assay, compounds to be tested were provided in assay ready plates. For nicotinic receptor ion channel expressing cells, the assay was initiated by the addition of 20 μl/well of Hanks buffer containing test compounds. For all assays, data were collected at 1 Hz for 10 seconds (baseline), at which time the compound containing stimulus buffers are added, and further measurements collected at 0.33Hz for 3 min.

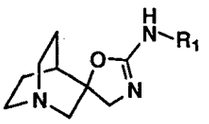
Data Analysis: The statistical robustness of the nicotinic receptor Ca^{2+} flux assays is determined from blanks and totals wells. The totals wells define maximal channel activation for each compound test plate (Maximum efficacious dose of acetylcholine), and the blanks wells which contain matched DMSO only, define zero channel activation. The raw fluorescence units data files generated on the FLIPR plate reader are automatically exported and processed by in-house data analysis tools. The reduced percent activation data for each concentration of test compound are fit using MathIQ fitting engine (ID Business Solutions Limited, Surrey, UK). Data were analyzed by fitting maximum amplitudes of change in fluorescence, for Ca^{2+} flux for a given condition of test compound. Potencies (EC_{50} values) of compounds are calculated from the average of three assay wells from a twenty point CRC. Test compound efficacy values (Ymax values) are expressed relative to a maximal response to acetylcholine in the total wells.

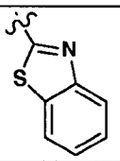
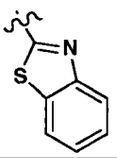
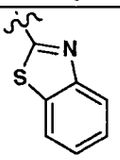
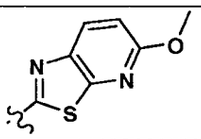
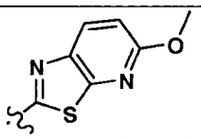
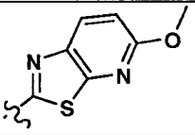
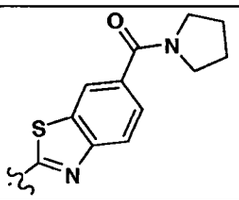
III) Fos quantification assay: Male Wistar rats are treated with drug (1-10 mg/kg) or vehicle (2 ml/kg, sc). Two hours after treatments, the rats are rapidly decapitated and discrete brain regions of interest are isolated on ice and weighed and flash frozen with liquid nitrogen and stored at -80 deg. C. Further processing of the brain tissue for nuclear extracts as well as for Fos quantification are in accordance with the protocol prescribed by a commercially available ELISA-based chemiluminiscence detection kit (catalog #89860, EZ-detect c-Fos Trans kit, Pierce Biotechnology Inc., Rockford, IL).

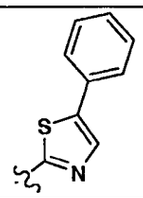
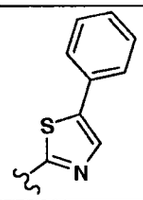
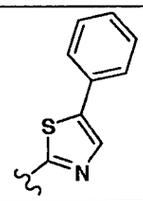
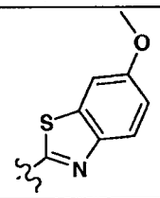
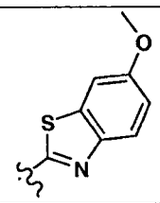
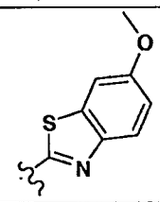
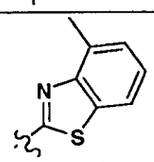
IV) MK-801 Disrupted Set-Shift Assay in rats: This assay uses a modification of the protocol described by Stefani et al. (*Behavioral Neuroscience*, 2003, **117**: 728-737). Test compounds are assessed for their ability to reverse an MK-801-induced performance deficit (0.03 mg/kg, i.p., single dose) in this assay.

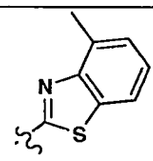
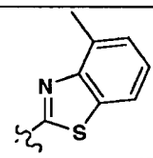
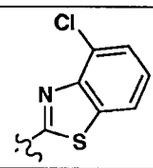
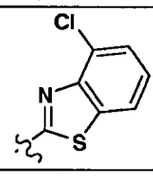
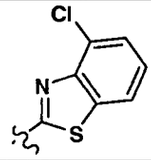
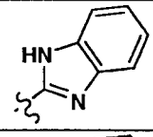
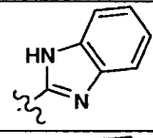
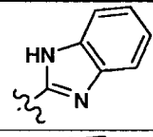
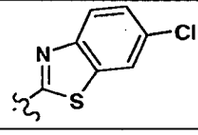
The activity of specific compounds described herein and tested in the above assay (II) is provided in Table 1.

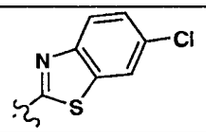
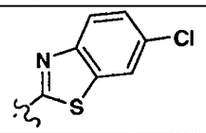
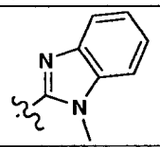
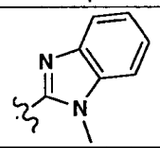
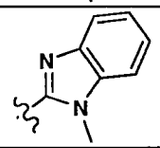
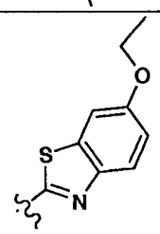
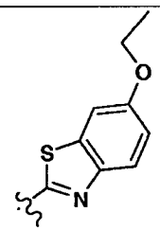
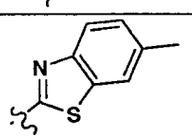
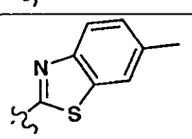
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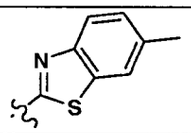
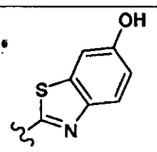
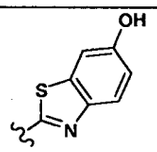
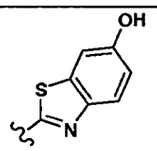
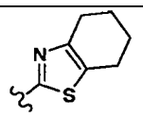
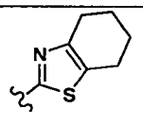
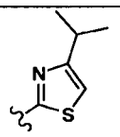
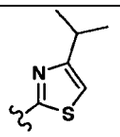
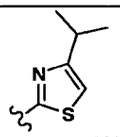


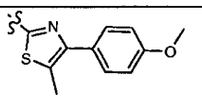
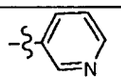
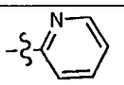
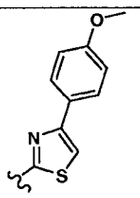
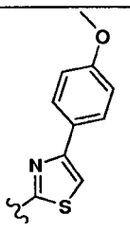
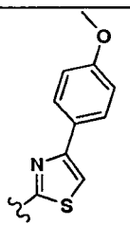
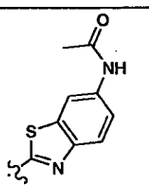
Example Number	R_1	FLIPR α7–HI (EC_{50}, nM)	FLIPR α7–HI (EC_{50}, nM)
1			+++
1a			+
1b			+++
2			++
2a			+
2b			++
3		3840	+

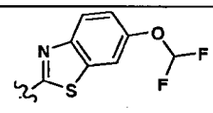
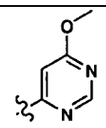
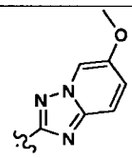
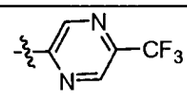
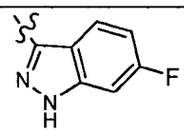
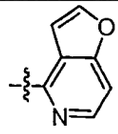
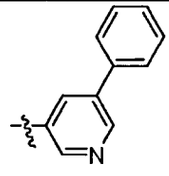
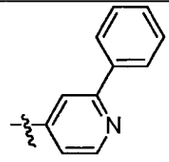
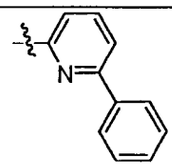
Example Number	R_1	FLIPR α7–HI (EC_{50}, nM)	FLIPR α7–HI (EC_{50}, nM)
4			+++
4a			+
4b		230	++
5			++
5a			+
5b			+++
6			++

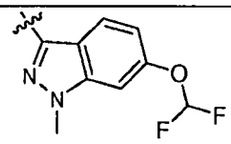
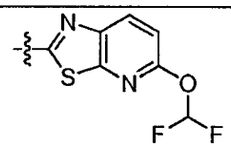
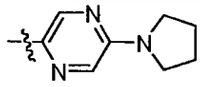
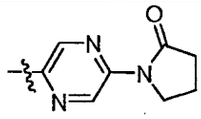
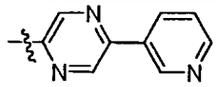
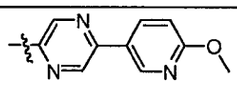
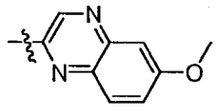
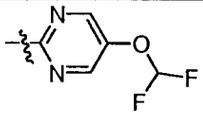
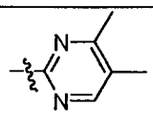
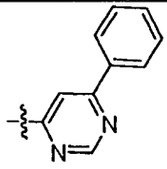
Example Number	R_1	FLIPR α7–HI (EC_{50}, nM)	FLIPR α7–HI (EC_{50}, nM)
6a		4340	+
6b			+++
7			++
7a			+
7b			+++
8			++
8a		120	++
8b			+
9			++

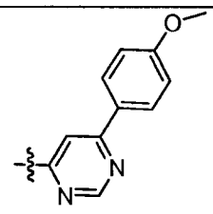
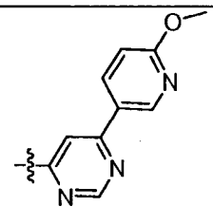
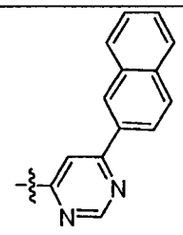
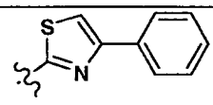
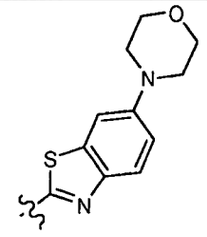
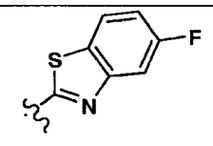
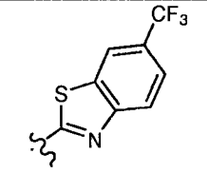
Example Number	R_1	FLIPR α7–HI (EC_{50}, nM)	FLIPR α7–HI (EC_{50}, nM)
9a		7315	+
9b			+++
10			++
10a			++
10b			++
11			++
11b		213	++
12			++
12a			++

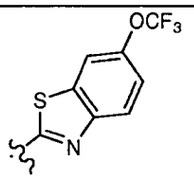
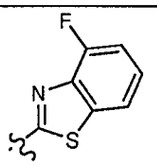
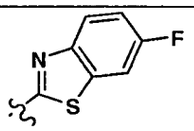
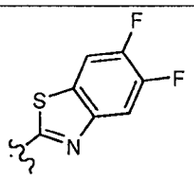
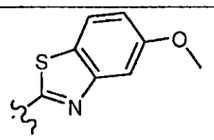
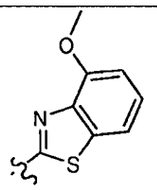
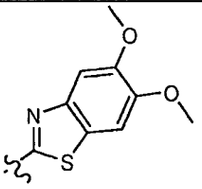
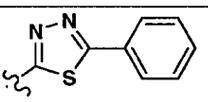
Example Number	R_1	FLIPR α7–HI (EC_{50}, nM)	FLIPR α7–HI (EC_{50}, nM)
12b			+
13			+++
13a			++
13b			+++
14			++
14b			++
15			++
15a		6345	+
15b			++
16			++

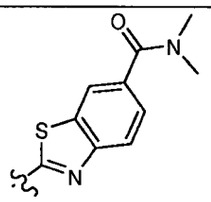
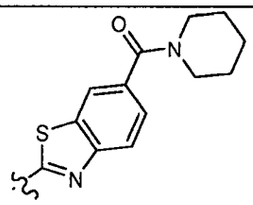
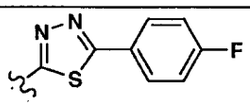
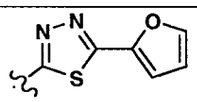
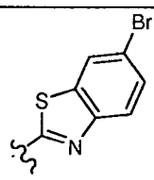
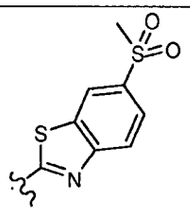
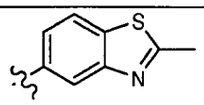
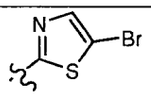
Example Number	R_1	FLIPR α7–HI (EC_{50}, nM)	FLIPR α7–HI (EC_{50}, nM)
16a		3174	+
16b			++
17			++
18		3930	+
19			++
20			++
20a			++
20b		318	++
21			+++

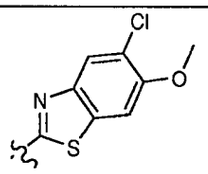
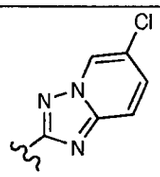
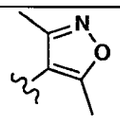
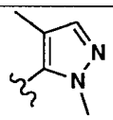
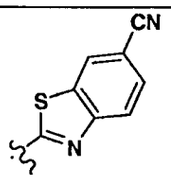
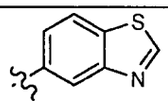
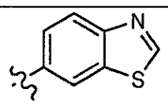
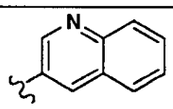
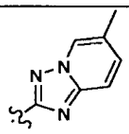
Example Number	R_1	FLIPR α7–HI (EC_{50}, nM)	FLIPR α7–HI (EC_{50}, nM)
22			++
23			+++
24			+++
25		510	++
26			+++
27			+++
28		4010	+
29			++
30			++

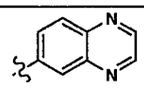
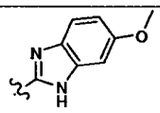
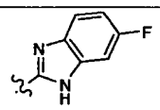
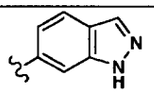
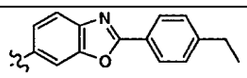
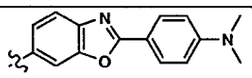
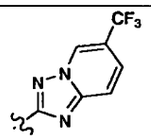
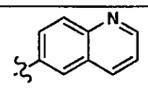
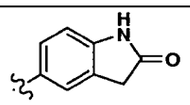
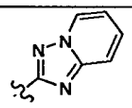
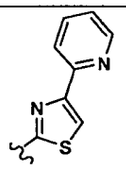
Example Number	R_1	FLIPR α7–HI (EC_{50}, nM)	FLIPR α7–HI (EC_{50}, nM)
31			++
32			++
34			+
35		4035	+
36			++
37			+
38			+++
39			+++
40			+++
41			+++

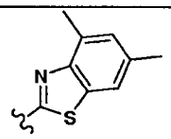
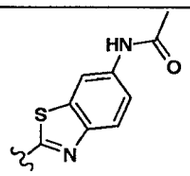
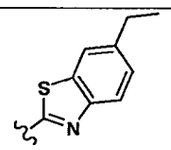
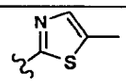
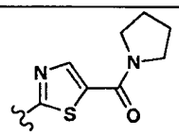
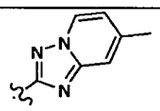
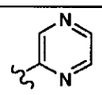
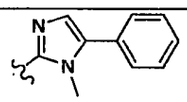
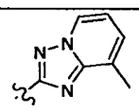
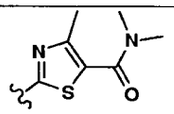
Example Number	R_1	FLIPR α7–HI (EC_{50}, nM)	FLIPR α7–HI (EC_{50}, nM)
42			+++
43			+++
44			++
45			++
46		2000	+
47			+++
48		790	++

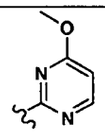
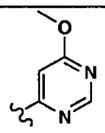
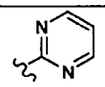
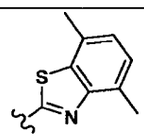
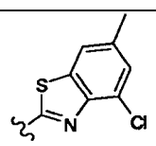
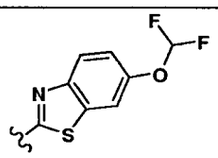
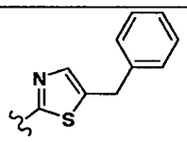
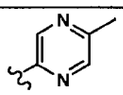
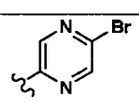
Example Number	R_1	FLIPR α7–HI (EC_{50}, nM)	FLIPR α7–HI (EC_{50}, nM)
49		3330	+
50			+++
51			NT[b]
52		325	++
53			+
54			+
55			+
56			+

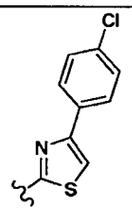
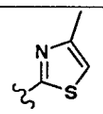
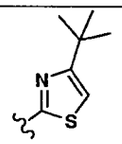
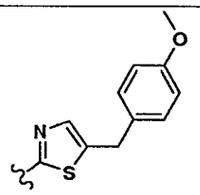
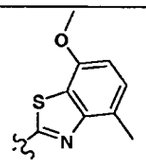
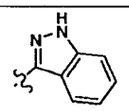
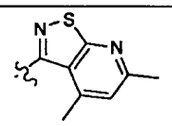
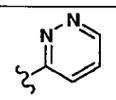
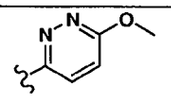
Example Number	R_1	FLIPR α7–HI (EC_{50}, nM)	FLIPR α7–HI (EC_{50}, nM)
57		3900	+
58			+
59		4240	+
60		2550	+
61			++
62			+
63		2600	+
64			+++

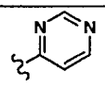
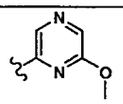
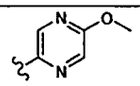
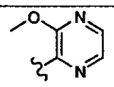
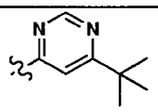
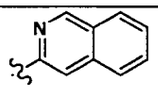
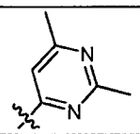
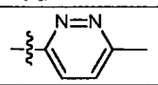
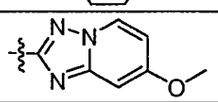
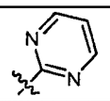
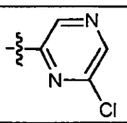
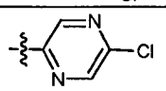
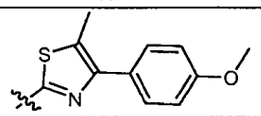
Example Number	R_1	FLIPR α7–HI (EC_{50}, nM)	FLIPR α7–HI (EC_{50}, nM)
65			+
66		360	++
67			+
68			+
70			++
71			+
72			+
73		7550	+
74			+++

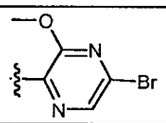
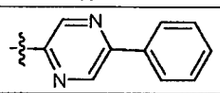
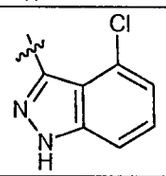
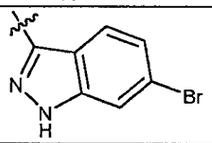
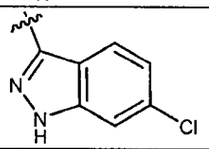
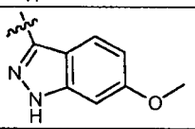
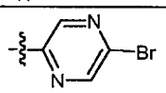
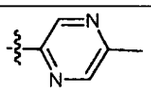
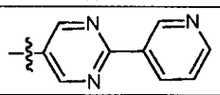
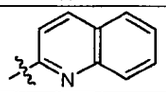
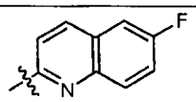
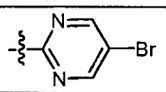
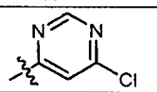
Example Number	R_1	FLIPR α7–HI (EC_{50}, nM)	FLIPR α7–HI (EC_{50}, nM)
75			+
76			++
77		355	++
78			+
81			NT[b]
82			NT[b]
83		240	++
85			+
86			+
87			+++
88			++

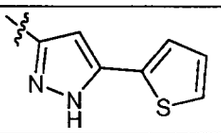
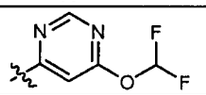
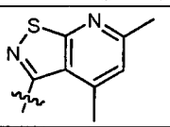
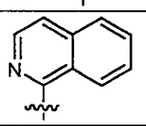
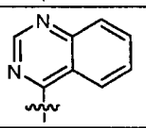
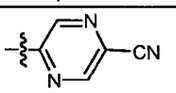
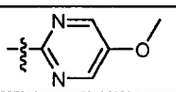
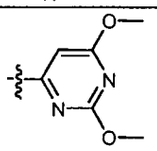
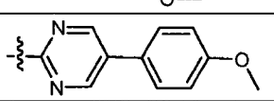
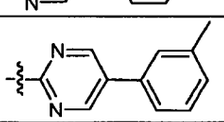
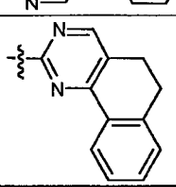
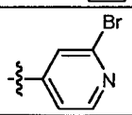
Example Number	R_1	FLIPR α7–HI (EC_{50}, nM)	FLIPR α7–HI (EC_{50}, nM)
89			+++
90		130	++
91			++
92			+++
93			++
94			+++
95			++
96			+
97			++
98			+

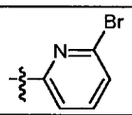
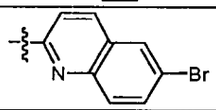
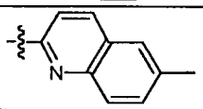
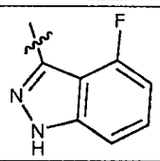
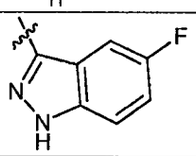
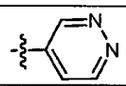
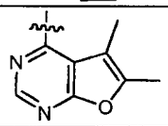
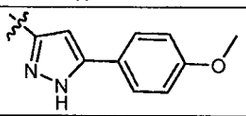
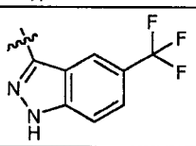
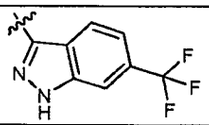
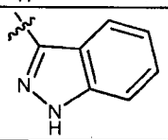
Example Number	R_1	FLIPR α7–HI (EC_{50}, nM)	FLIPR α7–HI (EC_{50}, nM)
99			++
100			+++
101			++
102			+++
103		280	++
104			++
105			++
106			++
107			++

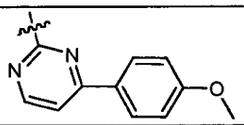
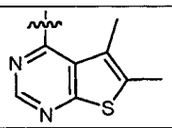
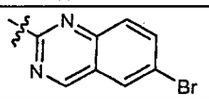
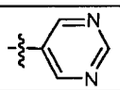
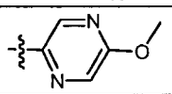
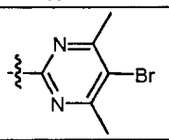
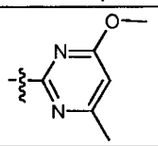
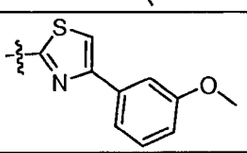
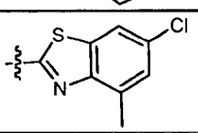
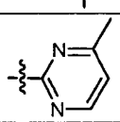
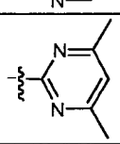
Example Number	R_1	FLIPR α7–HI (EC_{50}, nM)	FLIPR α7–HI (EC_{50}, nM)
108			NT[b]
109			++
110		450	++
111			++
112			+++
113			+++
114			++
115			+
116			+

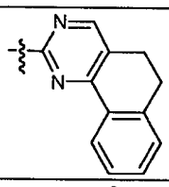
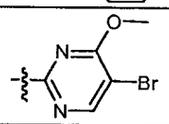
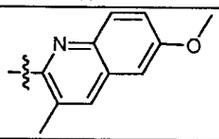
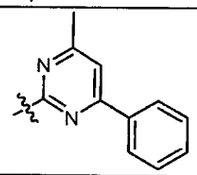
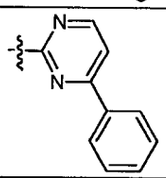
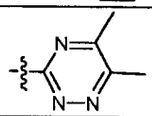
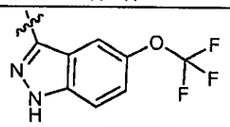
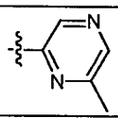
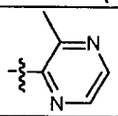
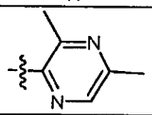
Example Number	R_1	FLIPR α7–HI (EC_{50}, nM)	FLIPR α7–HI (EC_{50}, nM)
117			++
118			+
119			+++
120		875	++
121			+
122			+++
123			+
124			+
125		17	+++
126			+++
127			+
128			+++
129			++

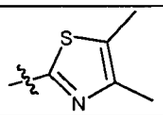
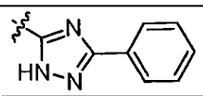
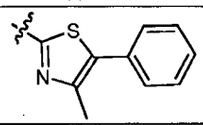
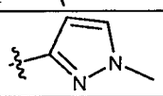
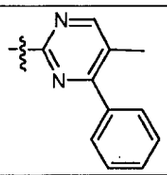
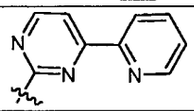
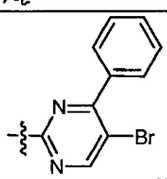
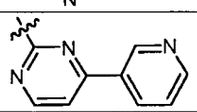
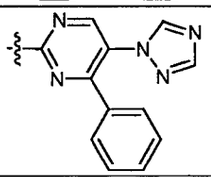
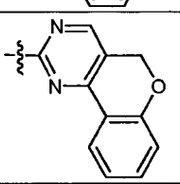
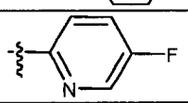
Example Number	R_1	FLIPR α7–HI (EC_{50}, nM)	FLIPR α7–HI (EC_{50}, nM)
130			++
131			+
132			++
133			+++
134			+++
135			+++
136			+++
137		137	++
138			+
139		16	+++
140			++
141		4	+++
142			++

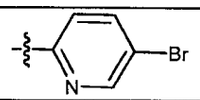
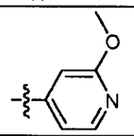
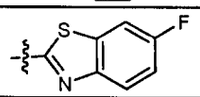
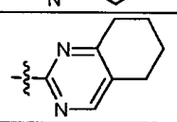
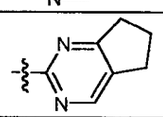
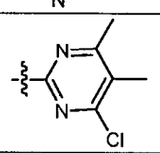
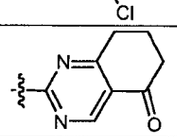
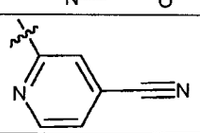
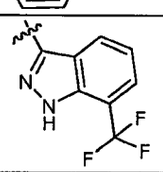
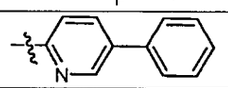
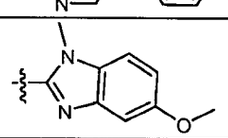
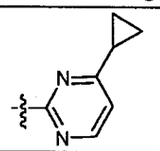
Example Number	R_1	FLIPR α7–HI (EC_{50}, nM)	FLIPR α7–HI (EC_{50}, nM)
143			++
144			+++
145			+
146			++
147			++
148			+
149		17	+++
150			++
151			++
152		233	++
153			++
154			+

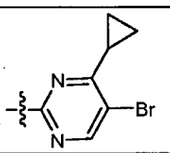
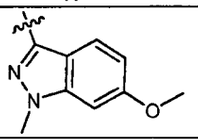
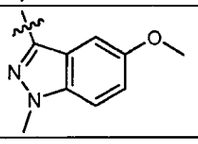
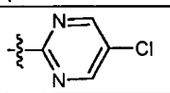
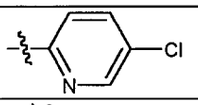
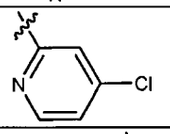
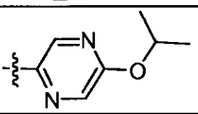
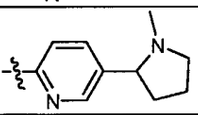
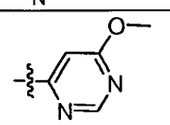
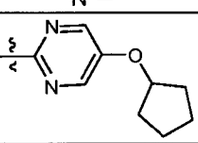
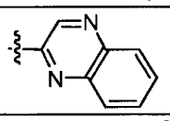
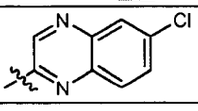
Example Number	R_1	FLIPR α7–HI (EC_{50}, nM)	FLIPR α7–HI (EC_{50}, nM)
155			++
156			++
157			++
158		135	++
159			+++
160			+
161			+
162			+
163			+++
164			++
165		13	+++

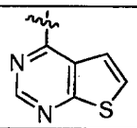
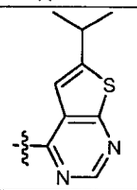
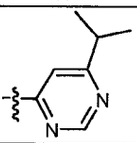
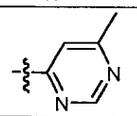
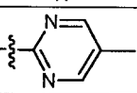
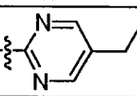
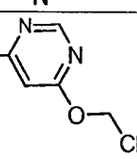
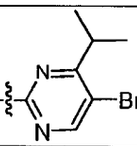
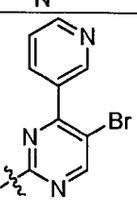
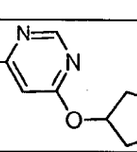
Example Number	R_1	FLIPR α7–HI (EC_{50}, nM)	FLIPR α7–HI (EC_{50}, nM)
166		11	+++
167			+
168			+++
169			+
170			+++
171			+++
172			++
173			++
174		245	++
175			++
176			++

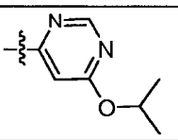
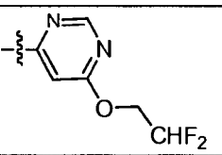
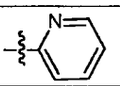
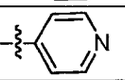
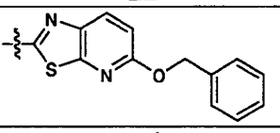
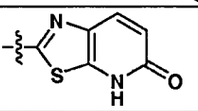
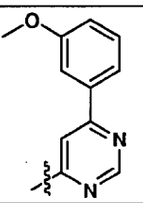
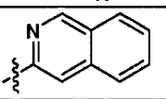
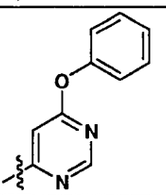
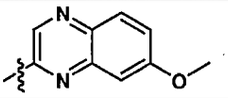
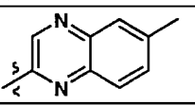
Example Number	R_1	FLIPR α7–HI (EC_{50}, nM)	FLIPR α7–HI (EC_{50}, nM)
177			+++
178		17	+++
179			++
180			++
181		13	+++
182			++
183			+++
184			+
185			+
186			++

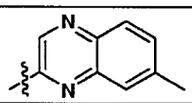
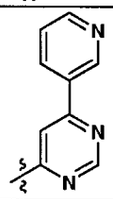
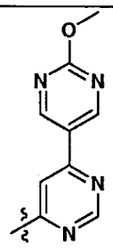
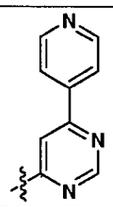
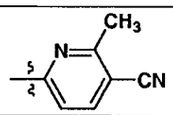
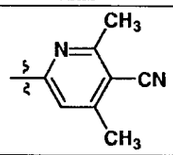
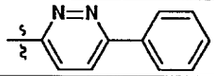
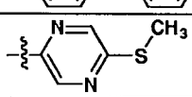
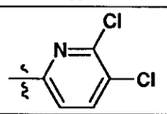
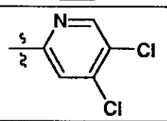
Example Number	R_1	FLIPR α7–HI (EC_{50}, nM)	FLIPR α7–HI (EC_{50}, nM)
187		424	++
188			+
189			++
190			+
191			+++
192			++
193		17	+++
194		18	+++
195			+
196		13	+++
197			+++

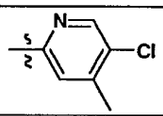
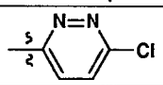
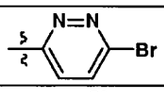
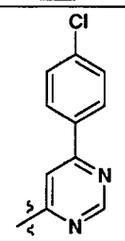
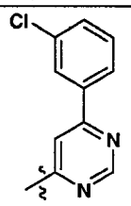
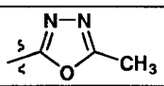
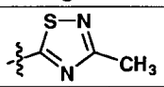
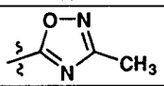
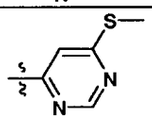
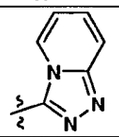
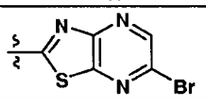
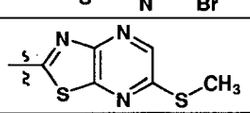
Example Number	R_1	FLIPR α7–HI (EC_{50}, nM)	FLIPR α7–HI (EC_{50}, nM)
198		15	+++
199			+
200			+++
201			+++
202		16	+++
203			+++
204			++
205			++
206			+
207			++
208			+
209			+++

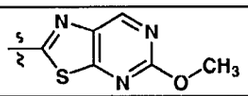
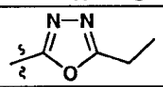
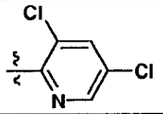
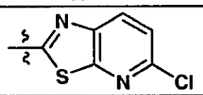
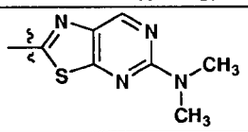
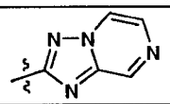
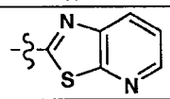
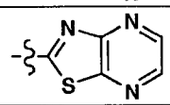
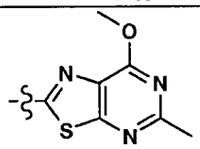
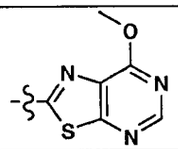
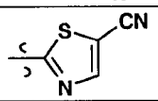
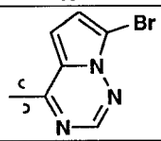
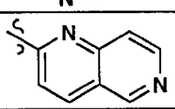
Example Number	R_1	FLIPR α7–HI (EC_{50}, nM)	FLIPR α7–HI (EC_{50}, nM)
210		9	+++
211			++
212			+
213		9	+++
214			+++
215			+++
216			+
217			+
218		285	++
219			+
220			+++
221			++

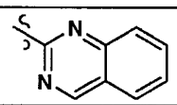
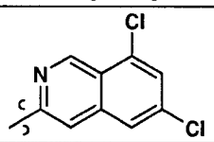
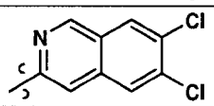
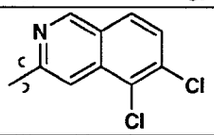
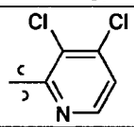
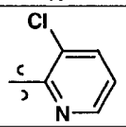
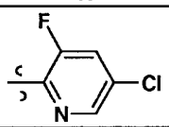
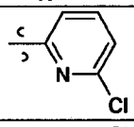
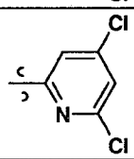
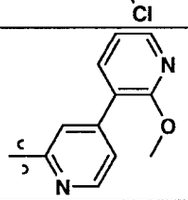
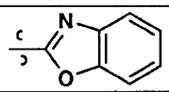
Example Number	R_1	FLIPR α7–HI (EC_{50}, nM)	FLIPR α7–HI (EC_{50}, nM)
222			++
223			++
224			++
225			++
226			+++
227			++
228			+++
229			+++
230			+++
231			++

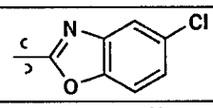
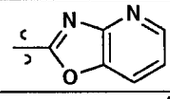
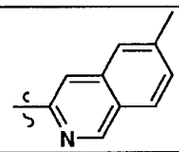
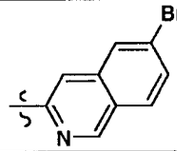
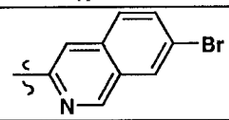
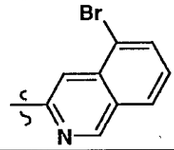
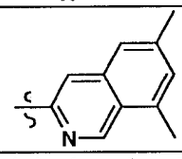
Example Number	R_1	FLIPR α7–HI (EC_{50}, nM)	FLIPR α7–HI (EC_{50}, nM)
232			++
233			+++
234			+++
235			+
236			+
237			+++
238		16	+++
239		15	+++
240			++
241			+
242			++

Example Number	R_1	FLIPR α7–HI (EC_{50}, nM)	FLIPR α7–HI (EC_{50}, nM)
243			+
244			+++
245			+++
246			+++
247			++
248			++
249			+
250			+++
251			+++
252			+++

Example Number	R_1	FLIPR α7–HI (EC_{50}, nM)	FLIPR α7–HI (EC_{50}, nM)
253			+++
254			++
255			++
256			+++
257			+++
258			+
259			+
260			++
261			+++
262			+
263			+++
264			++

Example Number	R_1	FLIPR α7–HI (EC_{50}, nM)	FLIPR α7–HI (EC_{50}, nM)
265			+++
266			+
267			+++
268			+++
269			+
270			+++
271			+++
272			+++
273			+
274			+
275			++
276			+++
277			+++

Example Number	R_1	FLIPR α7–HI (EC_{50}, nM)	FLIPR α7–HI (EC_{50}, nM)
278			+++
279			++
280			
281			+++
282			++
283			++
284			+++
285			++
286			++
287			++
288			+++

Example Number	R_1	FLIPR α7–HI (EC_{50}, nM)	FLIPR α7–HI (EC_{50}, nM)
289			+++
290			+++
291			+++
292			+++
293			++
294			+++
295			++

[a] Activity based on EC_{50} nM values:

+++ = < 100 nM

++ = 100 - 1000 nM

\+ = 1000 - 100000 nM

[b] NT = Not tested

NA = Not active (> 1000000 nM)

Pharmaceutical Compositions and Methods of Treatment

Compounds of formula I bind to alpha 7 and can be useful in treating affective disorders and neurodegenerative disorders. Therefore, another aspect of the invention is a composition comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Another aspect of the invention is the use of a compound of formula I in the manufacture of a medicament for the treatment of affective disorders or neurodegenerative disorders.

Another aspect of the invention is the use of a compound of formula I in the manufacture of a medicament for the treatment of schizophrenia or Alzheimer's Disease.

Another aspect of the invention is a method of treating affective disorders or neurodegenerative disorders comprising administering to a patient a therapeutically effective amount of a compound of formula I.

Another aspect of the invention is a method of treating schizophrenia or Alzheimer's Disease comprising comprising administering to a patient a therapeutically effective amount of a compound of formula I.

Another aspect of the invention is a method of treating schizophrenia comprising administering to a patient a therapeutically effective amount of a compound of formula I.

Another aspect of the invention is a method of treating Alzheimer's Disease comprising comprising administering to a patient a therapeutically effective amount of a compound of formula I.

"Patient" means a person suitable for therapy as understood by practitioners in the field of affective disorders and neurodegenerative disorders.

"Treatment," "therapy," and related terms are used as understood by practitioners in the field of affective disorders and neurodegenerative disorders.

The compounds of this invention are generally given as pharmaceutical compositions comprised of a therapeutically effective amount of a compound or its pharmaceutically acceptable salt and a pharmaceutically acceptable carrier and may contain conventional excipients. Pharmaceutically acceptable carriers are those conventionally known carriers having acceptable safety profiles. Compositions

encompass all common solid and liquid forms including for example capsules, tablets, losenges, and powders as well as liquid suspensions, syrups, elixers, and solutions. Compositions are made using common formulation techniques, and conventional excipients (such as binding and wetting agents) and vehicles (such as water and alcohols) are generally used for compositions. See, for example, *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Easton, PA, 17th edition, 1985.

Solid compositions are normally formulated in dosage units and compositions providing from about 1 to 1000 mg of the active ingredient per dose are preferred. Some examples of dosages are 1 mg, 10 mg, 100 mg, 250 mg, 500 mg, and 1000 mg. Generally, other agents will be present in a unit range similar to agents of that class used clinically. Typically, this is 0.25-1000 mg/unit.

Liquid compositions are usually in dosage unit ranges. Generally, the liquid composition will be in a unit dosage range of 1-100 mg/mL. Some examples of dosages are 1 mg/mL, 10 mg/mL, 25 mg/mL, 50 mg/mL, and 100 mg/mL. Generally, other agents will be present in a unit range similar to agents of that class used clinically. Typically, this is 1-100 mg/mL.

The invention encompasses all conventional modes of administration; oral and parenteral methods are preferred. Generally, the dosing regimen will be similar to other agents used clinically. Typically, the daily dose will be 1-100 mg/kg body weight daily. Generally, more compound is required orally and less parenterally. The specific dosing regime, however, will be determined by a physician using sound medical judgement.

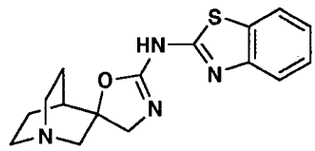
DESCRIPTION OF SPECIFIC EMBODIMENTS

^{1}H-NMR spectra were run on a Bruker 500, 400, or 300 MHz instrument and chemical shifts were reported in ppm (δ) with reference to tetramethylsilane (δ=0.0). All evaporations were carried out under reduced pressure. Unless otherwise stated, LC/MS analyses were carried out on a Shimadzu instrument using a Phenomenex-Luna 4.6x50mm S 10 reverse phase column employing a flow rate of 4 mL/min using a 0.1% TFA in methanol/water gradient [0-100% in 3 min, with 4 min run time] and a UV detector set at 220 nm or Gemini C18 4.6x50mm 5u reverse phase column

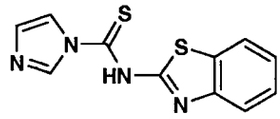
employing a flow rate of 5 mL/min using a 10 mM ammonium acetate acetonitrile/water gradient [5-95% in 3 min, with 4 min run time] and a UV detector set at 220 nm (negative-ion mass spectrometry). Unless otherwise stated, purification could be done by preparative C-18 column employing gradients of methanol-water containing 0.1% of trifluoroacetic acid (TFA), and using a Shimadzu High Performance Liquid Preparative Chromatographic System employing an XTERRA 30x100 mm S5 column at 40 mL/min flow rate with a 12 min gradient.

EXAMPLE 1

N-(benzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

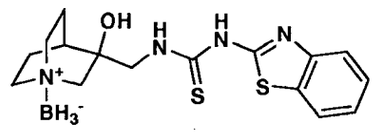


Step A: N-(Benzo[d]thiazol-2-yl)-^{1}H-imidazole-1-carbothioamide



To benzo[d]thiazol-2-amine (20 g, 133 mmol) in acetonitrile (300 mL) was added 1,1'- thiocarbonyldiimidazole (30.8 g, 173 mmol). The reaction was stirred at 50 °C for 24 hours. The reaction was cooled to room temperature and the precipitate was filtered and washed with acetonitrile (2 x 50 mL). The yellow powder was dried in a vacuum oven (40°C) for 2 hours. The product, N-(benzo[d]thiazol-2-yl)-^{1}H-imidazole-1-carbothioamide (28.9 g, 111 mmol), was taken directly to the next step without any further purification.

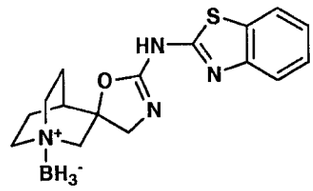
Step B: (3-((3-Benzo[d]thiazol-2-ylthioureido)methyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate



To N-(benzo[d]thiazol-2-yl)-^{1}H-imidazole-1-carbothioamide (9.2 g, 35 mmol) in N,N-dimethylformamide (100 mL) was added (3-(aminomethyl)-3-

hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (6.0 g, 35 mmol) which was synthesized according to Swain C.J., et. al., *J. Med. Chem.*, **35**:1019-1031 (1992). The reaction was stirred at 65 °C for 15 hours. The reaction was cooled and concentrated to yield the crude product. The crude material was purified via flash chromatography (50-100% ethyl acetate/hexanes) yielding the first spot/fractions detected by TLC as the product. The fractions were combined and concentrated to yield (3-((3-benzo[d]thiazol-2-ylthioureido)methyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (10.6 g, 29.1 mmol, 83 % yield) as an off-white powder. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.88 (s, 1 H), 10.30 (s, 1 H), 7.94 (d, *J*=7.63 Hz, 1 H), 7.55 - 7.74 (m, 1 H), 7.37 - 7.53 (m, *J*=7.32, 7.32 Hz, 1 H), 7.16 - 7.37 (m, *J*=7.63, 7.63 Hz, 1 H), 5.39 (s, 1 H), 3.85 (d, 2 H), 2.65 - 3.08 (m, 6 H), 1.99 - 2.22 (m, 1 H), 1.79 - 1.97 (m, 2 H), 1.66 - 1.79 (m, 1 H), 1.08 - 1.63 (m, 4 H). MS (LC/MS) R.T. = 3.40; $[M+H]^+$ = 363.1

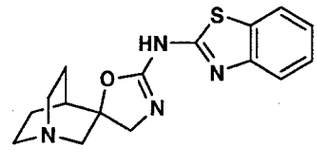
Step C: (2-(Benzo[d]thiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate



To (3-((3-benzo[d]thiazol-2-ylthioureido)methyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (10.6 g, 29.1 mmol) in N,N-dimethylformamide (100 mL) was added N,N'-diisopropylcarbodiimide (11.4 mL, 72.8 mmol). The reaction was stirred at 70 °C for 4 hours. The reaction was concentrated to yield a crude residue. A small amount of ethyl acetate (20 mL) was added and the suspension was sonicated. The solids were filtered and washed with small portions of ethyl acetate (2 x 10 mL). The solids were dried in a vacuum oven (80 °C) to yield (2-(benzo[d]thiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate (6.83 g, 20.8 mmol, 72 % yield) as a white powder. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.09 (br. s., 1 H) 7.81 (d, *J*=7.63 Hz, 1 H) 7.63 (d, *J*=7.93 Hz, 1 H) 7.30 - 7.40 (m, 1 H) 7.15 - 7.24 (m, 1 H) 3.88 (d, *J*=10.38 Hz, 1 H) 3.77 (d, *J*=10.38 Hz, 1 H) 3.25 - 3.37 (m, 1 H) 3.17 (dd, *J*=14.95,

1.83 Hz, 1 H) 2.99 - 3.10 (m, 1 H) 2.79 - 2.98 (m, 3 H) 2.27 (br. s., 1 H) 1.98 - 2.11 (m, 1 H) 1.71 - 1.88 (m, 3 H) 1.45 (br. s., 3 H). MS (LC/MS) R.T. = 2.44; $[M+H-BH_3]^+ = 315.1$.

Step D: N-(Benzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



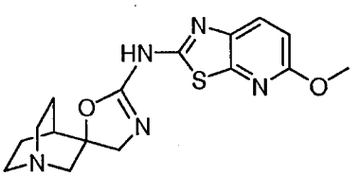
To (2-(benzo[d]thiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate (6.6 g, 20.1 mmol) in acetone (9 mL) was added 3M HCl (50.3 mL, 151 mmol). The reaction was stirred at room temperature for 4 hours. The reaction was complete by TLC (lower spot). Ethyl acetate was added and the aqueous layer was then separated. The aqueous layer was neutralized with 1N sodium hydroxide. The product was extracted with ethyl acetate (2 x 150 mL). The organics were combined, dried with magnesium sulfate, filtered, and concentrated *in vacuo* to afford a white powder. A small amount of ethyl acetate (20 mL) was added to the powder. The solids were sonicated and filtered to yield racemic N-(benzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (5.13 g, 16.3 mmol, 81 % yield) as a white powder. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.02 (br. s., 1 H) 7.79 (d, *J*=7.02 Hz, 1 H) 7.62 (d, *J*=7.63 Hz, 1 H) 7.29 - 7.38 (m, 1 H) 7.15 - 7.22 (m, 1 H) 3.90 (d, *J*=10.07 Hz, 1 H) 3.65 (d, *J*=10.07 Hz, 1 H) 2.98 - 3.10 (m, 2 H) 2.73 - 2.88 (m, 2 H) 2.67 (t, *J*=7.78 Hz, 2 H) 2.07 (br. s., 1 H) 1.93 (br. s., 1 H) 1.42 - 1.67 (m, 3 H). MS (LC/MS) R.T. = 1.15; $[M+H]^+ = 315.3$.

The enantiomers were separated using a Chiralpak AD-H (3x25 cm, 5 uM) column with a mobile phase consisting of CO_2/(methanol/ACN/DEA = 70/30/0.1 (v/v/v)) = 77/23. The wavelength was set at 300 nM. The separated peaks were concentrated *in vacuo* to yield white powders. The first peak off the column was (S)-N-(benzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (1.45 g, 4.61 mmol, 29.4 % yield). (1a; S-isomer): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.03 (br. s., 1 H) 7.78 (d, *J*=7.05 Hz, 1 H) 7.61 (d, *J*=7.55 Hz, 1 H) 7.27 - 7.37

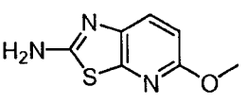
(m, 1 H) 7.11 - 7.23 (m, 1 H) 3.89 (d, *J*=10.07 Hz, 1 H) 3.64 (d, *J*=10.07 Hz, 1 H) 2.96 - 3.09 (m, 2 H) 2.71 - 2.88 (m, 2 H) 2.66 (t, *J*=7.81 Hz, 2 H) 2.02 - 2.11 (m, 1 H) 1.85 - 1.97 (m, 1 H) 1.41 - 1.65 (m, 3 H). MS (LC/MS) R.T. = 1.15; $[M+H]^+$ = 315.3. Optical rotation (1.23 mg/mL, DMSO) = +5.20°. The second peak was (R)-N-(benzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (1.21 g, 3.85 mmol, 24.5 % yield). (1b; R-isomer): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.02 (br. s., 1 H) 7.79 (d, *J*=7.32 Hz, 1 H) 7.62 (d, *J*=7.63 Hz, 1 H) 7.33 (t, *J*=7.63 Hz, 1 H) 7.18 (t, *J*=7.48 Hz, 1 H) 3.90 (d, *J*=10.07 Hz, 1 H) 3.65 (d, *J*=10.07 Hz, 1 H) 2.98 - 3.10 (m, 2 H) 2.73 - 2.87 (m, 2 H) 2.67 (t, *J*=7.63 Hz, 2 H) 2.08 (br. s., 1 H) 1.93 (br. s., 1 H) 1.42 - 1.67 (m, 3 H). MS (LC/MS) R.T. = 1.15; $[M+H]^+$ = 315.3; Optical rotation (3.9 mg/mL, DMSO) = -3.92°.

EXAMPLE 2

N-(5-Methoxythiazolo[5,4-b]pyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



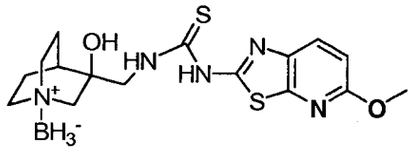
Step A: 5-Methoxythiazolo[5,4-b]pyridin-2-amine



In a 500ml, 3-neck flask equipped with a mechanical stirrer, dropping funnel and thermometer, acetic acid (100 mL) was added and cooled in an ice bath. Potassium thiocyanate (40 g, 412 mmol) and 6-methoxypyridin-3-amine (6.2 g, 49.9 mmol) were added to the reaction mixture. The reaction was cooled in an ice-salt bath until the reaction temperature reached <0 °C. A solution of bromine (8 mL, 156 mmol) in acetic acid (30.0 mL) was added dropwise over 2 hours at a rate that maintained the reaction temperature <0 °C. Mechanical stirring was required. After the addition was complete, the mixture was left to stir and allowed to slowly warm to room temperature overnight. Water (30 mL) was then added and the mixture was heated to 85 °C in an oil bath. This mixture was then filtered while still hot. The

orange filter cake was returned to the reaction flask, and an additional 50 ml acetic acid was added. The mixture was heated again to 85 °C, and then filtered while still hot once more. The combined filtrates were cooled in an ice bath and neutralized to pH 8 with conc. ammonium hydroxide. A purple precipitate formed which was then collected by filtration to afford 5 g of crude material. This crude material was recrystallized from methanol (40 mL) to yield 5-methoxythiazolo[5,4-b]pyridin-2-amine (3 g, 16.55 mmol, 33.1 % yield) as purple crystals. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.60 (1 H, d, J=8.42 Hz), 7.41 (2 H, s), 6.67 (1 H, d, J=8.78 Hz), 3.81 (3 H, s).

Step B: (3-Hydroxy-3-((3-(5-methoxythiazolo[5,4-b]pyridin-2-yl)thioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate

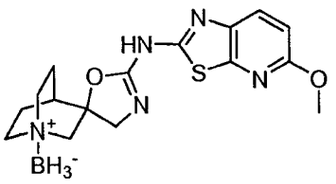


5-Methoxythiazolo[5,4-b]pyridin-2-amine (2.4g, 13.24 mmol) was divided among 5 x 20 mL screw-cap vials. To each vial was added acetonitrile (10 mL) and thiocarbonyl diimidazole (600 mg). All vials were heated at 60 °C overnight. The reaction vials were combined and concentrated to yield crude N-(5-methoxythiazolo[5,4-b]pyridin-2-yl)-1H-imidazole-1-carbothioamide product.

This crude product was suspended in N,N-dimethylformamide (50ml) and (3-(aminomethyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (2.7g, 15.88 mmol) was then added. The reaction was heated at 70 °C for 4 hours. LC/MS showed essentially complete conversion. The reaction was cooled to room temperature and then poured into water. The product was extracted first with toluene, and then with chloroform. The organics were combined, washed with water and brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford crude material. This crude material was purified via flash chromatography (20-100% ethyl acetate-hexane). The product fractions were collected and concentrated *in vacuo* to afford (3-hydroxy-3-((3-(5-methoxythiazolo[5,4-b]pyridin-2-yl)thioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (1.36 g, 3.46 mmol, 26.1 % yield). ^{1}HNMR showed a 1: 0.55 molar ratio of (3-hydroxy-3-

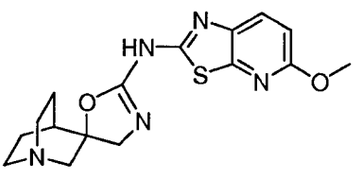
((3-(5-methoxythiazolo[5,4-b]pyridin-2-yl)thioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (1.36 g, 3.46 mmol, 26.1 % yield) to 5-methoxythiazolo[5,4-b]pyridin-2-amine (.34 g, 1.876 mmol, 14.17 % yield). The mixture was taken directly to the next step without any further purification. MS (LC/MS) R.T. = 3.23; $[M+H]^+$ = 392.1.

Step C: (2-(5-Methoxy-3a,7a-dihydrothiazolo[5,4-b]pyridin-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate



To (3-hydroxy-3-((3-(5-methoxythiazolo[5,4-b]pyridin-2-yl)thioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (1.7 g, 3.46 mmol) in N,N-dimethylformamide (10 mL) was added N,N'-diisopropylcarbodiimide (1.89 mL, 12.10 mmol). The reaction was stirred at 70 °C for 2 hours. The mixture was cooled and then poured into water. The product was extracted with toluene and chloroform. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford crude material. This solid material was triturated with ether. The solids were then filtered and dried to yield (2-(5-methoxy-3a,7a-dihydrothiazolo[5,4-b]pyridin-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate (700 mg, 1.94 mmol, 56.0 % yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.98 (1 H, s), 7.86 (1 H, d, *J*=8.78 Hz), 6.81 (1 H, d, *J*=8.42 Hz), 3.87 (3 H, s), 3.83 (1 H, s), 3.68 - 3.78 (1 H, m), 3.31 (1 H, s), 3.15 - 3.29 (1 H, m), 2.78 - 3.14 (4 H, m), 2.26 (1 H, br. s.), 2.04 (1 H, br. s.), 1.63 - 1.89 (3 H, m).

Step D: N-(5-Methoxythiazolo[5,4-b]pyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



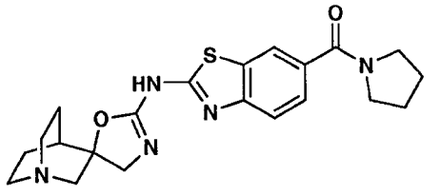
To (2-(5-methoxythiazolo[5,4-b]pyridin-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate (780 mg, 2.17 mmol) in acetone (10 mL) was added 3M HCl (10 mL, 329 mmol). The reaction was stirred at room temperature for 2 hours. Chloroform and water were added and the aqueous layer was then separated. The aqueous layer was neutralized with sodium bicarbonate. The product was extracted with chloroform (2x). The organics were combined, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford racemic N-(5-methoxythiazolo[5,4-b]pyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (588 mg, 1.70 mmol, 78 % yield) as a white powder. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.90 (1 H, br. s.), 7.82 - 7.86 (1 H, m), 6.80 (1 H, d, *J*=8.85 Hz), 3.84 - 3.89 (4 H, m), 3.61 (1 H, d, *J*=10.07 Hz), 3.03 (2 H, d, *J*=5.19 Hz), 2.73 - 2.86 (2 H, m), 2.66 (2 H, t, *J*=7.78 Hz), 2.07 (1 H, br. s.), 1.92 (1 H, br. s.), 1.45 - 1.65 (3 H, m). MS (LC/MS) R.T. = 1.29; $[M+H]^+$ = 346.1.

The enantiomers were separated using a Chiralpak AD-H (30 x 250mm, 5μm) column with a mobile phase consisting of 35% methanol (0.1% DEA) in CO_2. The wavelength was set at 300 nM. The separated peaks were concentrated *in vacuo* to yield white powders. The first peak off the column was (S)-N-(5-methoxythiazolo[5,4-b]pyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (212 mg, 0.61 mmol, 36.1 % yield). (2a; S-isomer): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.89 (1 H, br. s.), 7.84 (1 H, d, *J*=8.85 Hz), 6.77 - 6.82 (1 H, m), 3.84 - 3.89 (4 H, m), 3.61 (1 H, d, *J*=10.07 Hz), 3.03 (2 H, d, *J*=5.19 Hz), 2.74 - 2.86 (2 H, m), 2.66 (2 H, t, *J*=7.63 Hz), 2.06 (1 H, br. s.), 1.92 (1 H, br. s.), 1.44 - 1.65 (3 H, m). MS (LC/MS) R.T. = 1.47; $[M+H]^+$ = 346.2. Optical rotation (3.57 mg/ml, DMSO) = -2.58°. The second peak was (R)-N-(5-methoxythiazolo[5,4-b]pyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (242 mg, 0.70 mmol, 41.2 % yield). (2b; R-isomer): ^{1}H

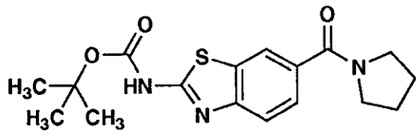
NMR (500 MHz, DMSO-d_6) δ ppm 8.89 (1 H, br. s.), 7.84 (1 H, d, *J*=8.85 Hz), 6.79 (1 H, d, *J*=8.55 Hz), 3.82 - 3.90 (4 H, m), 3.61 (1 H, d, *J*=10.07 Hz), 3.03 (2 H, d, *J*=5.49 Hz), 2.74 - 2.86 (2 H, m), 2.66 (2 H, t, *J*=7.78 Hz), 2.06 (1 H, br. s.), 1.92 (1 H, br. s.), 1.42 - 1.67 (3 H, m). MS (LC/MS) R.T. = 1.30; $[M+H]^+$ = 346.2. Optical rotation (3.29 mg/ml, DMSO) = +2.43°.

EXAMPLE 3

(2-(5H-1'-Azaspiro[oxazole-4,3'-bicyclo[2.2.2]octane]-2-ylamine)benzo[d]thiazol-6-yl)pyrrolidin-1-yl)methanone

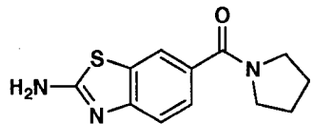


Step A: tert-Butyl 6-(pyrrolidine-1-carbonyl)benzo[d]thiazol-2-ylcarbamate



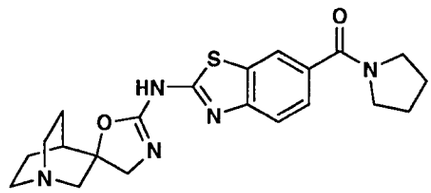
In a 250 ml flask was added 2-(*tert*-butoxycarbonyl-amino)benzo[d]thiazole-6-carboxylic acid (1.0 g, 3.4 mmol) and pyrrolidine (0.559 mL, 6.8 mmol) in tetrahydrofuran (50 mL). To this solution was added EDC (1.3 g, 6.8 mmol), 1-hydroxybenzotriaxole (1.041 g, 6.8 mmol) and Hunig's Base (2.37 mL, 13.59 mmol). The reaction was stirred at 25 °C for 1 hour. The reaction was then poured into water and dichloromethane. The water was extracted 3 times with dichloromethane and the organic layers were combined and concentrated. The residue was taken up in a small amount of dichloromethane and precipitated out with diethyl ether/hexanes. The flask was put in the freezer for 1 hour and filtered. The white precipitate was collected to yield *tert*-butyl 6-(pyrrolidine-1-carbonyl)benzo[d]thiazol-2-ylcarbamate (1.09 g, 3.14 mmol, 92 % yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.95 (s, 1 H), 8.14 (s, 1 H), 7.61 - 7.77 (m, *J*=8.39, 1.98 Hz, 1 H), 7.46 - 7.63 (m, 1 H), 3.39 - 3.63 (m, 4 H), 1.74 - 2.00 (m, 4 H), 1.45 - 1.62 (m, 9 H). MS (LC/MS) R.T. = 3.40; $[M+H]^+$ = 363.1.

Step B: (2-Aminobenzo[d]thiazol-6-yl)(pyrrolidin-1-yl)methone



tert-Butyl 6-(pyrrolidine-1-carbonyl)benzo[d]thiazol-2-ylcarbamate (1.09 g, 3.14 mmol) was dissolved in dichloromethane (10 mL) and TFA (3 mL, 38.9 mmol) and the reaction was stirred at 25 °C overnight. The reaction was poured into a separatory funnel and carefully neutralized with sodium bicarbonate. The liquid was extracted 3 times with chloroform/methanol (4:1). The organic layers were concentrated to a white residue and triturated in diethyl ether. The precipitate was collected to yield (2-aminobenzo[d]thiazol-6-yl)(pyrrolidin-1-yl)methone (0.497 g, 2.0 mmol, 64 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.86 (d, *J*=1.51 Hz, 1 H), 7.65 (s, 2 H), 7.35 - 7.46 (m, 1 H), 7.26 - 7.35 (m, 1 H), 3.41 - 3.57 (m, 4 H), 1.64 - 1.97 (m, 4 H). MS (LC/MS) R.T. = 1.39; $[M+H]^+$ = 248.1.

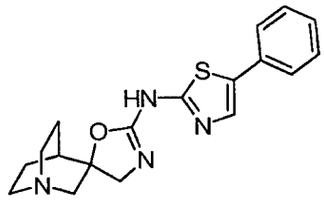
Step C: (2-(5H-1'-Azaspiro[oxazole-4,3'-bicyclo[2.2.2]octane]-2-ylamine)benzo[d]thiazol-6-yl)pyrrolidin-1-yl)methanone



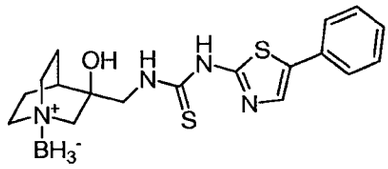
(2-(5H-1'-Azaspiro[oxazole-4,3'-bicyclo[2.2.2]octane]-2-ylamine)benzo-[d]thiazol-6-yl)pyrrolidin-1-yl)methanone was prepared by following the general procedures of Example 1, Steps A-D and using (2-aminobenzo[d]thiazol-6-yl)(pyrrolidin-1-yl)methone (Example 3, Step B) as the starting material. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.05 (br. s., 1 H) 7.99 (d, *J*=1.76 Hz, 1 H) 7.60 (d, *J*=8.31 Hz, 1 H) 7.48 (dd, *J*=8.31, 1.76 Hz, 1 H) 3.90 (d, *J*=10.07 Hz, 1 H) 3.65 (d, *J*=10.07 Hz, 1 H) 3.42 - 3.52 (m, 4 H) 3.04 (s, 2 H) 2.75 - 2.87 (m, 2 H) 2.67 (t, *J*=7.81 Hz, 2 H) 2.08 (br. s., 1 H) 1.76 - 1.98 (m, 5 H) 1.41 - 1.65 (m, 3 H). MS (LC/MS) R.T. = 1.33; $[M+H]^+$ = 412.2.

EXAMPLE 4

N-(5-Phenylthiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

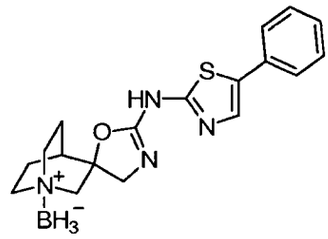


Step A: (3-Hydroxy-3-((3-(5-phenylthiazol-2-yl)thioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate



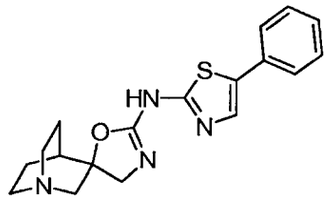
To 5-phenylthiazol-2-amine (0.52 g, 2.9 mmol) in acetonitrile (6 mL) was added 1,1'-thiocarbonyldiimidazole (0.68 g, 3.8 mmol). The reaction mixture was stirred at 65 °C for 2 hours. The precipitate was filtered and washed with acetonitrile (2 x 20 mL) to yield intermediate N-(5-phenylthiazol-2-yl)-^{1}H-imidazole-1-carbothioamide. The intermediate was taken up in N,N-dimethylformamide (30 mL) and treated with (3-(aminomethyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (0.5 g, 2.9 mmol). The reaction mixture was stirred for 5 hours at 65 °C. The reaction was concentrated *in vacuo* and purified via silica gel chromatography (30-100% ethyl acetate/hexane). The product fractions were combined and concentrated *in vacuo* to yield (3-hydroxy-3-((3-(5-phenylthiazol-2-yl)thioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (.85 g, 2.19 mmol, 74.4 % yield) as a white powder. LC/MS confirmed product with loss of BH_3 in the LC/MS conditions: retention time 3.26 (M+1-BH_3= 375.33).

Step B: (2-(5-Phenylthiazol-2-ylamino)-4H-1'-ammoniospiro-[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate



To (3-hydroxy-3-((3-(5-phenylthiazol-2-yl)thioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (0.8 g, 2.1 mmol) in N,N-dimethylformamide (20 mL) was added N,N'-diisopropylcarbodiimide (1.12 mL, 7.2 mmol). The reaction mixture was stirred at 70 °C for 4 hours. The reaction was concentrated *in vacuo* and purified via silica gel chromatography (40-100% ethyl acetate/hexane). The combined product fractions were concentrated *in vacuo* to yield (2-(5-phenylthiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate (0.51 g, 1.44 mmol, 70 % yield) as a white powder. LCMS- mass corresponds to BH_3 lost in the LC/MS conditions: retention time 2.46 (M+1-BH_3 = 341.36).

Step C: N-(5-Phenylthiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



To (2-(5-phenylthiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate (0.56 g, 1.58 mmol) in acetone (9 mL) was added 3 M HCl (3.95 mL, 11.86 mmol). The reaction mixture was stirred at room temperature for 4 hours and then neutralized with 1N sodium hydroxide. The product was extracted with ethyl acetate (2 x 20 mL), followed by chloroform (2 x 20 mL). The organics were combined, dried with magnesium sulfate, filtered, and concentrated *in vacuo* to afford a white powder. The crude product was purified by reverse phase HPLC (Phenomenex Luna 30 X 100mm; 220 wavelength; gradient

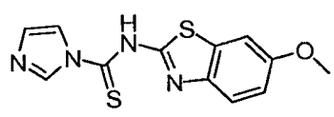
time 10 min; flow rate 40 ml/min; solvent A; 10% methanol-90% water-0.1% TFA, solvent B; 90% methanol-10% water-0.1% TFA). The fractions were combined, neutralized with 1N sodium hydroxide and extracted with ethyl acetate (2 x 30 mL) and chloroform (2 x 30 mL). The organics were combined, dried with magnesium sulfate, filtered and concentrated *in vacuo* to yield N-(5-phenylthiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.4 g, 1.175 mmol, 74.3 % yield) as a white powder. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.63 (1 H, br. s.), 7.71 (1 H, s), 7.52 (2 H, d, *J*=7.32 Hz), 7.37 (2 H, t, *J*=7.78 Hz), 7.25 (1 H, t, *J*=7.32 Hz), 3.82 (1 H, d, *J*=10.07 Hz), 3.57 (1 H, d, *J*=9.77 Hz), 3.02 (2 H, d, *J*=4.27 Hz), 2.79 (2 H, t, *J*=7.63 Hz), 2.66 (2 H, t, *J*=7.63 Hz), 2.04 (1 H, br. s.), 1.92 - 1.97 (1 H, m), 1.44 - 1.65 (3 H, m). MS (LC/MS) R.T. = 1.52; $[M+H]^+$ = 341.3.

The enantiomers were separated using a Chiralpak AS-H (30 x 250mm, 5μm) column with a mobile phase consisting of 30% methanol (0.1%DEA) in CO_2 and UV monitored at 300 nm. The separated peaks were concentrated *in vacuo* to yield white powders. The first peak off the column yielded 0.4 g, 1.15 mmol, 32.7 % (4a, S-isomer): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.69 (s, 1 H), 7.69 - 7.87 (m, 1 H), 7.52 - 7.66 (m, *J*=10.99 Hz, 2 H), 7.37 - 7.51 (m, 2 H), 7.21 - 7.38 (m, 2 H), 3.52 - 4.00 (m, 2 H), 2.98 - 3.23 (m, 2 H), 2.78 - 2.94 (m, 2 H), 2.64 - 2.78 (m, 2 H), 1.88 - 2.19 (m, *J*=60.43 Hz, 2 H), 1.40 - 1.77 (m, 3 H). MS (LC/MS) R.T. = 1.77; $[M+H]^+$ = 341.1. The second peak yielded 0.4 g, 1.15 mmol, 32.7 %. (4b, R-isomer):L M.P. 187-9 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.64 (s, 1 H), 7.62 - 7.84 (m, 1 H), 7.44 - 7.61 (m, 2 H), 7.33 - 7.46 (m, 2 H), 7.18 - 7.31 (m, 1 H), 3.50 - 3.99 (m, 2 H), 2.94 - 3.14 (m, 2 H), 2.74 - 2.91 (m, 2 H), 2.61 - 2.72 (m, 2 H), 2.05 (s, 1 H), 1.82 - 2.00 (m, 1 H), 1.34 - 1.72 (m, 3 H). MS (LC/MS) R.T. = 1.78; $[M+H]^+$ = 341.1.

EXAMPLE 5

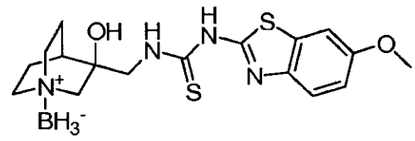
N-(6-Methoxybenzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

Step A: N-(6-Methoxybenzo[d]thiazol-2-yl)-^{1}H-imidazole-1-carbothioamide



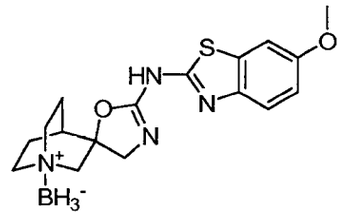
To 6-methoxybenzo[d]thiazol-2-amine (0.53 g, 2.94 mmol) in acetonitrile (20 mL) was added 1,1'-thiocarbonyldiimidazole (0.681 g, 3.82 mmol). The reaction mixture was stirred at 65 °C for 24 hours. The precipitate was filtered and washed with acetonitrile (2 x 20 mL) to yield the product. The product was taken directly to the next step without any further purification or characterization.

Step B: (3-Hydroxy-3-((3-(6-methoxybenzo[d]thiazol-2-yl)-thioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate



To N-(6-methoxybenzo[d]thiazol-2-yl)-^{1}H-imidazole-1-carbothioamide (.82 g, 2.82 mmol) in N,N-dimethylformamide (20 mL) was added (3-(aminomethyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (0.48 g, 2.82 mmol). The reaction mixture was stirred at 65°C for 6 hours. The reaction was concentrated *in vacuo* and then purified by silica gel chromatography (30%-100% ethyl acetate/hexanes). The pure fractions were combined and concentrated to yield (3-hydroxy-3-((3-(6-methoxybenzo[d]thiazol-2-yl)thioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (0.7 g, 1.78 mmol, 63.2 % yield) as a white powder. LC/MS confirmed product as loss of BH_3 in the LC/MS conditions: retention time 3.11 (M+1-BH_3 = 379.4).

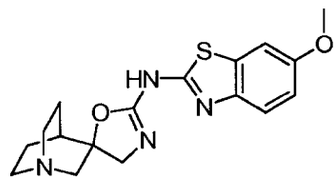
Step C: (2-(6-Methoxybenzo[d]thiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate



To (3-hydroxy-3-((3-(6-methoxybenzo[d]thiazol-2-yl)thioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (0.68 g, 1.73 mmol) in N,N-dimethylformamide (20 mL) was added N,N'-diisopropylcarbodiimide (0.95 mL, 6.1 mmol). The reaction mixture was stirred at 70 °C for 4 hours. The reaction was

concentrated and purified via silica gel chromatography (40-100% ethyl acetate/hexane). The product fractions were combined and concentrated *in vacuo* to yield (2-(6-methoxybenzo[d]thiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate (0.35 g, 0.98 mmol, 56.4 % yield) as a white powder. LC/MS $MH^+ - BH_3 = 345.2$.

Step D: N-(6-Methoxybenzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



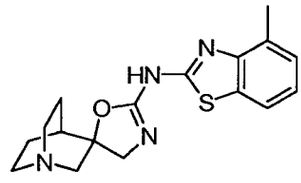
To (2-(6-methoxybenzo[d]thiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate (0.33 g, 0.921 mmol) in acetone (9 mL) was added 3 M HCl (2.30 mL, 6.91 mmol). The reaction was stirred at room temperature for 4 hours and then neutralized with 1N sodium hydroxide. The product was extracted with ethyl acetate (2 x 20 mL), followed by chloroform (2 x 20 mL). The organics were combined, dried with magnesium sulfate, filtered, and concentrated *in vacuo* to afford a white powder. The crude product was purified by reverse phase HPLC (Phenomenex Luna 30 X 100mm; 220 wavelength; gradient time 10 min; flow rate 40 ml/min; solvent A; 10% methanol-90% water-0.1% TFA, solvent B; 90% methanol-10% water-0.1% TFA). The fractions were combined, neutralized with 1N sodium hydroxide and extracted with ethyl acetate (2 x 30 mL). The organics were combined, dried with magnesium sulfate, filtered and concentrated *in vacuo* to yield N-(6-methoxybenzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.25 g, 0.73 mmol, 79 % yield) as a white powder. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 8.88 (1 H, d, *J*=1.22 Hz), 7.48 - 7.52 (1 H, m), 7.40 (1 H, d, *J*=2.75 Hz), 6.92 (1 H, dd, *J*=8.70, 2.59 Hz), 3.87 (1 H, d, *J*=9.77 Hz), 3.77 (3 H, s), 3.61 (1 H, d, *J*=9.77 Hz), 3.03 (2 H, s), 2.75 - 2.86 (2 H, m), 2.67 (2 H, t, *J*=7.78 Hz), 2.06 (1 H, br. s.), 1.91 (1 H, br. s.), 1.41 - 1.65 (3 H, m). MS (LC/MS) R.T. = 1.44; $[M+H]^+ = 345.3$.

The enantiomers were separated using a Chiralpak AD-H (30 x 250mm, 5μm) column with a mobile phase consisting of 23% methanol (0.1%DEA) in CO_2 and UV

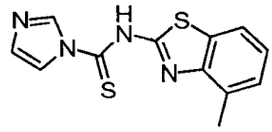
monitored at 220 nm. The separated peaks were concentrated *in vacuo* to yield white powders. The first peak off the column yielded 205.5 mg, 0.60 mmol, 34.1 %. (5a, S-isomer): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.88 (1 H, br. s.), 7.50 (1 H, d, *J*=8.81 Hz), 7.40 (1 H, d, *J*=2.52 Hz), 6.92 (1 H, dd, *J*=8.81, 2.77 Hz), 3.87 (1 H, d, *J*=9.82 Hz), 3.77 (3 H, s), 3.58 - 3.65 (1 H, m), 3.02 (2 H, s), 2.74 - 2.86 (2 H, m), 2.66 (2 H, t, *J*=7.68 Hz), 2.03 - 2.08 (1 H, m), 1.91 (1 H, br. s.), 1.39 - 1.65 (3 H, m). MS (LC/MS) R.T. = 1.40; $[M+H]^+$ = 345.2. The second peak yielded 206.9 mg, 0.6 mmol, 34 %. (5b, R-isomer): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.88 (1 H, br. s.), 7.50 (1 H, d, *J*=8.56 Hz), 7.40 (1 H, d, *J*=2.52 Hz), 6.93 (1 H, dd, *J*=8.81, 2.52 Hz), 3.87 (1 H, d, *J*=10.07 Hz), 3.77 (3 H, s), 3.62 (1 H, d, *J*=10.07 Hz), 3.02 (2 H, s), 2.75 - 2.86 (2 H, m), 2.67 (2 H, t, *J*=7.68 Hz), 2.04 - 2.09 (1 H, m), 1.92 (1 H, br. s.), 1.42 - 1.66 (3 H, m). MS (LC/MS) R.T. = 1.70; $[M+H]^+$ = 345.1.

EXAMPLE 6

N-(4-Methylbenzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

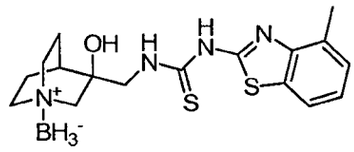


Step A: N-(4-Methylbenzo[d]thiazol-2-yl)-^{1}H-imidazole-1-carbothioamide



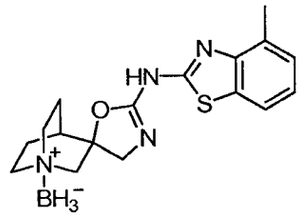
To 4-methylbenzo[d]thiazol-2-amine (1.1 g, 6.7 mmol) in acetonitrile (30 mL) was added 1,1'-thiocarbonyldiimidazole (1.552 g, 8.71 mmol). The reaction mixture was stirred at 50°C for 18 hours. The reaction was cooled to room temperature and the precipitate was filtered and washed with acetonitrile (2 x 50 mL). The yellow powder was dried in a vacuum oven (50 °C) for 1 hour to yield N-(4-methylbenzo[d]thiazol-2-yl)-^{1}H-imidazole-1-carbothioamide (900 mg, 3.28 mmol, 49 % yield) and then used in the next step without any further purification or characterization.

Step B: (3-Hydroxy-3-((3-(4-methylbenzo[d]thiazol-2-yl)thioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate



To N-(4-methylbenzo[d]thiazol-2-yl)-^{1}H-imidazole-1-carbothioamide (0.71 g, 2.59 mmol) in N,N-dimethylformamide (20 mL) was added (3-(aminomethyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (0.44 g, 2.59 mmol). The reaction mixture was stirred at 70 °C for 4 hours. The reaction was concentrated and purified via silica gel chromatography (40-100% ethyl acetate/hexanes). The product fractions were concentrated *in vacuo* to yield (3-hydroxy-3-((3-(4-methylbenzo[d]thiazol-2-yl)thioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (0.65 g, 1.73 mmol, 66.7 % yield) as a white powder. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.93 (1 H, s), 7.74 (1 H, d, *J*=7.63 Hz), 7.22 - 7.26 (1 H, m), 7.19 (1 H, t, *J*=7.63 Hz), 3.75 - 3.93 (2 H, m), 2.72 - 2.95 (6 H, m), 2.56 (3 H, s), 2.03 - 2.14 (1 H, m), 1.95 (1 H, br. s.), 1.78 - 1.87 (1 H, m), 1.73 (1 H, ddd, *J*=13.81, 9.23, 5.04 Hz), 1.56 (1 H, td, *J*=9.99, 7.78 Hz), 1.38 (2 H, br. s.). (LC/MS) R.T. = 3.70; $[M+H]^+$ = 375.2.

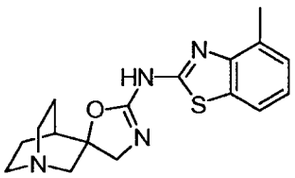
Step C: (2-(4-Methylbenzo[d]thiazol-2-ylamino)-4H-1'-ammonio-spiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate



To (3-hydroxy-3-((3-(4-methylbenzo[d]thiazol-2-yl)thioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (0.62 g, 1.65 mmol) in N,N-dimethylformamide (20 mL) was added N,N'-diisopropylcarbodiimide(0.33 mL, 2.14 mmol). The reaction mixture was stirred at 70 °C for 4 hours. The reaction was concentrated and purified via silica gel chromatography (40-100% ethyl acetate/hexanes). The product fractions were concentrated *in vacuo* to yield (2-(4-methylbenzo[d]thiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-

bicyclo[2.2.2]octane]-1'-yl)trihydroborate (0.4 g, 1.17 mmol, 70.9 % yield) as a white powder. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.90 (s, 1 H), 7.61 (d, *J*=7.63 Hz, 1 H), 7.13 - 7.17 (m, 1 H), 7.09 (t, *J*=7.48 Hz, 1 H), 3.90 (d, *J*=10.38 Hz, 1 H), 3.77 (d, *J*=10.38 Hz, 1 H), 3.32 (s, 3 H), 3.30 (d, *J*=1.53 Hz, 1 H), 3.13 - 3.20 (m, 2 H), 3.00 - 3.09 (m, 1 H), 2.85 - 2.94 (m, 4 H), 2.57 (s, 4 H), 2.28 (s, 1 H), 2.06 (s, 1 H), 1.75 - 1.83 (m, 4 H), 1.45 (s, 1 H). (LC/MS) R.T. = 2.73; $[M+H]^+$ = 343.2.

Step D: N-(4-Methylbenzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



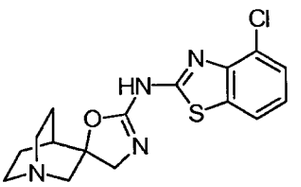
To (2-(4-methylbenzo[d]thiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate (0.38 g, 1.11 mmol) in acetone (9 mL) was added 3 M HCl (2.78 mL, 8.33 mmol). The reaction mixture was stirred at room temperature for 4 hours. Ethyl acetate was added and the aqueous layer was collected and neutralized with 1N sodium hydroxide. The product was extracted with ethyl acetate (2 x 40 mL). The organics were combined, dried with magnesium sulfate, filtered and concentrated *in vacuo* to afford N-(4-methylbenzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.195 g, 0.594 mmol, 53.5 % yield) as a white powder. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.84 (s, 1 H), 7.60 (d, *J*=7.32 Hz, 1 H), 7.13-7.17 (m, 1 H), 7.08 (t, *J*=7.63 Hz, 1 H), 3.92 (d, *J*=10.07 Hz, 1 H), 3.66 (d, *J*=9.77 Hz, 1 H), 3.04 (s, 2 H), 2.76 - 2.85 (m, 2 H), 2.68 (t, *J*=7.48 Hz, 2 H), 2.56 (s, 3 H), 2.09 (s, 1 H), 1.93 (s, 1 H), 1.61 (d, *J*=3.05 Hz, 1 H), 1.60 (s, 1 H), 1.50 (dd, *J*=7.17, 2.59 Hz, 1 H). (LC/MS) R.T. = 1.76; $[M+H]^+$ = 329.2.

The enantiomers were separated using a Chiralcel OJ-H (30 x 250mm, 5μm) column with a mobile phase consisting of 30% methanol (0.1%DEA) in CO_2 and UV monitored at 300 nm. The separated peaks were concentrated *in vacuo* to yield white powders. The first peak off the column yielded 0.07 g, 0.21 mmol, 38.9 %. (6a, S-isomer): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.83 (br. s., 1 H) 7.59 (d, *J*=7.63 Hz, 1 H) 7.11 - 7.18 (m, 1 H) 7.08 (t, *J*=7.63 Hz, 1 H) 3.92 (d, *J*=10.38 Hz, 1 H) 3.66 (d,

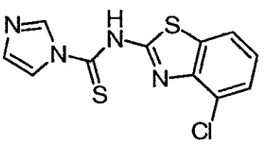
J=9.77 Hz, 1 H) 3.04 (s, 2 H) 2.73 - 2.89 (m, 2 H) 2.61 - 2.72 (m, 2 H) 2.56 (s, 3 H) 2.09 (br. s., 1 H) 1.93 (br. s., 1 H) 1.43 - 1.71 (m, 3 H). MS (LC/MS) R.T. = 1.75; $[M+H]^+$ = 329.1. The second peak yielded 0.07 g, 0.21 mmol, 38.1 %. (6b, R-isomer): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.84 (br. s., 1 H) 7.59 (d, *J*=7.63 Hz, 1 H) 7.15 (d, *J*=7.20 Hz, 1 H) 7.08 (t, *J*=7.48 Hz, 1 H) 3.92 (d, *J*=9.77 Hz, 1 H) 3.66 (d, *J*=10.07 Hz, 1 H) 3.00 - 3.09 (m, 2 H) 2.73 - 2.87 (m, 2 H) 2.62 - 2.72 (m, 2 H) 2.56 (s, 3 H) 2.05 - 2.12 (m, 1 H) 1.93 (br. s., 1 H) 1.56 - 1.67 (m, 2 H) 1.45 - 1.55 (m, 1 H). MS (LC/MS) R.T. = 1.75; $[M+H]^+$ = 329.1.

EXAMPLE 7

N-(4-Chlorobenzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

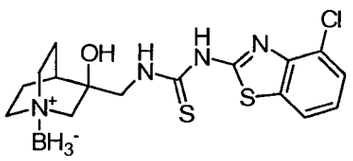


Step A: N-(4-Chlorobenzo[d]thiazol-2-yl)-^{1}H-imidazole-1-carbothioamide



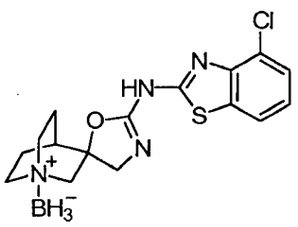
To 4-chlorobenzo[d]thiazol-2-amine (1.12 g, 6.07 mmol) in acetonitrile (30 mL) was added 1,1'-thiocarbonyldiimidazole (1.405 g, 7.89 mmol). The reaction mixture was stirred at 50 °C for 18 hours. The reaction was cooled to room temperature and the precipitate was filtered and washed with acetonitrile (2 x 50 mL). The yellow powder was dried in a vacuum oven (40 °C) for 1 hour to yield N-(4-chlorobenzo[d]thiazol-2-yl)-^{1}H-imidazole-1-carbothioamide (0.33 g, 1.12 mmol, 18.5 % yield) and then used in the next step without any further purification or characterization.

Step B: (3-((3-(4-Chlorobenzo[d]thiazol-2-yl)thioureido)methyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate



To N-(4-chlorobenzo[d]thiazol-2-yl)-^{1}H-imidazole-1-carbothioamide (0.3 g, 1.018 mmol) in N,N-dimethylformamide (20 mL) was added (3-(aminomethyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (0.173 g, 1.018 mmol). The reaction mixture was stirred at 70 °C for 4 hours. The reaction was concentrated and purified via silica gel chromatography (60-100% ethyl acetate/hexanes). The product fractions were concentrated *in vacuo* to yield (3-((3-(4-chlorobenzo[d]thiazol-2-yl)thioureido)methyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (0.25 g, 0.63 mmol, 61.9 % yield) as a white powder. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.19 (s, 1 H) 9.72 (br. s., 1 H) 7.93 (d, *J*=7.93 Hz, 1 H) 7.51 (d, *J*=7.93 Hz, 1 H) 7.26 - 7.32 (m, 1 H) 5.32 (s, 1 H) 3.88 (dd, *J*=13.73, 4.88 Hz, 1 H) 3.75 (dd, *J*=13.73, 4.88 Hz, 1 H) 2.73 - 2.95 (m, 6 H) 2.08 (br. s., 1 H) 1.96 (br. s., 1 H) 1.79 - 1.89 (m, 1 H) 1.68 - 1.78 (m, 1 H) 1.52 - 1.61 (m, 1 H) 1.39 (br. s., 3 H).

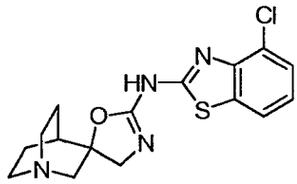
Step C: (2-(4-Chlorobenzo[d]thiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate



To (3-((3-(4-chlorobenzo[d]thiazol-2-yl)thioureido)methyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (0.23 g, 0.58 mmol) in N,N-dimethylformamide (20 mL) was added N,N'-diisopropylcarbodiimide (0.117 mL, 0.75 mmol). The reaction mixture was stirred at 70 °C for 4 hours. The reaction was concentrated and purified via silica gel chromatography (40-100% ethyl acetate/hexanes). The product fractions were concentrated *in vacuo* to yield (2-(4-

chlorobenzo[d]thiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate (0.1 g, 0.27 mmol, 47.6 % yield) as a white powder. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.95 (s, 1 H) 7.79 (d, *J*=7.93 Hz, 1 H) 7.42 (d, *J*=7.63 Hz, 1 H) 7.18 (t, *J*=7.93 Hz, 1 H) 3.92 (d, *J*=10.38 Hz, 1 H) 3.77 (d, *J*=10.38 Hz, 1 H) 3.26 - 3.38 (m, 1 H) 3.19 (dd, *J*=15.26, 1.53 Hz, 1 H) 3.01 - 3.11 (m, 1 H) 2.81 - 3.00 (m, 3 H) 2.31 (br. s., 1 H) 2.03 - 2.15 (m, 1 H) 1.70 - 1.89 (m, 3 H) 1.45 (br. s., 3 H).

Step D: N-(4-Chlorobenzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



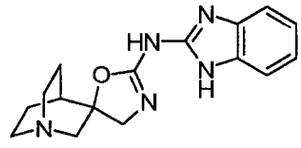
To (2-(4-chlorobenzo[d]thiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate (0.08 g, 0.221 mmol) in acetone (9 mL) was added 3 M HCl (0.551 mL, 1.654 mmol). The reaction mixture was stirred at room temperature for 4 hours. Ethyl acetate was added and the aqueous layer was collected and neutralized with 1N sodium hydroxide. The product was extracted with ethyl acetate (2 x 40 mL). The organics were combined, dried with magnesium sulfate, filtered and concentrated *in vacuo* to afford N-(4-chlorobenzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.05 g, 0.14 mmol, 65.0 % yield) as a white powder. ^{1}H NMR(500 MHz, DMSO-d_6) δ ppm 8.90 (br. s., 1 H) 7.77 (dd, *J*=7.78, 1.07 Hz, 1 H) 7.41 (dd, *J*=7.78, 1.07 Hz, 1 H) 7.17 (t, *J*=7.78 Hz, 1 H) 3.94 (d, *J*=10.07 Hz, 1 H) 3.67 (d, *J*=10.07 Hz, 1 H) 3.00 - 3.11 (m, 2 H) 2.76 - 2.88 (m, 2 H) 2.68 (t, *J*=7.63 Hz, 2 H) 2.11 (br. s., 1 H) 1.91 - 2.00 (m, 1 H) 1.47 - 1.67 (m, 3 H). MS (LC/MS) R.T. = 2.11; $[M+H]^+$ = 349.1.

The enantiomers were separated using a Chiralcel OJ-H (30 x 250mm, 5μm) column with a mobile phase consisting of 30% methanol (0.1% DEA) in CO_2. The wavelength was set at 220 nM. The separated peaks were concentrated *in vacuo* to yield white powders. The first peak off the column was (S)-N-(4-chlorobenzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-

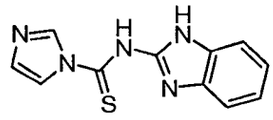
amine (0.11 g, 0.30 mmol, 34.8 % yield). (7a, S-isomer): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.90 (br. s., 1 H) 7.77 (d, *J*=7.32 Hz, 1 H) 7.41 (d, *J*=7.93 Hz, 1 H) 7.17 (t, *J*=7.93 Hz, 1 H) 3.94 (d, *J*=10.07 Hz, 1 H) 3.67 (d, *J*=10.07 Hz, 1 H) 3.00 - 3.11 (m, 2 H) 2.76 - 2.90 (m, 2 H) 2.68 (t, *J*=7.78 Hz, 2 H) 2.11 (br. s., 1 H) 1.91 - 2.01 (m, 1 H) 1.47 - 1.68 (m, 3 H). MS (LC/MS) R.T. = 2.06; $[M+H]^+$ = 349.1. The second peak was (R)-N-(4-chlorobenzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.11 g, 0.30 mmol, 35.2 % yield). (7b, R-isomer): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.89 (br. s., 1 H) 7.77 (d, *J*=7.93 Hz, 1 H) 7.40 (d, *J*=7.93 Hz, 1 H) 7.16 (t, *J*=7.93 Hz, 1 H) 3.94 (d, *J*=10.07 Hz, 1 H) 3.67 (d, *J*=10.07 Hz, 1 H) 2.99 - 3.11 (m, 2 H) 2.74 - 2.88 (m, 2 H) 2.68 (t, *J*=7.78 Hz, 2 H) 2.11 (br. s., 1 H) 1.90 - 2.01 (m, 1 H) 1.44 - 1.68 (m, 3 H). MS (LC/MS) R.T. = 2.07; $[M+H]^+$ = 349.1.

EXAMPLE 8

N-(^{1}H-Benzo[d]imidazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

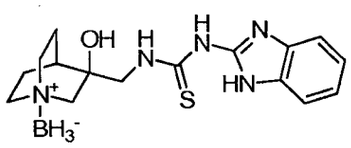


Step A: N-(^{1}H-Benzo[d]imidazol-2-yl)-^{1}H-imidazole-1-carbothioamide



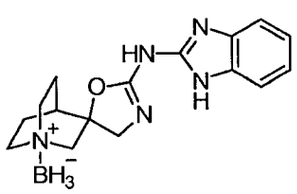
To ^{1}H-benzo[d]imidazol-2-amine (1.28 g, 9.61 mmol) in acetonitrile (30 mL) was added 1,1'-thiocarbonyldiimidazole (2.227 g, 12.5 mmol). The reaction mixture was stirred at 50 °C for 18 hours. The reaction was cooled to room temperature and the precipitate was filtered and washed with acetonitrile (2 x 50 mL). The yellow powder was dried in a vacuum oven (40°C) for 1 hour to yield N-(^{1}H-benzo[d]imidazol-2-yl)-^{1}H-imidazole-1-carbothioamide (1.8 g, 7.4 mmol, 77 % yield) and then used in the next step without any further purification or characterization.

Step B: (3-((3-^{1}H-Benzo[d]imidazol-2-ylthioureido)methyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate



To N-(^{1}H-benzo[d]imidazol-2-yl)- ^{1}H-imidazole-1-carbothioamide (1.07 g, 4.4 mmol) in N,N-dimethylformamide (20 mL) was added (3-(aminomethyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (0.748 g, 4.4 mmol). The reaction mixture was stirred at 70 °C for 4 hours. The reaction was concentrated and purified via silica gel chromatography (60-100% ethyl acetate/hexane). The product fractions were concentrated *in vacuo* to yield (3-((3-^{1}H-benzo[d]imidazol-2-ylthioureido)methyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (1.28 g, 3.71 mmol, 84 % yield) as a white powder. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.41 (s, 1 H), 11.16 (s, 1 H), 7.43 (d, J=3.05 Hz, 3 H), 7.13 (ddd, J=9.46, 3.81, 3.51 Hz, 3 H), 5.36 (s, 1 H), 4.01-4.07 (m, 3 H), 3.79 (dd, J=13.28, 4.12 Hz, 1 H), 2.83-2.92 (m, 6 H), 2.71 (d, J=14.04 Hz, 2 H), 2.04-2.13 (m, 2 H), 1.89-1.94 (m, 3 H), 1.74 (td, J=9.46, 5.49 Hz, 2 H), 1.51-1.59 (m, 2 H), 1.38 (s, 2 H), 1.31 (s, 1 H). LC/MS confirmed product as loss of BH_3 in the LC/MS conditions: retention time 2.75 (M+1-BH_3 = 332.2).

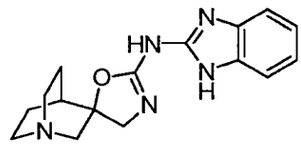
Step C: (2-(^{1}H-Benzo[d]imidazol-2-ylamino)-4H-1'-ammoniospiro-[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate



To (3-((3-^{1}H-benzo[d]imidazol-2-ylthioureido)methyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (1.0 g, 2.9 mmol) in N,N-dimethylformamide (20 mL) was added N,N'-diisopropylcarbodiimide (0.587 mL, 3.77 mmol). The reaction mixture was stirred at 70 °C for 4 hours. The reaction was concentrated and purified via silica gel chromatography (40-100% ethyl acetate/hexane). The product fractions were concentrated *in vacuo* to yield (2-(^{1}H-

benzo[d]imidazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate (0.81 g, 2.6 mmol, 90 % yield) as a white powder. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.29 (s, 1 H), 6.99 - 7.05 (m, 2 H), 3.90 (t, *J*=9.77 Hz, 1 H), 3.75 (d, *J*=10.38 Hz, 1 H), 3.26 - 3.35 (m, 1 H), 3.13 (dd, *J*=14.95, 1.53 Hz, 1 H), 2.98 - 3.06 (m, 1 H), 2.84 - 2.92 (m, 3 H), 2.22 (s, 1 H), 1.98 - 2.05 (m, 1 H), 1.72 - 1.82 (m, 3 H), 1.45 (s, 1 H). LC/MS confirmed product as loss of BH_3 in the LC/MS conditions: retention time 2.29 (M+1-BH_3 = 298.2).

Step D: N-(1H-Benzo[d]imidazol-2-yl)-4H-1'-azaspiro-[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



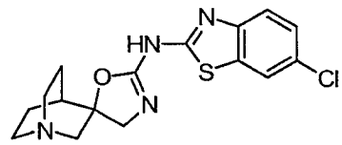
To (2-(^{1}H-benzo[d]imidazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octanc]-1'-yl)trihydroboratc (0.77 g, 2.5 mmol) in acctonc (9 mL) was added 3 M HCl (6.2 mL, 18.6 mmol). The reaction was stirred at room temperature for 4 hours. Ethyl acetate was added and the aqueous layer was collected and neutralized with 1N sodium hydroxide. The product was extracted with ethyl acetate (2 x 40 mL). The organics were combined, dried with magnesium sulfate, filtered and concentrated *in vacuo* to afford N-(^{1}H-benzo[d]imidazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.5 g, 1.68 mmol, 68 % yield) as a white powder. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.45 (s, 1 H), 9.20 (s, 1 H), 7.32 (s, 1 H), 7.00 (dd, *J*=5.65, 2.90 Hz, 4 H), 3.91 (d, *J*=10.07 Hz, 2 H), 3.64 (d, *J*=10.07 Hz, 2 H), 2.98 - 3.05 (m, 4 H), 2.73 - 2.82 (m, 4 H), 2.67 (t, *J*=7.63 Hz, 4 H), 2.03 (d, *J*=2.75 Hz, 2 H), 1.85 - 1.92 (m, 2 H), 1.54 - 1.63 (m, 4 H), 1.44 - 1.51 (m, 2 H). MS (LC/MS) R.T. = 1.30; $[M+H]^+$ = 298.2.

The enantiomers were separated using a Chiralpak AS-H (30 x 250mm, 5μm) column with a mobile phase consisting of 30% methanol (0.1%DEA) in CO_2 and UV monitored at 330 nm. The separated peaks were concentrated *in vacuo* to yield white powders. The first peak off the column yielded 0.11 g, 0.36 mmol, 33.0 %. (8a; R-isomer): M.P. 255 °C(dec). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.43 (br. s., 1 H) 9.16 (br. s., 1 H) 7.14 - 7.53 (m, 2 H) 6.82 - 7.09 (m, 2 H) 3.91 (d, *J*=9.77 Hz, 1

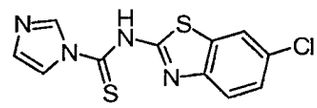
H) 3.64 (d, *J*=10.07 Hz, 1 H) 2.96 - 3.09 (m, 2 H) 2.71 - 2.87 (m, 2 H) 2.62 - 2.73 (m, 2 H) 2.01 - 2.08 (m, 1 H) 1.81 - 1.97 (m, 1 H) 1.54 - 1.66 (m, 2 H) 1.40 - 1.53 (m, 1 H). MS (LC/MS) R.T. = 1.26; $[M+H]^+$ = 298.2. The second peak yielded 0.11 g, 0.36 mmol, 33.0 %. (8b; S-isomer): ^{1}H NMR(500 MHz, DMSO-d_6) δ ppm 11.43 (br. s., 1 H) 9.20 (br. s., 1 H) 7.10 - 7.60 (m, 2 H) 6.83 - 7.11 (m, 2 H) 3.91 (d, *J*=9.77 Hz, 1 H) 3.64 (d, *J*=9.77 Hz, 1 H) 2.94 - 3.16 (m, 2 H) 2.71 - 2.86 (m, 2 H) 2.59 - 2.72 (m, 2 H) 1.97 - 2.09 (m, 1 H) 1.81 - 1.95 (m, 1 H) 1.53 - 1.71 (m, 2 H) 1.41 - 1.53 (m, 1 H). MS (LC/MS) R.T. = 1.28; $[M+H]^+$ = 298.2.

EXAMPLE 9

N-(6-Chlorobenzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

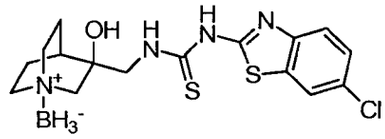


Step A: N-(6-Chlorobenzo[d]thiazol-2-yl)-^{1}H-imidazole-1-carbothioamide



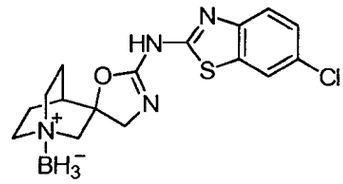
To 6-chlorobenzo[d]thiazol-2-amine (1.14 g, 6.17 mmol) in acetonitrile (30 mL) was added 1,1'-thiocarbonyldiimidazole (1.43 g, 8 mmol). The reaction was stirred at 50 °C for 18 hours. The reaction was cooled to room temperature and the precipitate was filtered and washed with acetonitrile (2 x 50 mL). The yellow powder was dried in a vacuum oven (40 °C) for 1 hour to yield N-(6-chlorobenzo[d]thiazol-2-yl)-^{1}H-imidazole-1-carbothioamide (1.16 g, 3.9 mmol, 64 % yield) and then used in the next step without any further purification or characterization.

Step B: (3-((3-(6-Chlorobenzo[d]thiazol-2-yl)thioureido)methyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate



To N-(6-chlorobenzo[d]thiazol-2-yl)-^{1}H-imidazole-1-carbothioamide (0.86 g, 2.9 mmol) in N,N-dimethylformamide (20 mL) was added (3-(aminomethyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (0.5 g, 2.9 mmol). The reaction was stirred at 70 °C for 4 hours. The reaction was concentrated and purified via silica gel chromatography (60-100% ethyl acetate/hexanes). The product fractions were concentrated *in vacuo* to yield (3-((3-(6-chlorobenzo[d]thiazol-2-yl)thioureido)methyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (0.4 g, 1.01 mmol, 34.6 % yield) as a white powder. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.92 (br. s., 1 H) 9.89 (br. s., 1 H) 8.08 (br. s., 1 H) 7.62 (br. s., 1 H) 7.40 - 7.50 (m, 1 H) 5.40 (br. s., 1 H) 3.88 (d, *J*=10.20 Hz, 1 H) 3.76 (d, *J*=10.20 Hz, 1 H) 2.67 - 3.02 (m, 6 H) 2.08 (br. s., 1 H) 1.80 - 1.95 (m, 2 H) 1.73 (br. s., 1 H) 1.01 - 1.63 (m, 4 H). MS (LC/MS) R.T. = 3.87; $[M+H]^+$ = 395.1.

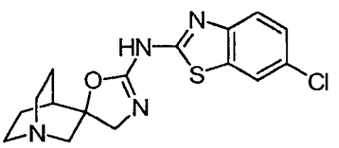
Step C: (2-(6-Chlorobenzo[d]thiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate



To (3-((3-(6-chlorobenzo[d]thiazol-2-yl)thioureido)methyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (0.37 g, 0.93 mmol) in N,N-dimethylformamide (20 mL) was added N,N'-diisopropylcarbodiimide (0.19 mL, 1.2 mmol). The reaction was stirred at 70 °C for 4 hours. The reaction was concentrated and purified via silica gel chromatography (40-100% ethyl acetate/hexane). The product fractions were concentrated *in vacuo* to yield (2-(6-chlorobenzo[d]thiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate (0.12 g, 0.33 mmol, 35.5 % yield) as a white powder. ^{1}H NMR

(500 MHz, DMSO-d_6) δ ppm 9.10 (br. s., 1 H) 7.95 (d, *J*=2.14 Hz, 1 H) 7.60 (d, *J*=8.55 Hz, 1 H) 7.36 (dd, *J*=8.55, 2.14 Hz, 1 H) 3.88 (d, *J*=10.38 Hz, 1 H) 3.76 (d, *J*=10.38 Hz, 1 H) 3.26 - 3.37 (m, 1 H) 3.17 (dd, *J*=14.95, 1.83 Hz, 1 H) 3.00 - 3.11 (m, 1 H) 2.80 - 2.97 (m, 3 H) 2.28 (br. s., 1 H) 2.00 - 2.11 (m, 1 H) 1.69 - 1.88 (m, 3 H) 1.46 (br. s., 3 H). LC/MS : retention time 2.94 (M+1-BH_3 = 349.1).

Step D: N-(6-Chlorobenzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



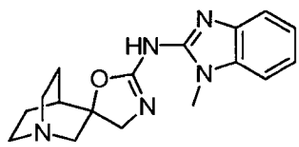
To (2-(6-chlorobenzo[d]thiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate (0.1 g, 0.28 mmol) in acetone (9 mL) was added 3 M HCl (0.69 mL, 2.07 mmol). The reaction was stirred at room temperature for 4 hours. Ethyl acetate was added and the aqueous layer was collected and neutralized with 1N sodium hydroxide. The product was extracted with ethyl acetate (2 x 40 mL). The organics were combined, dried with magnesium sulfate, filtered and concentrated *in vacuo* to afford N-(6-chlorobenzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.06 g, 0.17 mmol, 62.4 % yield) as a white powder. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.03 (br. s., 1 H) 7.93 (d, *J*=2.14 Hz, 1 H) 7.58 (d, *J*=8.55 Hz, 1 H) 7.35 (dd, *J*=8.55, 2.14 Hz, 1 H) 3.90 (d, *J*=10.07 Hz, 1 H) 3.65 (d, *J*=10.07 Hz, 1 H) 2.99 - 3.11 (m, 2 H) 2.73 - 2.89 (m, 2 H) 2.67 (t, *J*=7.63 Hz, 2 H) 2.08 (br. s., 1 H) 1.82 - 1.99 (m, 1 H) 1.43 - 1.67 (m, 3 H). MS (LC/MS) R.T. = 2.07; $[M+H]^+$ = 349.1.

The enantiomers were separated using a Chiralpak AS-H (30 x 250mm, 5μm) column with a mobile phase consisting of 30% methanol (0.1%DEA) in CO_2 and UV monitored at 220 nm. The separated peaks were concentrated *in vacuo* to yield white powders. The first peak off the column yielded 0.034 g, 0.10 mmol, 36.2 %. (9a; S-isomer): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.02 (br. s., 1 H) 7.93 (d, *J*=2.14 Hz, 1 H) 7.58 (d, *J*=8.55 Hz, 1 H) 7.35 (dd, *J*=8.55, 2.14 Hz, 1 H) 3.90 (d, *J*=10.07 Hz, 1 H) 3.65 (d, *J*=10.07 Hz, 1 H) 2.97 - 3.11 (m, 2 H) 2.73 - 2.89 (m, 2 H) 2.67 (t, *J*=7.48 Hz, 2 H) 2.08 (br. s., 1 H) 1.93 (br. s., 1 H) 1.43 - 1.69 (m, 3 H). MS (LC/MS) R.T.

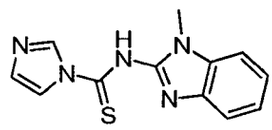
= 2.05; $[M+H]^+$ = 349.1. Optical rotation = + 4.00°. The second peak yielded 0.037 g, 0.10 mmol, 39.4 %. (9b; R-isomer): ^{1}H NMR(500 MHz, DMSO-d_6) δ ppm 9.02 (br. s., 1 H) 7.93 (d, *J*=2.14 Hz, 1 H) 7.58 (d, *J*=8.55 Hz, 1 H) 7.35 (dd, *J*=8.55, 2.44 Hz, 1 H) 3.90 (d, *J*=10.07 Hz, 1 H) 3.65 (d, *J*=10.07 Hz, 1 H) 2.93 - 3.13 (m, 2 H) 2.72 - 2.91 (m, 2 H) 2.62 - 2.73 (m, 2 H) 2.08 (br. s., 1 H) 1.93 (d, *J*=1.22 Hz, 1 H) 1.44 - 1.68 (m, 3 H). MS (LC/MS) R.T. = 2.04; $[M+H]^+$ = 349.1. Optical rotation = -3.74°.

EXAMPLE 10

N-(1-Methyl-^{1}H-benzo[d]imidazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

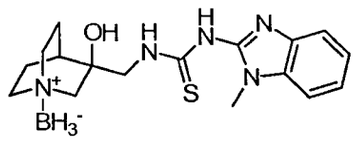


Step A: N-(1-Methyl-^{1}H-benzo[d]imidazol-2-yl)-^{1}H-imidazole-1-carbothioamide



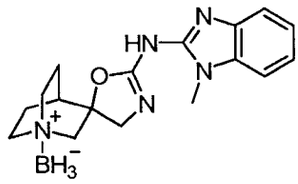
To 1-methyl-^{1}H-benzo[d]imidazol-2-amine (1.28 g, 8.7 mmol) in acetonitrile (30 mL) was added 1,1'-thiocarbonyldiimidazole (2.015 g, 11.31 mmol). The reaction was stirred at 50 °C for 18 hours. The reaction was cooled to room temperature and the precipitate was filtered and washed with acetonitrile (2 x 50 mL). The yellow powder was dried in a vacuum oven (40 °C) for 1 hour to yield N-(1-methyl-^{1}H-benzo[d]imidazol-2-yl)-^{1}H-imidazole-1-carbothioamide (1.6 g, 6.22 mmol, 71.5 % yield) and then used in the next step without any further purification or characterization.

Step B: (3-Hydroxy-3-((3-(1-methyl-^{1}H-benzo[d]imidazol-2-yl)thioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate



To N-(1-methyl-^{1}H-benzo[d]imidazol-2-yl)-^{1}H-imidazole-1-carbothioamide (1.04 g, 4.04 mmol) in N,N-dimethylformamide (20 mL) was added (3-(aminomethyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (0.687 g, 4.04 mmol). The reaction was stirred at 70 °C for 4 hours. The reaction was concentrated and purified via silica gel chromatography (60-100% ethyl acetate/hexane). The product fractions were concentrated *in vacuo* to yield (3-hydroxy-3-((3-(1-methyl-^{1}H-benzo[d]imidazol-2-yl)thioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (1.28 g, 3.56 mmol, 88 % yield) as a white powder. LC/MS confirmed product as loss of BH_3 in the LC/MS conditions: retention time 3.01 (M+1-BH_3 = 346.2).

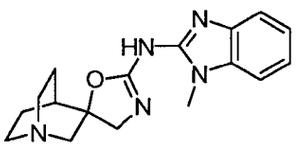
Step C: (2-(1-Methyl-^{1}H-benzo[d]imidazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate



To (3-hydroxy-3-((3-(1-methyl-^{1}H-benzo[d]imidazol-2-yl)thioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (1.19 g, 3.31 mmol) in N,N-dimethylformamide (20 mL) was added N,N'-diisopropylcarbodiimide (1.55 mL, 9.9 mmol). The reaction was stirred at 70 °C for 4 hours. The reaction was concentrated and purified via silica gel chromatography (40-100% ethyl acetate/hexane). The product fractions were concentrated *in vacuo* to yield (2-(1-methyl-^{1}H-benzo[d]imidazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate (0.94 g, 2.9 mmol, 87 % yield) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.36 (br. s., 1 H) 7.34 - 7.44 (m, 1 H) 7.26 - 7.34 (m, 1 H) 7.00 - 7.12 (m, 2 H) 3.90 (d, *J*=10.32 Hz, 1 H) 3.77 (d,

J=10.32 Hz, 1 H) 3.57 (s, 3 H) 3.28 (dd, *J*=14.86, 2.27 Hz, 1 H) 3.13 (dd, *J*=14.86, 1.51 Hz, 1 H) 2.95 - 3.08 (m, 1 H) 2.75 - 2.95 (m, 3 H) 2.22 (br. s., 1 H) 1.96 - 2.11 (m, 1 H) 1.67 - 1.89 (m, 3 H) 1.43 (br. s., 3 H). LC/MS : retention time 2.37 (M+1-BH_3 = 312.2).

Step D: N-(1-Methyl-^{1}H-benzo[d]imidazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



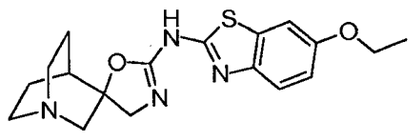
To (2-(1-methyl-^{1}H-benzo[d]imidazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate (0.92 g, 2.8 mmol) in acetone (9 mL) was added 3 M HCl (7.1 mL, 21.2 mmol). The reaction was stirred at room temperature for 4 hours. Ethyl acetate was added and the aqueous layer was collected and neutralized with 1N sodium hydroxide. The product was extracted with ethyl acetate (2 x 40 mL). The organics were combined, dried with magnesium sulfate, filtered, and concentrated *in vacuo* to afford N-(1-methyl-^{1}H-benzo[d]imidazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.84 g, 2.7 mmol, 95 % yield) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.24 - 9.39 (m, 1 H) 7.33 - 7.42 (m, 1 H) 7.25 - 7.33 (m, 1 H) 6.99 - 7.10 (m, 2 H) 3.92 (d, *J*=10.07 Hz, 1 H) 3.66 (d, *J*=10.07 Hz, 1 H) 3.57 (s, 3 H) 2.97 - 3.08 (m, 2 H) 2.78 (t, *J*=7.81 Hz, 2 H) 2.67 (t, *J*=7.81 Hz, 2 H) 2.01 - 2.09 (m, 1 H) 1.80 - 1.96 (m, 1 H) 1.40 - 1.66 (m, 3 H). MS (LC/MS) R.T. = 1.49; $[M+H]^+$ = 312.2.

The enantiomers were separated using a Chiralcel OJ-H (30 x 250mm, 5μm) column with a mobile phase consisting of 22% methanol (0.1%DEA) in CO_2 and UV monitored at 300 nm. The separated peaks were concentrated *in vacuo* to yield white powders. The first peak off the column yielded 0.065 g, 0.205 mmol, 39.8 %. (10a, R-isomer): ^{1}H NMR(500 MHz, DMSO-d_6) δ ppm 9.31 (br. s., 1 H) 7.35 - 7.45 (m, 1 H) 7.26 - 7.34 (m, 1 H) 7.00 - 7.15 (m, 2 H) 3.93 (d, *J*=10.10 Hz, 1 H) 3.67 (d, *J*=10.10 Hz, 1 H) 3.59 (s, 3 H) 2.93 - 3.13 (m, 2 H) 2.74 - 2.89 (m, 2 H) 2.61 - 2.74 (m, 2 H) 2.05 (br. s., 1 H) 1.91 (br. s., 1 H) 1.38 - 1.68 (m, 3 H). MS (LC/MS) R.T. = 1.37; $[M+H]^+$ = 312.2. Optical rotation = - 16.02°. The second peak yielded 0.06 g,

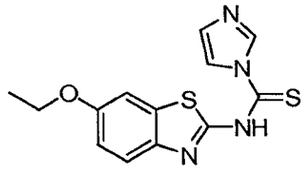
0.19 mmol, 36.8 %. (10b; S-isomer): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.31 (br. s., 1 H) 7.33 - 7.43 (m, 1 H) 7.25 - 7.33 (m, 1 H) 6.93 - 7.11 (m, 2 H) 3.93 (dd, *J*=9.92, 3.20 Hz, 1 H) 3.67 (dd, *J*=9.92, 3.20 Hz, 1 H) 3.58 (s, 3 H) 2.94 - 3.13 (m, 2 H) 2.74 - 2.85 (m, 2 H) 2.59 - 2.72 (m, 2 H) 2.04 (br. s., 1 H) 1.90 (br. s., 1 H) 1.37 - 1.70 (m, 3 H). MS (LC/MS) R.T. = 1.37; $[M+H]^+$ = 312.2. Optical rotation = + 35.99°.

EXAMPLE 11

N-(6-Ethoxybenzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

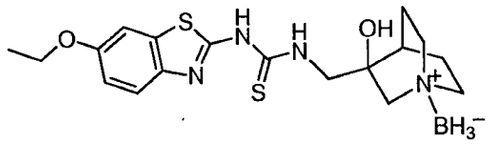


Step A: N-(6-Ethoxybenzo[d]thiazol-2-yl)- 1H-imidazole-1-carbothioamide



In a vial was placed 6-ethoxybenzo[d]thiazol-2-amine (1.5 g, 7.72 mmol) and di(^{1}H-imidazol-1-yl)methanethione (1.789 g, 10.04 mmol) in acetonitrile (15 mL). The reaction was heated to 80 °C overnight. The reaction mixture was filtered and the precipitate was collected to afford 2.4 grams (7.88 mmol, 102 %) of rust-colored solids.

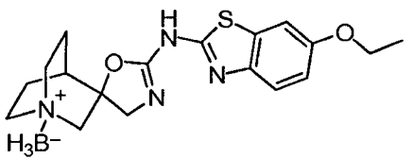
Step B: (3-((3-(6-Ethoxybenzo[d]thiazol-2-yl)thioureido)methyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate



In a vial was placed N-(6-ethoxybenzo[d]thiazol-2-yl)- ^{1}H-imidazole-1-carbothioamide (2.4 g, 7.88 mmol) and (3-(aminomethyl)-3-hydroxy-1-

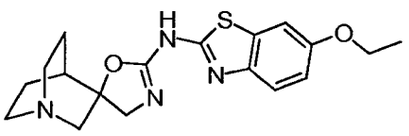
ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (1.341 g, 7.88 mmol) in N,N-dimethylformamide (8 mL). The reaction was heated to 80 °C. After 2 hours the reaction was poured into water and chloroform and the organic was extracted and concentrated to a red oil. This material was used in the next reaction without any further purification or characterization.

Step C: (2-(6-Ethoxybenzo[d]thiazol-2-ylamino)-4H-1'-ammoniospiro-[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate



In a flask was placed (3-((3-(6-ethoxybenzo[d]thiazol-2-yl)thioureido)-methyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (3.2 g, 7.9 mmol) and N,N'-diisopropylcarbodiimide (4.3 mL, 27.6 mmol) in N,N-dimethylformamide (10 mL). The reaction was heated to 70 °C for 2 hours and then poured into water and chloroform. The organic was collected and concentrated to a residue. The residue was triturated in ether and the precipitate was collected via vacuum filtration to yield 1.11 grams (2.98 mmol, 37.8 %) of gray powder.

Step D: N-(6-Ethoxybenzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



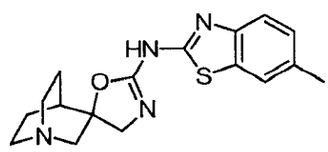
In a vial was placed (2-(6-ethoxybenzo[d]thiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate (500 mg, 1.34 mmol) and HCl (8.06 mL, 24.17 mmol) in acetone (10 mL). The reaction was monitored by HPLC. After 2 hours, the reaction was complete by LC/MS. The reaction was poured into water and chloroform, and the organic layer was set aside. The aqueous layer was neutralized and extracted with chloroform (2x). The second chloroform fraction was concentrated to a white residue. The solid was triturated in ether and the precipitate collected to yield 314.4 mg (0.877 mmol, 65.3 %) of the

desired material. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.89 (1 H, br. s.), 7.50 (1 H, d, *J*=8.81 Hz), 7.38 (1 H, d, *J*=2.52 Hz), 6.91 (1 H, dd, *J*=8.81, 2.52 Hz), 4.03 (2 H, q, *J*=7.05 Hz), 3.87 (1 H, d, *J*=10.07 Hz), 3.62 (1 H, d, *J*=10.07 Hz), 3.02 (2 H, s), 2.78 (2 H, t, *J*=7.81 Hz), 2.66 (2 H, t, *J*=7.68 Hz), 2.05 (1 H, br. s.), 1.91 (1 H, br. s.), 1.42 - 1.67 (3 H, m), 1.33 (3 H, t, *J*=7.05 Hz). MS (LC/MS) R.T. = 1.60; $[M+H]^+$ = 359.0.

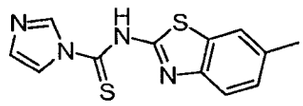
The enantiomers were separated using a Chiralpak AS-H (30 x 250mm, 5μm) column with a mobile phase consisting of 30% methanol (0.1%DEA) in CO_2 and UV monitored at 300 nm. The separated peaks were concentrated *in vacuo* to yield white powders. The first peak off the column yielded 62.4 mg, 0.17 mmol, 31.2 %. (11a; S-isomer): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.87 (1 H, br. s.), 7.49 (1 H, d, *J*=8.55 Hz), 7.38 (1 H, d, *J*=2.44 Hz), 6.91 (1 H, dd, *J*=8.85, 2.44 Hz), 4.03 (2 H, q, *J*=7.02 Hz), 3.87 (1 H, d, *J*=10.07 Hz), 3.61 (1 H, d, *J*=10.07 Hz), 3.02 (2 H, s), 2.72 - 2.85 (2 H, m), 2.66 (2 H, t, *J*=7.63 Hz), 2.05 (1 H, br. s.), 1.91 (1 H, br. s.), 1.43 - 1.64 (3 H, m), 1.33 (3 H, t, *J*=7.02 Hz). MS (LC/MS) R.T. = 1.81; $[M+H]^+$ = 359.1. The second peak yielded 58.9 mg, 0.164 mmol, 29.5 %. (11b; R-isomer): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.86 (1 H, br. s.), 7.48 (1 H, d, *J*=8.85 Hz), 7.37 (1 H, d, *J*=2.44 Hz), 6.91 (1 H, d, *J*=2.75 Hz), 4.02 (2 H, q, *J*=7.02 Hz), 3.86 (1 H, d, *J*=9.77 Hz), 3.61 (1 H, d, *J*=9.77 Hz), 3.01 (2 H, s), 2.72 - 2.85 (2 H, m), 2.62 - 2.69 (2 H, m), 2.04 (1 H, d, *J*=2.44 Hz), 1.90 (1 H, d, *J*=4.27 Hz), 1.42 - 1.63 (3 H, m), 1.29 - 1.35 (3 H, m). MS (LC/MS) R.T. = 1.52; $[M+H]^+$ = 359.1.

EXAMPLE 12

N-(6-Methylbenzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

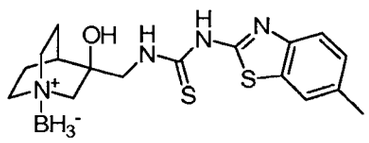


Step A: N-(6-Methylbenzo[d]thiazol-2-yl)-^{1}H-imidazole-1-carbothioamide



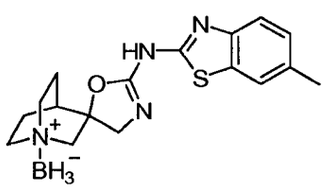
To 6-methylbenzo[d]thiazol-2-amine (1. g, 6.2 mmol) in acetonitrile (30 mL) was added 1,1'-thiocarbonyldiimidazole (1.44 g, 8.1 mmol). The reaction was stirred at 50 °C for 18 hours. The reaction was cooled to room temperature and the precipitate was filtered and washed with acetonitrile (2 x 50 mL). The yellow powder was dried in a vacuum oven (40 °C) for 1 hour to yield N-(6-methylbenzo[d]thiazol-2-yl)-^{1}H-imidazole-1-carbothioamide (1.06 g, 3.86 mmol, 62 % yield) and then used in the next step without any further purification or characterization.

Step B: (3-Hydroxy-3-((3-(6-methylbenzo[d]thiazol-2-yl)thioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate



To N-(6-methylbenzo[d]thiazol-2-yl)-^{1}H-imidazole-1-carbothioamide (0.96 g, 3.5 mmol) in N,N-dimethylformamide (20 mL) was added (3-(aminomethyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (0.595 g, 3.5 mmol). The reaction was stirred at 70°C for 4 hours. The reaction mixture was concentrated and purified via silica gel chromatography (40-100% ethyl acetate/hexanes). The product fractions were concentrated *in vacuo* to yield (3-hydroxy-3-((3-(6-methylbenzo[d]thiazol-2-yl)thioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (0.88 g, 2.338 mmol, 66.8 % yield) as a white powder. MS (LC/MS) R.T. = 3.71; $[M+H]^+$ = 375.2.

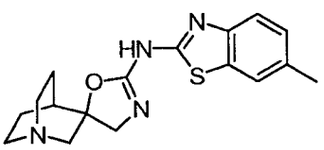
Step C: (2-(6-Methylbenzo[d]thiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate



To (3-hydroxy-3-((3-(6-methylbenzo[d]thiazol-2-yl)thioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (0.86 g, 2.285 mmol) in N,N-

dimethylformamide (20 mL) was added N,N'-diisopropylcarbodiimide (0.288 g, 2.285 mmol). The reaction was stirred at 70 °C for 4 hours. The reaction was concentrated and ethyl acetate was added. The precipitate was filtered and washed with additional ethyl acetate. The powder was dried in a vacuum oven (70°C) to yield (2-(6-methylbenzo[d]thiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate (0.65 g, 1.899 mmol, 83 % yield) as a white powder. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.03 (1 H, br. s.), 7.59 (1 H, s), 7.51 (1 H, d, *J*=8.24 Hz), 7.15 (1 H, d, *J*=8.24 Hz), 3.86 (1 H, d, *J*=10.38 Hz), 3.74 (1 H, d, *J*=10.38 Hz), 3.29 (1 H, dd, *J*=15.26, 1.83 Hz), 3.14 (1 H, d, *J*=15.26 Hz), 2.99 - 3.09 (1 H, m), 2.80 - 2.95 (3 H, m), 2.36 (3 H, s), 2.25 (1 H, br. s.), 2.03 (1 H, t, *J*=10.22 Hz), 1.70 - 1.85 (3 H, m). MS (LC/MS) R.T. = 2.78; $[M+H]^+$ = 343.2.

Step D: N-(6-Methylbenzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

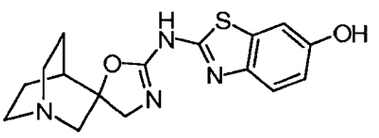


To (2-(6-methylbenzo[d]thiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate (0.24 g, 0.70 mmol) in acetone (9 mL) was added 3 M HCl (1.753 mL, 5.26 mmol). The reaction mixture was stirred at room temperature for 4 hours. Ethyl acetate was added and the aqueous layer was collected and neutralized with 1N sodium hydroxide. The product was extracted with ethyl acetate (2 x 40 mL). The organics were combined, dried with magnesium sulfate, filtered and concentrated *in vacuo* to afford N-(6-methylbenzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.19 g, 0.58 mmol, 83 % yield) as a white powder. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.96 (1 H, br. s.), 7.57 (1 H, s), 7.49 (1 H, d, *J*=8.24 Hz), 7.13 (1 H, d, *J*=8.24 Hz), 3.88 (1 H, d, *J*=10.07 Hz), 3.63 (1 H, d, *J*=9.77 Hz), 2.98 - 3.04 (2 H, m), 2.72 - 2.85 (2 H, m), 2.66 (2 H, t, *J*=7.63 Hz), 2.36 (3 H, s), 2.05 (1 H, d, *J*=2.14 Hz), 1.91 (1 H, br. s.), 1.53 - 1.64 (2 H, m), 1.42 - 1.53 (1 H, m). MS (LC/MS) R.T. = 1.79; $[M+H]^+$ = 329.2.

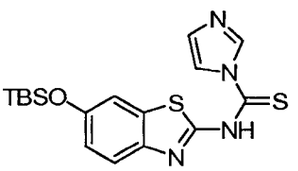
The enantiomers were separated using a Chiralcel OJ-H (4.6 x 25 cm, 5μm) column with 30% methanol (0.1%DEA) in CO_2 and UV monitored at 300 nm. The separated peaks were concentrated *in vacuo* to yield white powders. The first peak off the column yielded 0.11 g, 0.34 mmol, 55 %. (12a; R-isomer): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.95 (s, 1 H), 7.57 (s, 2 H), 7.48 (d, *J*=8.24 Hz, 2 H), 7.13 (d, *J*=8.24 Hz, 2 H), 3.89 (d, *J*=10.38 Hz, 2 H), 3.63 (d, *J*=10.38 Hz, 2 H), 2.99 - 3.06 (m, 4 H), 2.75 - 2.84 (m, 4 H), 2.67 (t, *J*=7.63 Hz, 4 H), 2.37 (s, 7 H), 2.06 (s, 2 H), 1.92 (s, 2 H), 1.55 - 1.64 (m, 4 H), 1.49 (dd, *J*=9.77, 2.44 Hz, 2 H). MS (LC/MS) R.T. = 1.80; $[M+H]^+$ = 329.2. Optical rotation = -4.52. The second peak yielded 0.11 g, 0.34 mmol, 55 %. (12b; S-isomer): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.96 (s, 1 H), 7.58 (s, 1 H), 7.49 (d, *J*=8.24 Hz, 1 H), 7.14 (d, *J*=8.24 Hz, 1 H), 3.89 (d, *J*=10.07 Hz, 1 H), 3.63 (d, *J*=10.07 Hz, 1 H), 3.03 (d, *J*=2.44 Hz, 2 H), 2.75 - 2.84 (m, 2 H), 2.67 (t, *J*=7.78 Hz, 2 H), 2.37 (s, 3 H), 2.06 (s, 1 H), 1.92 (s, 1 H), 1.55 - 1.64 (m, 2 H), 1.49 (dd, *J*=9.77, 2.75 Hz, 1 H). MS (LC/MS) R.T. = 1.80; $[M+H]^+$ = 329.2. Optical rotation= + 10.08.

EXAMPLE 13

2-(4H-1'-Azaspiro[oxazole-5,3'-bicyclo[2.2.2]octane]-2-ylamino)benzo[d]thiazol-6-ol



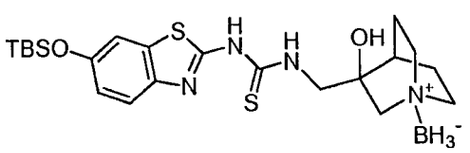
Step A: N-(6-(tert-Butyldimethylsilyloxy)benzo[d]thiazol-2-yl)-1H-imidazole-1-carbothioamide



To 6-(tert-butyldimethylsilyloxy)benzo[d]thiazol-2-amine (prepared as described in WO 2007/086800 p.102) (3.1 g, 11.05 mmol) in acetonitrile (30 mL) was added thiocarbonyl diimidazole (2.56 g, 14.37 mmol). The reaction was heated to 70°C overnight. The reaction was cooled to room temperature and the precipitate

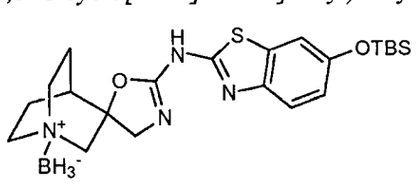
was filtered and washed with acetonitrile to afford a yellow solid. The product, N-(6-(tert-butyldimethylsilyloxy)benzo[d]thiazol-2-yl)-1H-imidazole-1-carbothioamide (3.85 g, 9.86 mmol, 89 % yield), was taken directly to the next step without any further purification. MS (LC/MS) R.T. = 2.56; $[M+H]^+ = 388.9$.

Step B: (3-((3-(6-(tert-Butyldimethylsilyloxy)benzo[d]thiazol-2-yl)thioureido)methyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate



To N-(6-(tert-butyldimethylsilyloxy)benzo[d]thiazol-2-yl)-1H-imidazole-1-carbothioamide (3.85 g, 9.86 mmol) in N,N-dimethylformamide (40 mL) was added (3-(aminomethyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (1.68 g, 9.86 mmol). The reaction was heated at 80 °C for 2 hours. The reaction was cooled and then poured into a mixture of chloroform and water. The organic layer was collected and concentrated *in vacuo* to afford (3-((3-(6-(tert-butyldimethylsilyloxy)benzo[d]thiazol-2-yl)thioureido)methyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (6.2 g) as a yellow oil.

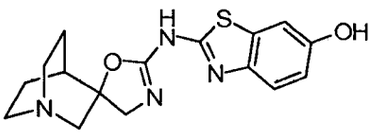
Step C: (2-(6-(tert-Butyldimethylsilyloxy)benzo[d]thiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate



To (3-((3-(6-(tert-butyldimethylsilyloxy)benzo[d]thiazol-2-yl)thioureido)methyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (4.9 g, 9.9 mmol) in N,N-dimethylformamide (10 mL) was added 1,3-diisopropylcarbodiimide (5.4 mL, 34.5 mmol). The reaction was heated to 80 °C and monitored by LC/MS. The reaction was cooled and then poured into a mixture of chloroform and water. The organic layer was collected and concentrated *in vacuo*. The remaining residue was triturated in ether. The precipitate was collected to afford (2-(6-(tert-butyldimethylsilyloxy)benzo[d]thiazol-2-ylamino)-4H-1'-

ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate (3.28 g, 7.15 mmol, 72.6 % yield). MS (LC/MS) R.T. = 3.60; $[M+H-BH_3]^+$ = 445.2.

Step D: 2-(4H-1'-Azaspiro[oxazole-5,3'-bicyclo[2.2.2]octane]-2-ylamino)benzo[d]thiazol-6-ol



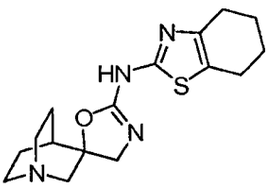
To (2-(6-(tert-butyldimethylsilyloxy)benzo[d]thiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate (3.2 g, 6.98 mmol) in acetone (10 mL) was added HCl (8.14 mL, 24.43 mmol). The reaction was stirred at room temperature for 3 hours. The mixture was poured into water and neutralized with saturated sodium bicarbonate. The aqueous layer was then extracted with chloroform. The organic layer was collected and concentrated *in vacuo*. The remaining residue was triturated in ether to afford racemic 2-(4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octane]-2-ylamino)benzo[d]thiazol-6-ol (958 mg, 2.90 mmol, 41.5 % yield) as a white powder. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.36 (1 H, br. s.), 8.85 (1 H, br. s.), 7.41 (1 H, d, *J*=8.85 Hz), 7.12 (1 H, d, *J*=2.44 Hz), 6.78 (1 H, dd, *J*=8.85, 2.44 Hz), 3.86 (1 H, d, *J*=10.07 Hz), 3.61 (1 H, d, *J*=10.07 Hz), 2.96 - 3.06 (2 H, m), 2.71 - 2.85 (2 H, m), 2.66 (2 H, t, *J*=7.78 Hz), 2.04 (1 H, br. s.), 1.90 (1 H, br. s.), 1.43 - 1.64 (3 H, m). MS (LC/MS) R.T. = 1.03; $[M+H]^+$ = 331.29.

The enantiomers were separated using a Chiralpak AD-H (30 x 250mm, 5μm) column with a mobile phase consisting of 30% methanol (0.1% DEA) in CO_2. The wavelength was set at 300 nM. The separated peaks were concentrated *in vacuo* to yield white powders. The first peak off the column was (S)-2-(4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octane]-2-ylamino)benzo[d]thiazol-6-ol (395.2 mg, 1.19 mmol, 41.4 % yield). (13a, S-isomer): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.36 (1 H, br. s.), 8.84 (1 H, br. s.), 7.41 (1 H, d, *J*=8.55 Hz), 7.12 (1 H, d, *J*=2.44 Hz), 6.78 (1 H, dd, *J*=8.55, 2.44 Hz), 3.86 (1 H, d, *J*=9.77 Hz), 3.61 (1 H, d, *J*=10.07 Hz), 2.96 - 3.05 (2 H, m), 2.72 - 2.84 (2 H, m), 2.65 (2 H, t, *J*=7.63 Hz), 2.04 (1 H, br. s.), 1.90 (1 H, br. s.), 1.52 - 1.64 (2 H, m), 1.43 - 1.52 (1 H, m). MS

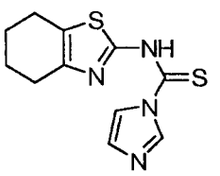
(LC/MS) R.T. = 1.30; $[M+H]^+$ = 331.4. The second peak was (R)-2-(4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octane]-2-ylamino)benzo[d]thiazol-6-ol (375 mg, 1.14 mmol, 39.3 % yield). (13b, R-isomer): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.40 (1 H, d, *J*=8.55 Hz), 7.11 (1 H, d, *J*=2.44 Hz), 6.77 (1 H, dd, *J*=8.55, 2.44 Hz), 3.86 (1 H, d, *J*=10.07 Hz), 3.60 (1 H, d, *J*=10.07 Hz), 3.01 (2 H, s), 2.73 - 2.84 (2 H, m), 2.65 (2 H, t, *J*=7.78 Hz), 2.04 (1 H, br. s.), 1.90 (1 H, br. s.), 1.54 - 1.62 (2 H, m), 1.43 - 1.52 (1 H, m). MS (LC/MS) R.T. = 1.43; $[M+H]^+$ = 331.4.

EXAMPLE 14

N-(4,5,6,7-Tetrahydrobenzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

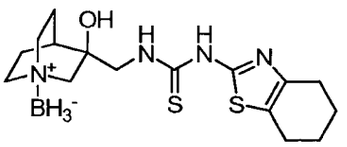


Step A: N-(4,5,6,7-Tetrahydrobenzo[d]thiazol-2-yl)-1H-imidazole-1-carbothioamide



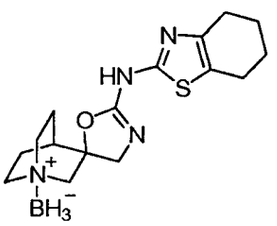
To 4,5,6,7-tetrahydrobenzo[d]thiazol-2-amine (0.5 g, 3.24 mmol) in acetonitrile (20 mL) was added di(1H-imidazol-1-yl)methanethione (0.58 g, 3.24 mmol). The reaction was stirred at 50 °C for 4 hours. The reaction was cooled and concentrated to yield crude product. The crude material was purified via flash chromatography (50-100% ethyl acetate-hexane) to yield N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)-1H-imidazole-1-carbothioamide (0.60 g, 2.27 mmol, 70.0 % yield) as a white powder.

Step B: (3-Hydroxy-3-((3-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)thioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate



To N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)-1H-imidazole-1-carbothioamide (0.54 g, 2 mmol) in N,N-dimethylformamide (20 mL) was added (3-(aminomethyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (0.35 g, 2 mmol). The reaction was stirred at 50 °C for 3 hours. The reaction was cooled and concentrated to yield crude product. The crude material was purified via flash chromatography (50-100% ethyl acetate-hexanes) yielding the first spot/fractions (TLC) as the product. The fractions were combined and concentrated to yield (3-hydroxy-3-((3-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)thioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (0.51 g, 1.39 mmol, 68.2 % yield) as a white powder. ^{1}H NMR (500 MHz, *DMSO-D6*) δ ppm 11.46 (s, 1 H), 5.26 (s, 1 H), 3.89 (dd, *J*=13.58, 5.34 Hz, 1 H), 3.68 (dd, *J*=13.73, 4.88 Hz, 1 H), 2.55 - 2.94 (m, 8 H), 2.06 (dd, *J*=9.31, 3.20 Hz, 1 H), 1.66 - 1.90 (m, 6 H), 1.21 - 1.59 (m, 4 H); $[M+H]^+ = 365.1$.

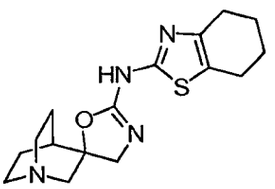
Step C: (2-(4,5,6,7-Tetrahydrobenzo[d]thiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate



To (3-hydroxy-3-((3-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)thioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (0.5 g, 1.37 mmol) in N,N-dimethylformamide (20 mL) was added N,N-diisopropylcarbodiimide (0.74 mL, 4.78 mmol). The reaction was stirred at 70°C for 4 hours. The reaction was concentrated to yield a crude residue. The crude material was purified via flash chromatography (50-100% ethyl acetate-hexanes) yielding the second spot/fractions

(TLC) as the product. The fractions were combined and concentrated to yield (2-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate (0.38 g, 1.14 mmol, 84 % yield) as a white powder. ^{1}H NMR (500 MHz, *DMSO-D6*) δ ppm 8.26 - 8.86 (m, 1 H), 3.78 (d, *J*=9.46 Hz, 1 H), 3.66 (d, *J*=9.77 Hz, 1 H), 3.19 - 3.30 (m, *J*=14.95, 2.14 Hz, 1 H), 2.96 - 3.12 (m, 2 H), 2.78 - 2.94 (m, 3 H), 2.54 - 2.65 (m, 4 H), 2.19 (s, 1 H), 2.00 (s, 1 H), 1.66 - 1.85 (m, 7 H), 1.43 (m, 3 H). MS (LC/MS) R.T. = 2.50; $[M+H-BH_3]^+$ = 319.1.

Step D: N-(4,5,6,7-Tetrahydrobenzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



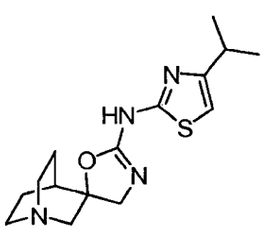
To (2-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate (0.36 g, 1.08 mmol) in acetone (9 mL) was added 3M HCl (0.36 mL, 1.08 mmol). The reaction was stirred at room temperature for 4 hours. The reaction was complete by TLC (lower spot). Ethyl acetate was added and the aqueous layer was then separated. The aqueous layer was neutralized with 1N sodium hydroxide. The product was extracted with ethyl acetate (2 x 40 mL). The organics were combined, dried with magnesium sulfate, filtered, and concentrated *in vacuo* to afford racemic N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.28 g, 0.84 mmol, 78 % yield) as a white powder. ^{1}H NMR (500 MHz, *DMSO-D6*) δ ppm 8.30 - 8.75 (br.s, 1 H), 3.79 (d, *J*=9.44 Hz , 1 H), 3.55 (d, *J*=9.76 Hz , 1 H), 2.90 - 3.03 (m, 2 H), 2.54 - 2.84 (m, 8 H), 2.00 (s, 1 H), 1.81 - 1.93 (m, 1 H), 1.75 (d, *J*=2.44 Hz, 4 H), 1.36 - 1.67 (m, 3 H). MS (LC/MS) R.T. = 1.39; $[M+H]^+$ = 319.1.

The enantiomers were separated using a Chiralpak AD-H (30 x 250mm, 5μm) column with a mobile phase consisting of 23% methanol (0.1% DEA) in CO_2. The wavelength was set at 300 nM. The separated peaks were concentrated *in vacuo* to yield white powders. The first peak off the column was (S)-N-(4,5,6,7-

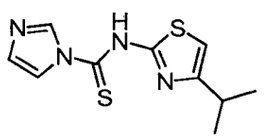
tetrahydrobenzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.1 g, 0.29 mmol, 36.8 % yield). (14a, S-isomer): ^{1}H NMR (500 MHz, *DMSO-D6*) δ ppm 8.29 - 8.89 (br.s, 1 H), 3.80 (d, *J*=9.46 Hz, 1 H), 3.54 (d, *J*=9.77 Hz, 1 H), 2.94 - 3.04 (m, 2 H), 2.55 - 2.85 (m, 8 H), 2.00 (s, 1 H), 1.85 - 1.94 (m, 1 H), 1.70 - 1.81 (m, *J*=2.43 Hz , 4 H), 1.39 - 1.65 (m, 3 H). MS (LC/MS) R.T. = 1.54; $[M+H]^+$ = 319.1. The second peak was (R)-N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.11 g, 0.30 mmol, 38.2 % yield). (14b, R-isomer): ^{1}H NMR (500 MHz, *DMSO-D6*) δ ppm 8.24 - 8.96 (br.s, 1 H), 3.79 (d, *J*=9.46 Hz, 1 H), 3.52 (d, *J*=9.76 Hz, 1 H), 2.95 - 3.08 (m, 2 H), 2.55 - 2.80 (m, 8 H), 2.00 (s, 1 H), 1.85 - 1.90 (m, 1 H), 1.70 - 1.79 (m, *J*=2.42 Hz , 4 H), 1.39 - 1.63 (m, 3 H); $[M+H]^+$ = 319.1.

EXAMPLE 15

N-(4-Isopropylthiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

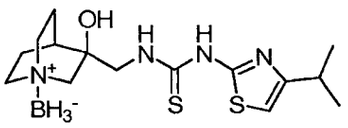


Step A: N-(4-Isopropylthiazol-2-yl)-1H-imidazole-1-carbothioamide



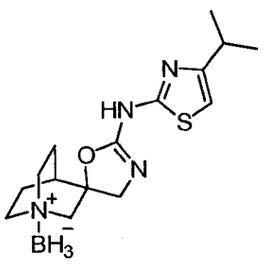
To 4-isopropylthiazol-2-amine (1.04 g, 7.31 mmol) in acetonitrile (30 mL) was added 1,1-thiocarbonyldiimidazole (1.7 g, 9.5 mmol). The reaction was stirred at 50 °C for 18 hours. The reaction was cooled to room temperature and the precipitate was filtered and washed with acetonitrile (2 x 50 mL). The yellow powder was dried in a vacuum oven (40°C) for 2 hours. The product, N-(4-isopropylthiazol-2-yl)-1H-imidazole-1-carbothioamide (1.02 g, 4.04 mmol, 55.3 % yield), was taken directly to the next step without any further purification.

Step B: (3-Hydroxy-3-((3-(4-isopropylthiazol-2-yl)thioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate



To N-(4-isopropylthiazol-2-yl)-1H-imidazole-1-carbothioamide (0.57 g, 2.26 mmol) in N,N-dimethylformamide (20 mL) was added (3-(aminomethyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (0.38 g, 2.26 mmol). The reaction was stirred at 70°C for 24 hours. The reaction was cooled and concentrated to yield crude product. The crude material was purified via flash chromatography (50-100% ethyl acetate-hexane) to yield (3-hydroxy-3-((3-(4-isopropylthiazol-2-yl)thioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (0.56 g, 1.58 mmol, 70.0 % yield) as a white powder. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.62 (s, 1 H), 6.70 (s, 1 H), 5.31 (s, 1 H), 3.58 - 3.96 (m, 2 H), 2.63 - 3.11 (m, 7 H), 2.00 - 2.22 (m, 1 H), 1.65 - 1.97 (m, 3 H), 1.16 - 1.61 (m, 10 H). MS (LC/MS) R.T. = 3.43; $[M+H]^+$ = 353.2.

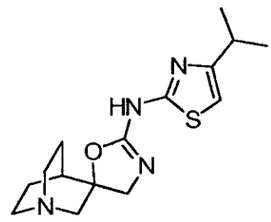
Step C: (2-(5-Isopropylthiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate



To (3-hydroxy-3-((3-(5-isopropylthiazol-2-yl)thioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (0.54 g, 1.52 mmol) in N,N-dimethylformamide (20 mL) was added N,N'-diisopropylcarbodiimide (0.83 mL, 5.33 mmol). The reaction was stirred at 50 °C for 24 hours. The reaction was concentrated to yield a crude residue. The crude material was purified via flash chromatography (50-100% ethyl acetate-hexanes) yielding the second spot/fractions (TLC) as the product. The fractions were combined and concentrated to yield (2-(5-isopropylthiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-

1'-yl)trihydroborate (0.39 g, 1.22 mmol, 80 % yield) as a white powder. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 6.55 (s, 1 H), 3.75 (m, 2 H), 3.20 - 3.31 (m, 1 H), 2.96 - 3.15 (m, 2 H), 2.77 - 2.97 (m, 4 H), 2.22 (s, 1 H), 2.01 (s, 1 H), 1.68 - 1.90 (m, 3 H), 1.43 (s, 3 H), 1.21 (d, *J*=7.02 Hz, 6 H). MS (LC/MS) R.T. = 2.36; $[M+H-BH_3]^+$ = 307.2.

Step D: N-(4-Isopropylthiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



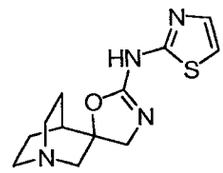
To (2-(4-isopropylthiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate (0.42 g, 1.31 mmol) in acetone (9 mL) was added 3M HCl (0.44 mL, 1.31 mmol). The reaction was stirred at room temperature for 4 hours. The reaction was complete by TLC (lower spot). Ethyl acetate was added and the aqueous layer was then separated. The aqueous layer was neutralized with 1N sodium hydroxide. The product was extracted with ethyl acetate (2 x 40 mL). The organics were combined, dried with magnesium sulfate, filtered, and concentrated *in vacuo* to afford racemic N-(4-isopropylthiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.34 g, 1.05 mmol, 80 % yield) as a white powder. ^{1}H NMR (500 MHz, *DMSO-D6*) δ ppm 8.20 - 8.91 (m, 1 H), 6.52 (s, 1 H), 3.83 (d, *J*=9.46 Hz, 1 H), 3.57 (d, *J*=9.46 Hz, 1 H), 2.99 (s, 2 H), 2.58 - 2.92 (m, 5 H), 2.02 (s, 1 H), 1.82 - 1.96 (m, 1 H), 1.38 - 1.66 (m, 3 H), 1.20 (d, *J*=7.02 Hz, 6 H). MS (LC/MS) R.T. = 1.27; $[M+H]^+$ = 307.1.

The enantiomers were separated using a Chiralcel OJ-H (30 x 250mm, 5μm) column with a mobile phase consisting of 23% methanol (0.1% DEA) in CO_2. The wavelength was set at 300 nM. The separated peaks were concentrated *in vacuo* to yield white powders. The first peak off the column was (S)-N-(4-isopropylthiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.01 g, 0.03 mmol, 2.95 % yield). (15a, S-isomer): ^{1}H NMR (500 MHz, *DMSO-D6*) δ ppm 8.35 - 8.95 (m, 1 H), 6.52 (s, 1 H), 3.82 (d, *J*=9.41 Hz , 1 H), 3.57 (d, *J*=9.46 Hz, 1 H), 2.99 (s, 2

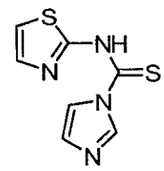
H), 2.60 - 2.88 (m, 5 H), 2.02 (s, 2 H), 1.82 - 1.96 (m, 1 H), 1.38 - 1.65 (m, 3 H), 1.20 (d, *J*=6.71 Hz, 6 H). MS (LC/MS) R.T. = 1.38; $[M+H]^+$ = 307.1. The second peak was (R)-N-(4-isopropylthiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.02 g, 0.05 mmol, 4.83 % yield). (15b, R-isomer): ^{1}H NMR (500 MHz, *DMSO-D6*) δ ppm 8.35 - 8.91 (m, 1 H), 6.52 (s, 1 H), 3.82 (d, *J*=9.44 Hz , 1 H), 3.57 (d, *J*=9.46 Hz, 1 H), 2.99 (s, 2 H), 2.60 - 2.90 (m, 5 H), 2.02 (s, 2 H), 1.82 - 1.96 (m, 1 H), 1.38 - 1.62 (m, 3 H), 1.20 (d, *J*=6.78 Hz, 6 H). MS (LC/MS) R.T. = 1.49; $[M+H]^+$ = 307.3.

EXAMPLE 16

N-(Thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

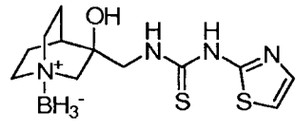


Step A: N-(Thiazol-2-yl)-1H-imidazole-1-carbothioamide



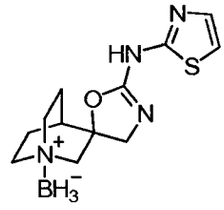
To thiazol-2-amine (2.12 g, 21.17 mmol) in acetonitrile (30 mL) and tetrahydrofuran (5 mL) was added di(1H-imidazol-1-yl)methanethione (4.90 g, 27.5 mmol). The reaction was stirred at 60 °C for 5 hours. The reaction was cooled to room temperature and the precipitate was filtered and washed with cold acetonitrile (2 x 15 mL) to afford an orange-brown powder. The product, N-(thiazol-2-yl)-1H-imidazole-1-carbothioamide (3.70 g, 17.60 mmol, 83 % yield), was taken directly to the next step without any further characterization.

Step B: (3-Hydroxy-3-((3-thiazol-2-ylthioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate



To N-(thiazol-2-yl)-1H-imidazole-1-carbothioamide (1.7 g, 8 mmol) in N,N-dimethylformamide (30 mL) was added (3-(aminomethyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (1.37 g, 8 mmol). The reaction was stirred at 50 °C for 4 hours. The reaction was cooled and concentrated to yield crude product. The crude material was purified via flash chromatography (50-100% ethyl acetate-hexane) yielding the first spot/fractions (TLC) as the product. The fractions were combined and concentrated to yield (3-hydroxy-3-((3-thiazol-2-ylthioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (1.5 g, 4.80 mmol, 59.8 % yield) as a white powder. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.64 (s, 1 H), 7.42 (d, *J*=3.36 Hz, 1 H), 7.14 (m, 1 H), 5.32 (s, 1 H), 3.78 (dd, 2 H), 2.59 - 3.02 (m, 6 H), 1.99 - 2.18 (m, 1 H), 1.79 - 1.92 (m, 2 H), 1.64 - 1.80 (m, 1 H), 1.19 - 1.65 (m, 4 H). MS (LC/MS) R.T. = 2.73; $[M+H]^+$ = 311.1.

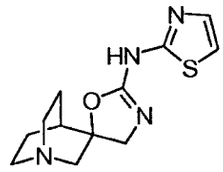
Step C: (2-(Thiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate



To (3-hydroxy-3-((3-thiazol-2-ylthioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (1.2 g, 3.84 mmol) in N,N-dimethylformamide (20 mL) was added N,N'-diisopropylcarbodiimide (2.09 mL, 13.45 mmol). The reaction was stirred at 50 °C for 24 hours. The reaction was concentrated to yield a crude residue. The crude material was purified via flash chromatography (50-100% ethyl acetate-hexane) yielding the first spot/fractions (TLC) as the product. The fractions were combined and concentrated to yield (2-(thiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-

yl)trihydroborate (0.84 g, 3.02 mmol, 79 % yield) as a white powder. ^{1}H NMR (500 MHz, *DMSO-D6*) δ ppm 8.37 - 9.14 (m, 1 H), 7.32 (d, *J*=3.66 Hz, 1 H), 7.04 (d, *J*=3.66 Hz, 2 H), 3.79 (d, *J*=10.07 Hz, 1 H), 3.67 (d, *J*=10.07 Hz, 1 H), 3.20 - 3.29 (m, *J*=14.95, 2.14 Hz, 1 H), 2.97 - 3.15 (m, 2 H), 2.78 - 2.94 (m, 3 H), 2.22 (s, 1 H), 1.95 - 2.08 (m, 1 H), 1.66 - 1.85 (m, 3 H), 1.43 (s, 3 H). MS (LC/MS) R.T. = 1.57; $[M+H-BH_3]^+$ = 265.1.

Step D: N-(Thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



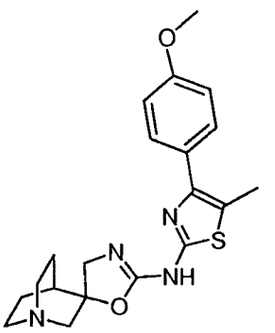
To (2-(thiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate (0.57 g, 2.05 mmol) in acetone (9 mL) was added 3M HCl (0.68 mL, 2.05 mmol). The reaction was stirred at room temperature for 4 hours. The reaction was complete by TLC (lower spot). Ethyl acetate was added and the aqueous layer was then separated. The aqueous layer was neutralized with 1N sodium hydroxide. The product was extracted with ethyl acetate (2 x 40 mL). The organics were combined, dried with magnesium sulfate, filtered, and concentrated *in vacuo* to afford racemic N-(thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.4 g, 1.44 mmol, 70.2 % yield) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.64 (s, 1 H), 7.24 (d, *J*=3.74 Hz, 2 H), 7.01 (d, *J*=3.75 Hz, 2 H), 3.78 (d, *J*=9.80 Hz, 2 H), 3.53 (d, *J*=9.80 Hz, 2 H), 2.97 - 3.05 (m, 4 H), 2.74 - 2.86 (m, 4 H), 2.65 (t, *J*=7.84 Hz, 4 H), 2.01 (s, 2 H), 1.88 (s, 2 H), 1.53 - 1.64 (m, 4 H), 1.45 - 1.56 (m, 2 H). MS (LC/MS) R.T. = 0.28; $[M+H]^+$ = 265.1.

The enantiomers were separated using a Chiralcel OJ-H (30 x 250mm, 5μm) column with a mobile phase consisting of 23% methanol (0.1% DEA) in CO_2. The wavelength was set at 300 nM. The separated peaks were concentrated *in vacuo* to yield white powders. The first peak off the column was (S)-N-(thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.12 g, 0.43 mmol, 18.80 % yield). (16a, S-isomer): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.64 (s, 1 H), 7.26 (d, *J*=3.75 Hz, 2 H), 7.00 (d, *J*=3.77 Hz, 2 H), 3.78 (d, *J*=9.81 Hz, 2 H), 3.54 (d, *J*=9.82 Hz, 2 H), 2.95 - 3.10 (m, 4 H), 2.75 - 2.82 (m, 4 H), 2.65 (t, *J*=7.80 Hz, 4 H), 2.01 (s,

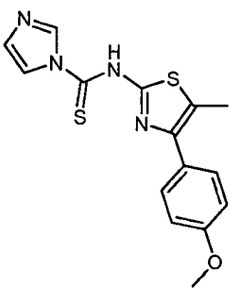
2 H), 1.88 (s, 2 H), 1.53 - 1.60 (m, 4 H), 1.42 - 1.51 (m, 2 H). MS (LC/MS) R.T. = 0.32; $[M+H]^+$ = 265.1. The second peak was (R)-N-(thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.15 g, 0.52 mmol, 22.96 % yield). (16b, R-isomer): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.64 (s, 1 H), 7.25 (d, J=3.74 Hz, 2 H), 7.00 (d, J=3.76 Hz, 2 H), 3.78 (d, J=9.80 Hz, 2 H), 3.53 (d, J=9.80 Hz, 2 H), 2.95 - 3.08 (m, 4 H), 2.75 - 2.84 (m, 4 H), 2.65 (t, J=7.80 Hz, 4 H), 2.01 (s, 2 H), 1.88 (s, 2 H), 1.54 - 1.62 (m, 4 H), 1.43 - 1.53 (m, 2 H). MS (LC/MS) R.T. = 0.28; $[M+H]^+$ = 265.3.

EXAMPLE 17

N-(4-(4-Methoxyphenyl)-5-methylthiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



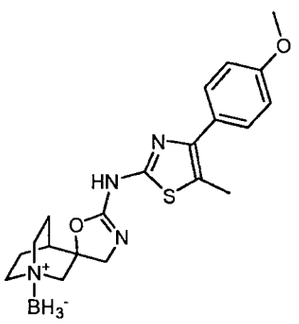
Step A: N-(4-(4-Methoxyphenyl)-5-methylthiazol-2-yl)-1H-imidazole-1-carbothioamide



To 4-(4-methoxyphenyl)-5-methylthiazol-2-amine (0.98 g, 4.45 mmol) in acetonitrile (25 mL) was added di(1H-imidazol-1-yl)methanethione (1.03 g, 5.78 mmol). The reaction was stirred at 50 °C for 3 hours. The reaction was cooled to room temperature and the precipate was filtered. The powder was washed with acetonitrile (2 x 10 mL) and dried to yield racemic N-(4-(4-methoxyphenyl)-5-

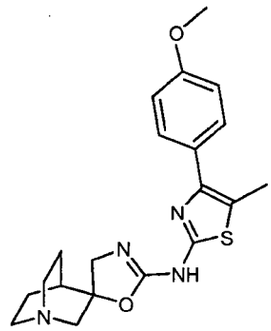
methylthiazol-2-yl)-1H-imidazole-1-carbothioamide (1.28 g, 3.87 mmol, 87 % yield) as a yellow powder. The product was taken directly to the next step.

Step B: (2-(4-(4-Methoxyphenyl)-5-methylthiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate



To N-(4-(4-methoxyphenyl)-5-methylthiazol-2-yl)-1H-imidazole-1-carboxamide (0.44 g, 1.39 mmol) in N,N-dimethylformamide (25 mL) was added (3-(aminomethyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (0.24 g, 1.39 mmol). The reaction was stirred at 70 °C for 2 hours. N,N'-Diisopropylcarbodiimide (0.65 mL, 4.16 mmol) was added and the reaction heated to 75 °C for 2 hours. The reaction was cooled and concentrated to afford the crude product. The crude material was purified *via* column chromatography (60-100% ethyl acetate/hexanes) to yield (2-(4-(4-methoxyphenyl)-5-methylthiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate (0.41 g, 1.029 mmol, 74.2 % yield) as a yellow powder. ^{1}H NMR (500 MHz, *DMSO-D6*) δ ppm 7.59 (d, *J*=7.63 Hz, 2 H), 6.98 (d, *J*=8.55 Hz, 2 H), 3.80 (s, 4 H), 3.67 (s, 1 H), 3.24 - 3.31 (m, 1 H), 3.13 (s, 1 H), 3.03 (s, 1 H), 2.83 - 2.92 (m, 3 H), 2.39 (s, 3 H), 2.23 (s, 1 H), 2.07 (s, 1 H), 1.73 - 1.82 (m, 2 H), 1.44 (s, 1 H). MS (LC/MS) R.T. = 2.88; $[M+H]^+$ = 399.34.

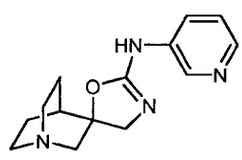
Step C: N-(4-(4-Methoxyphenyl)-5-methylthiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



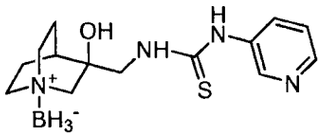
To (3-hydroxy-3-((3-(4-(4-methoxyphenyl)-5-methylthiazol-2-yl)thioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (0.08 g, 0.19 mmol) in acetone (9 mL) was added 2M HCl (0.09 mL, 0.19 mmol). The reaction was stirred at room temperature for 1 hour. The reaction was complete by TLC (lower spot). Ethyl acetate was added and the aqueous layer was collected and neutralized with 1N sodium hydroxide. The product was extracted wtih ethyl acetate (2 x 40 mL). The organics were combined, dried with magnesium sulfate, filtered, and concentrated *in vacuo* to afford racemic N-(4-(4-methoxyphenyl)-5-methylthiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.05 g, 0.12 mmol, 66.8 % yield) as a white powder. ^{1}H NMR (500 MHz, *DMSO-D6*) δ ppm 7.58 (d, *J*=8.24 Hz, 2 H), 6.98 (d, *J*=8.55 Hz, 2 H), 3.83 (d, *J*=9.16 Hz, 1 H), 3.80 (s, 3 H), 3.56 (d, *J*=9.46 Hz, 1 H), 3.00 (s, 2 H), 2.74 - 2.83 (m, 2 H), 2.66 (t, *J*=7.63 Hz, 2 H), 2.38 (s, 3 H), 2.03 (s, 1 H), 1.91 (s, 1 H), 1.54 - 1.62 (m, 2 H), 1.48 (d, *J*=7.02 Hz, 1 H). MS (LC/MS) R.T. = 2.04; $[M+H]^+$ = 385.28.

EXAMPLE 18

(E)-N-(1'-Azaspiro[oxazolidine-5,3'-bicyclo[2.2.2]octane]-2-ylidene)pyridin-3-amine

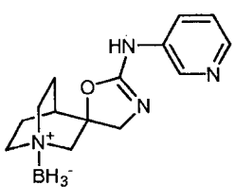


Step A: (3-Hydroxy-3-((3-pyridin-3-ylthioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate



To a stirring suspension of (3-(aminomethyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (247 mg, 1.45 mmol) in tetrahydrofuran (3 mL) was added a solution of 3-isothiocyanatopyridine (298 mg, 2.19 mmol) in tetrahydrofuran (1.5 mL) and the reaction mixture was stirred at room temperature overnight. The reaction mixture was evaporated *in vacuo* and the residue (white waxy solid) purified *via* column chromatography (3% methanol/ethyl acetate) to yield (3-hydroxy-3-((3-pyridin-3-ylthioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (294.6 mg, 0.96 mmol, 66.2 % yield) as a white foam. ^{1}H NMR (500 MHz, *MeOD-d$_4$*) δ ppm 8.56 - 8.70 (m, 1 H), 8.24 - 8.36 (m, 1 H), 8.08 - 8.16 (m, 1 H), 7.32 - 7.48 (m, 1 H), 4.02 - 4.18 (m, 1 H), 3.67 - 3.77 (m, 1 H), 3.53 - 3.62 (m, 1 H), 2.88 - 3.11 (m, 3 H), 2.70 - 2.88 (m, 1 H), 2.15 - 2.29 (m, 1 H), 1.92 - 2.12 (m, 2 H), 1.73 - 1.89 (m, 1 H), 1.54 - 1.69 (m, 2 H). MS (LC/MS) R.T. = 1.00; [MH$^+$-BH$_3$] = 293.10.

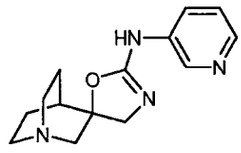
Step B: (E)-(2-(Pyridin-3-ylimino)-1'-ammoniospiro[oxazolidine-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate



To a solution of (3-hydroxy-3-((3-pyridin-3-ylthioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (294.6 mg, 0.96 mmol) in N,N-dimethylformamide (5 mL) was added a solution of N,N'-methanediylidenedipropan-2-amine (121 mg, 0.96 mmol) in N,N-dimethylformamide (1 mL) and the reaction mixture was allowed to stand at room temperature for 7 days. An additional 133 mg N,N'-methanediylidenedipropan-2-amine in 0.5 mL N,N-dimethylformamide was added and the reaction was left to continue for another 7 days. The reaction was

purified via column chromatography (5-10% methanol/ethyl acetate) to afford (E)-(2-(pyridin-3-ylimino)-1'-ammoniospiro[oxazolidine-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate (134.3 mg, 0.49 mmol, 51.3 % yield). ^{1}H NMR (500 MHz, *MeOD*) δ ppm 8.34 - 8.60 (m, 1 H), 8.16 (d, *J*=4.27 Hz, 1 H), 7.59 - 7.96 (m, 1 H), 7.35 (dd, *J*=8.24, 4.88 Hz, 1 H), 3.89 (br. s., 1 H), 3.65 (d, *J*=9.46 Hz, 1 H), 3.16 - 3.23 (m, 1 H), 3.04 - 3.16 (m, 1 H), 2.85 - 3.04 (m, 2 H), 2.23 (br. s., 1 H), 1.74 - 1.97 (m, 4 H), 1.36 - 1.70 (m, 2 H). MS (LC/MS) R.T. = 0.65; $[M+H-BH_3]^+$ = 259.21.

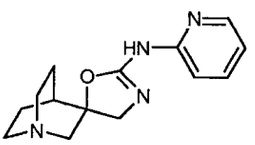
Step C: (E)-N-(1'-Azaspiro[oxazolidine-5,3'-bicyclo[2.2.2]octane]-2-ylidene)pyridin-3-amine



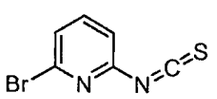
To a suspension of (E)-(2-(pyridin-3-ylimino)-1'-ammoniospiro[oxazolidine-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate (127 mg, 0.47 mmol) in acetone (5 mL) was added 3M hydrochloric acid (2 mL, 6.00 mmol) and the mixture was allowed to stand at room temperature for 2 hrs. It was then added it to a separatory funnel containing water and chloroform. The layers were separated, then the aqueous layer was made basic with sodium carbonate solution and the mixture was re-extracted with chloroform. Finally, the aqueous phase was washed with ethyl acetate. The organics were combined, dried with magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (1% ammonium hydroxide / 9% methanol / 90% dichloromethane) to afford racemic (E)-N-(1'-azaspiro[oxazolidine-5,3'-bicyclo[2.2.2]octane]-2-ylidene)pyridin-3-amine (19 mg, 0.074 mmol, 15.8 % yield) as a white solid. ^{1}H NMR (500 MHz, *MeOD-d$_4$*) δ ppm 8.39 (br. s., 1 H), 8.14 (d, *J*=4.27 Hz, 1 H), 7.72 (br. s., 1 H), 7.34 (dd, *J*=8.24, 4.88 Hz, 1 H), 3.89 (d, *J*=9.77 Hz, 1 H), 3.57 (d, *J*=10.38 Hz, 1 H), 3.14 - 3.27 (m, 1 H), 3.00 - 3.13 (m, 1 H), 2.70 - 3.00 (m, 4 H), 1.97 - 2.22 (m, 2 H), 1.54 - 1.84 (m, 3 H). MS (LC/MS) R.T. = 0.26; $[M+H]^+$ = 259.16.

EXAMPLE 19

N-(Pyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

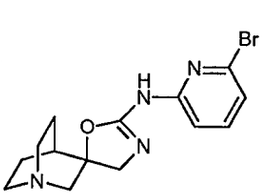


Step A: 2-Bromo-6-isothiocyanatopyridine



A mixture of 6-bromopyridin-2-amine (253 mg, 1.46 mmol), chloroform (2 mL), sodium bicarbonate (850 mg, 10.12 mmol) and water (3 mL) was assembled, and to this was added a solution of thiophosgene (190 mg, 1.65 mmol) in chloroform (1 mL). The reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was transferred to a separatory funnel and partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over magnesium sulfate, filtered and the solvent evaporated to give a yellow solid. The solid was purified by column chromatography (5% ethyl acetate/hexanes) to afford 2-bromo-6-isothiocyanatopyridine (281 mg, 1.31 mmol, 89 % yield) as a white solid. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 7.50 - 7.62 (m, 1 H), 7.34 - 7.43 (m, 1 H), 6.91 - 7.11 (m, 1 H). MS (LC/MS) R.T. = 1.92; $[M+H]^+$ = 216.86.

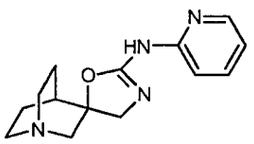
Step B: N-(6-Bromopyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



To a solution of 2-bromo-6-isothiocyanatopyridine (281 mg, 1.31 mmol) in N,N-dimethylformamide (8 mL) and Hunig's base (0.6 mL, 3.44 mmol) was added (+/-) 3-(aminomethyl)quinuclidin-3-ol dihydrochloride (300 mg, 1.31 mmol) and the resulting mixture was heated to 75 °C for 2.5 hrs. MS (LC/MS) R.T. = 1.04; $[M+H]^+$ = 373.01. To this reaction mixture was added di-isopropyl-carbodiimide (523 mg,

4.14 mmol) and the heating at 75 °C was continued for 2.25 hours. The mixture was allowed to cool to room temperature over the weekend. The reaction mixture was concentrated in vacuo. The material was purified by column chromatography then preparative HPLC to afford N-(6-bromopyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (291.5 mg, 0.86 mmol, 66.2 5 yield) as a yellow solid (containing 2-amino-6-bromopyridine impurity). MS (LC/MS) R.T. = 0.65; $[M+H]^+$ = 337.0.

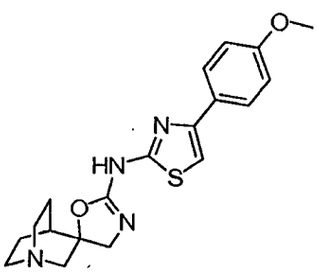
Step C: N-(Pyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



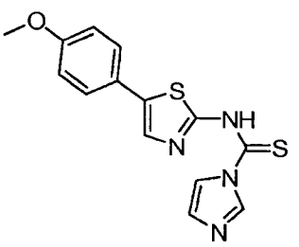
To N-(6-bromopyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (291 mg, 0.86 mmol) in methanol (20 mL) was hydrogenated over 10% palladium on carbon (23 mg) in the Parr apparatus for 2 hours. The catalyst was removed by filtration and the filtrated concentrated *in vacuo*. The residue was purified by column chromatography (0.7% ammonium hydroxide / 6.3% methanol / 93% chloroform) to give racemic N-(pyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (41.3 mg, 0.16 mmol, 18.6 5 yield). ^{1}H NMR (500 MHz, *MeOD*) δ ppm 8.13 - 8.33 (m, 1 H), 7.57 - 7.72 (m, 1 H), 6.83 - 7.04 (m, 2 H), 3.97 (d, *J*=10.07 Hz, 1 H), 3.66 (d, *J*=10.07 Hz, 1 H), 3.18 - 3.27 (m, 1 H), 3.03 - 3.14 (m, 1 H), 2.94 (t, *J*=7.63 Hz, 2 H), 2.70 - 2.90 (m, 2 H), 2.06 - 2.24 (m, 2 H), 1.57 - 1.87 (m, 3 H). MS (LC/MS) R.T. = 1.76; $[M+H]^+$ = 259.25.

EXAMPLE 20

N-(4-(4-Methoxyphenyl)thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

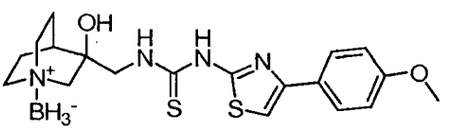


Step A: N-(5-(4-Methoxyphenyl)thiazol-2-yl)-1H-imidazole-1-carbothioamide



To 5-(4-methoxyphenyl)thiazol-2-amine (1.07 g, 5.19 mmol) in acetonitrile (30 mL) and tetrahydrofuran (5 mL) was added di(1H-imidazol-1-yl)methanethione (1.20 g, 6.74 mmol). The reaction was stirred at 60 °C for 18 hours. The reaction was cooled to room temperature and the precipitate was filtered. The powder was washed with cold acetonitrile (2 x 15 mL) and dried to yield N-(5-(4-methoxyphenyl)thiazol-2-yl)-1H-imidazole-1-carbothioamide (0.59 g, 1.86 mmol, 35.9 % yield) as a orange-brown powder. The product was taken directly to the next step without any further characterization.

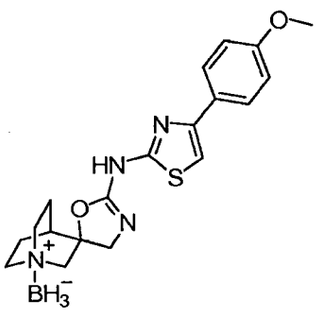
Step B: (3-Hydroxy-3-((3-(4-(4-methoxyphenyl)thiazol-2-yl)thioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate



To N-(4-(4-methoxyphenyl)thiazol-2-yl)-1H-imidazole-1-carbothioamide (0.57 g, 1.82 mmol) in N,N-dimethylformamide (20 mL) was added (3-

(aminomethyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (0.31 g, 1.82 mmol). The reaction was stirred at 60 °C for 4 hours. The reaction was cooled and concentrated to yield crude product. The crude material was purified via flash chromatography (60-100% ethyl acetate-hexane) yielding the first spot/fractions (TLC) as the product. The fractions were combined and concentrated *in vacuo* to yield (3-hydroxy-3-((3-(4-(4-methoxyphenyl)thiazol-2-yl)thioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (0.6 g, 1.43 mmol, 79 % yield) as a white powder. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.74 (s, 1 H), 7.91 (d, J=8.55 Hz, 2 H), 7.43 (s, 1 H), 6.97 (d, J=8.85 Hz, 2 H), 5.50 (s, 1 H), 3.62 - 3.98 (m, 5 H), 2.70 - 3.10 (m, 6 H), 2.13 (s, 1 H), 1.94 (s, 1 H), 1.66 - 1.91 (m, 2 H), 1.11 - 1.62 (m, 4 H). MS (LC/MS) R.T. = 3.54; $[M+H]^+$ = 417.1.

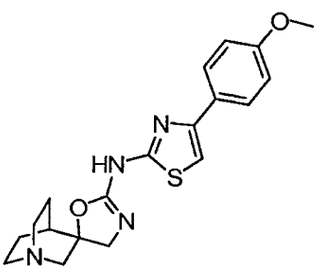
Step C: (2-(4-(4-Methoxyphenyl)thiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate



To (3-hydroxy-3-((3-(4-(4-methoxyphenyl)thiazol-2-yl)thioureido)methyl)-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (0.59 g, 1.41 mmol) in N,N-dimethylformamide (20 mL) was added N,N'-diisopropylcarbodiimide (0.66 mL, 4.23 mmol). The reaction was stirred at 70 °C for 24 hours. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (50-100% ethyl acetate-hexanes), collecting the first component as the product, to yield (2-(4-(4-methoxyphenyl)thiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate (0.45 g, 1.17 mmol, 83 % yield) as a white powder. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.65 (s, 1 H), 7.89 (d, J=7.32 Hz, 2 H), 7.15 - 7.43 (m, 1 H), 6.95 (d, J=8.85 Hz, 2 H), 3.64 - 3.93 (m, 5 H), 3.23 - 3.31 (m, J=1.53 Hz, 1 H), 3.09 - 3.21 (m, 1 H), 2.99 - 3.09 (m, 1 H), 2.79 - 2.97 (m, 3 H),

2.25 (s, 1 H), 1.96 - 2.16 (m, 1 H), 1.68 - 1.91 (m, 3 H), 1.45 (s, 3 H). MS (LC/MS) R.T. = 2.80; $[M+H-BH_3]^+ = 371.1$.

Step D: N-(4-(4-Methoxyphenyl)thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



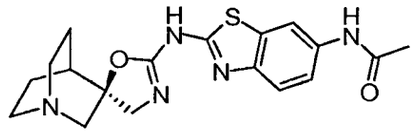
To (2-(4-(4-methoxyphenyl)thiazol-2-ylamino)-4H-1'-ammoniospiro[oxazole-5,3'-bicyclo[2.2.2]octane]-1'-yl)trihydroborate (0.41 g, 1.07 mmol) in acetone (9 mL) was added 3M HCl (0.36 mL, 1.07 mmol). The reaction was stirred at room temperature for 4 hours. The reaction was complete by TLC (lower spot). Ethyl acetate was added and the aqueous layer was then separated. The aqueous layer was neutralized with 1N sodium hydroxide. The product was extracted with ethyl acetate (2 x 40 mL). The organics were combined, dried with magnesium sulfate, filtered, and concentrated *in vacuo* to afford racemic N-(4-(4-methoxyphenyl)thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.3 g, 0.77 mmol, 72.1 % yield) as a white powder. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.56 (s, 1 H), 7.77 - 8.00 (m, J=8.55 Hz, 2 H), 7.27 (s, 1 H), 6.80 - 7.08 (m, 2 H), 3.87 (d, J=9.77 Hz, 1 H), 3.79 (s, 3 H), 3.61 (d, J=9.77 Hz, 1 H), 3.02 (s, 3 H), 2.60 - 2.92 (m, 4 H), 2.06 (s, 2 H), 1.82 - 2.00 (m, 1 H), 1.39 - 1.70 (m, 3 H). MS (LC/MS) R.T. = 1.95; $[M+H]^+ = 371.2$.

The enantiomers were separated using a Chiralpak AD-H (30 x 250mm, 5μm) column with a mobile phase consisting of 30% methanol (0.1% DEA) in CO_2. The wavelength was set at 220 nM. The separated peaks were concentrated *in vacuo* to yield white powders. The first peak off the column was (S)-N-(4-(4-methoxyphenyl)thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.035 g, 0.09 mmol, 22.87 % yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.56 (1 H, br. s.), 7.86 (2 H, d, J=8.55 Hz), 7.25 (1 H, s), 6.93 - 6.96 (2 H, m), 3.86 (1 H, d, J=9.77 Hz), 3.78 (3 H, s), 3.60 (1 H, d, J=9.46 Hz), 3.01 (2 H, s), 2.72 - 2.84 (2

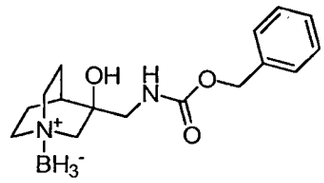
H, m), 2.62 - 2.71 (2 H, m), 2.05 (1 H, br. s.), 1.91 (1 H, br. s.), 1.55 - 1.64 (2 H, m), 1.44 - 1.52 (1 H, m). MS (LC/MS) R.T. = 2.03; $[M+H]^+$ = 371.3. The second peak was (R)-N-(4-(4-methoxyphenyl)thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.055 g, 0.15 mmol, 35.9 % yield). (21b, R-isomer): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.58 (1 H, br. s.), 7.87 (2 H, d, *J*=8.55 Hz), 7.26 (1 H, s), 6.92 - 6.97 (2 H, m), 3.86 (1 H, d, *J*=9.77 Hz), 3.78 (3 H, s), 3.60 (1 H, d, *J*=9.77 Hz), 3.01 (2 H, s), 2.73 - 2.85 (2 H, m), 2.63 - 2.71 (2 H, m), 2.05 (1 H, br. s.), 1.91 (1 H, br. s.), 1.54 - 1.64 (2 H, m), 1.43 - 1.53 (1 H, m). MS (LC/MS) R.T. = 2.03; $[M+H]^+$ = 371.3.

EXAMPLE 21

(R)-N-(2-(4H-1'-Azaspiro[oxazole-5,3'-bicyclo[2.2.2]octane]-2-ylamino)benzo[d]thiazol-6-yl)acetamide



Step A: (3-((Benzyloxycarbonylamino)methyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate

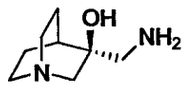


To (3-(aminomethyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (10 g, 47.0 mmol) in dichloromethane (150 mL) was added sodium carbonate (200 mL, 200 mmol) and benzyl chloroformate (9.5 mL, 66.5 mmol). The reaction mixture was stirred at room temperature for 40 minutes. Dichloromethane and water were added and the aqueous layer was then separated and extracted again with dichloromethane (2x). The organic layers were combined, dried over sodium sulfate, filtered and concentrated. The residue was purified via flash chromatography (12-100% ethyl acetate-hexanes). The product fractions were combined and concentrated to yield racemic (3-((benzyloxycarbonylamino)methyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (3 g, 9.86 mmol, 20.96 % yield) as

a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.30 - 7.43 (5 H, m), 5.27 (1 H, br. s.), 5.12 (2 H, s), 3.36 (2 H, d, *J*=6.04 Hz), 2.76 - 3.21 (6 H, m), 2.21 (1 H, br. s.), 1.97 (1 H, br. s.), 1.71 - 1.86 (2 H, m).

The enantiomers were separated using a Chiralpak OJ-H (5 x 25) column with a mobile phase consisting of 20% acetonitrile/methanol (1:1) in CO_2. The wavelength was set at 210 nM. The first peak off the column was (R)-(3-(aminomethyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (37.67 g, 123 mmol) as a colorless oil. Optical rotation: +28.2, c=2.9 in chloroform. The second peak off the column was (S)-(3-((benzyloxycarbonylamino)methyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (46.82 g, 153 mmol) as a light amber oil. Optical rotation: -27.4, c=2.5 in chloroform.

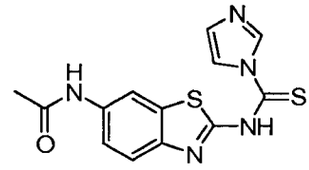
Step B: (S)-3-(Aminomethyl)quinuclidin-3-ol, 2 HCl



A solution of (S)-(3-((benzyloxycarbonylamino)methyl)-3-hydroxy-1-ammoniobicyclo[2.2.2]octan-1-yl)trihydroborate (20.5 g, 67 mmol) in acetone (120 mL) was cooled on an ice bath. 3M Aqueous HCl (120 mL, 360 mmol) was added over 2 minutes. Vigorous bubbling was observed. After 10 minutes, the cold ice bath was removed and the mixture was allowed to warm to room temperature. After 20 minutes, it was diluted with methanol (800 mL) and flushed with nitrogen. Palladium on carbon (2 g, 1.88 mmol) was added and the reaction was flushed with nitrogen and fitted with balloon of hydrogen. The reaction mixture was stirred at room temperature overnight. It was then flushed with nitrogen and filtered through a pad of Celite using methanol. The solvent was evaporated to yield a crude yellow solid. The solids were dissolved in water (25 mL), then ethanol (400 mL) was added. White crystals formed immediately. They were collected by filtration and washed with ethanol, followed by ether. A white crystalline solid was obtained, (S)-3-(aminomethyl)quinuclidin-3-ol, 2 HCl (10.7 g, 46.7 mmol, 69.3 % yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.93 (1 H, br. s.), 8.24 (3 H, br. s.), 6.02 (1 H, s), 3.26 (1 H, d, *J*=13.43 Hz), 2.99 - 3.22 (5 H, m), 2.10 - 2.19 (2 H, m), 1.81 - 1.90 (1 H, m),

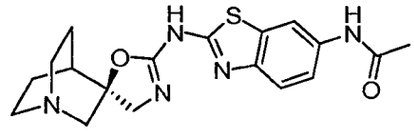
1.72 - 1.81 (1 H, m), 1.60 - 1.72 (1 H, m). Optical rotation: $[\alpha]^{20}_{D}$ = -50.9° (c=6.4, water).

Step C: N-(2-(1H-Imidazole-1-carbothioamido)benzo[d]thiazol-6-yl)acetamide



To N-(2-aminobenzo[d]thiazol-6-yl)acetamide (4 g, 19.3 mmol) in acetonitrile (100 mL) was added di(1H-imidazol-1-yl)methanethione (3.44 g, 19.30 mmol). The reaction was allowed to stir at 80 °C overnight. The reaction was cooled to room temperature and the precipitate was filtered. The product, N-(2-(1H-imidazole-1-carbothioamido)benzo[d]thiazol-6-yl)acetamide (3.6 g, 11.34 mmol, 58.8 5 yield), was taken directly to the next step without any further purification.

Step D: (R)-N-(2-(4H-1'-Azaspiro[oxazole-5,3'-bicyclo[2.2.2]octane]-2-ylamino)benzo[d]thiazol-6-yl)acetamide

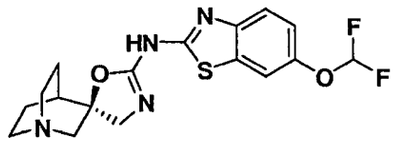


To N-(2-(1H-imidazole-1-carbothioamido)benzo[d]thiazol-6-yl)acetamide (300 mg, 0.95 mmol) in N,N-dimethylformamide (10 mL) was added (S)-3-(aminomethyl)quinuclidin-3-ol, 2 HCl (238 mg, 1 mmol) and triethylamine (0.39 mL, 2.84 mmol). The reaction was heated to 80 °C for 3 hours. N,N'-diisopropylcarbodiimide (0.59 mL, 3.78 mmol) was then added to the reaction mixture. The mixture was heated at 80 °C for another 2 hours. The reaction was cooled, then chloroform and water were added to the mixture. The organic layer concentrated *in vacuo* to yield crude product. The crude material was purified via flash chromatography (2-20% [10% ammonium hydroxide/methanol-chloroform). The product fractions were then triturated with ether to yield (R)-N-(2-(4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octane]-2-ylamino)benzo[d]thiazol-6-yl)acetamide (144.5 mg, 0.39 mmol, 41.2% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 9.98 (1 H, s), 8.93 (1 H, br. s.), 8.12 (1 H, d, *J*=1.83 Hz),

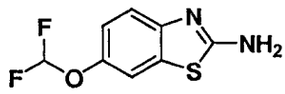
7.52 (1 H, d, *J*=8.42 Hz), 7.38 (1 H, dd, *J*=8.60, 2.01 Hz), 3.88 (1 H, d, *J*=9.88 Hz), 3.62 (1 H, d, *J*=9.88 Hz), 3.02 (2 H, s), 2.74 - 2.85 (2 H, m), 2.66 (2 H, t, *J*=7.68 Hz), 2.05 (4 H, s), 1.91 (1 H, br. s.), 1.41 - 1.64 (3 H, m). MS (LC/MS) R.T. = 1.55; $[M+H]^+ = 372.2$.

EXAMPLE 22

(R)-N-(6-(Difluoromethoxy)benzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

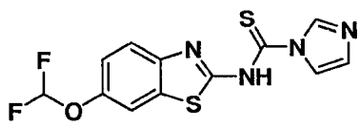


Step A: 6-(Difluoromethoxy)benzo[d]thiazol-2-amine



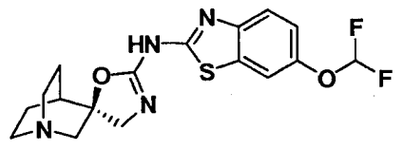
To 4-(difluoromethoxy)aniline (9.55 g, 60 mmol) in acetic acid (90 mL) was added potassium thiocyanate (KSCN) (12.41 mL, 240 mmol). The mixture was stirred for 20 minutes (KSCN dissolved into solution). To this mixture bromine (3.08 mL, 60.0 mmol) in acetic acid (40 mL) was added dropwise over 20 minutes. The reaction was stirred at room temperature overnight. It was poured into a mixture of 800 ml ice water and 200 ml saturated ammonium hydroxide. The product was extracted with ethyl acetate (5x). The organics were combined, washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 6-(difluoromethoxy)benzo[d]thiazol-2-amine (12.6 g, 52.4 mmol, 87 % yield) as a yellow solid.

Step B: N-(6-(Difluoromethoxy)benzo[d]thiazol-2-yl)-1H-imidazole-1-carbothioamide



To 6-(difluoromethoxy)benzo[d]thiazol-2-amine (0.5 g, 2.3 mmol) in acetonitrile (15 mL) was added 1,1'-thiocarbonyldiimidazole (0.49 g, 2.8 mmol). The reaction was stirred at 70 °C overnight. The reaction was cooled to room temperature and the precipitate was filtered to yield N-(6-(difluoromethoxy)benzo[d]thiazol-2-yl)-1H-imidazole-1-carbothioamide (500 mg, 1.53 mmol, 66.3 % yield) as a yellow solid.

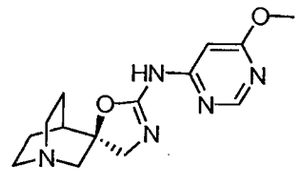
Step C: (R)-N-(6-(Difluoromethoxy)benzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



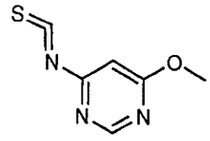
To a solution of N-(6-(difluoromethoxy)benzo[d]thiazol-2-yl)-1H-imidazole-1-carbothioamide (285 mg, 0.87 mmol) in N,N-dimethylformamide (5 mL) was added (S)-3-(aminomethyl)quinuclidin-3-ol, 2 HCl (200 mg, 0.87 mmol) and triethylamine (0.4 mL, 2.87 mmol). The reaction was heated to 70 °C for 2 hours. N,N'-diisopropylcarbodiimide (0.4 mL, 2.57 mmol) was then added to the reaction mixture. The mixture was heated at 70 °C for another 3 hours. It was cooled and then poured into toluene/0.3M sodium hydroxide. The product was extracted with toluene (4x) and chloroform (3x). The organics were combined, washed with water (3x), dried over sodium sulfate, filtered and concentrated *in vacuo* to yield crude product. The crude material was purified via flash chromatography (2-20% [10% ammonium hydroxide/methanol]-chloroform) to afford (R)-N-(6-(difluoromethoxy)benzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (186.2mg, 0.49 mmol, 55.5 % yield) as a white powder. M.P. 223-5 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.99 (1 H, br. s.), 7.69 (1 H, d, *J*=2.75 Hz), 7.61 (1 H, d, *J*=8.55 Hz), 7.02 - 7.34 (2 H, m), 3.89 (1 H, d, *J*=10.07 Hz), 3.64 (1 H, d, *J*=9.77 Hz), 3.03 (2 H, d, *J*=2.44 Hz), 2.73 - 2.86 (2 H, m), 2.62 - 2.70 (2 H, m), 2.07 (1 H, br. s.), 1.92 (1 H, br. s.), 1.54 - 1.65 (2 H, m), 1.44 - 1.53 (1 H, m). MS (LC/MS) R.T. = 1.43; $[M+H]^+$ = 381.1.

EXAMPLE 23

(R)-N-(6-Methoxypyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

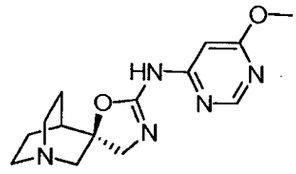


Step A: 4-Isothiocyanato-6-methoxypyrimidine



To a bright orange solution of 1,1'-thiocarbonyldipyridin-2(1H)-one (1.86 g, 7.99 mmol) in dichloromethane at room temperature was added 6-methoxypyrimidin-4-amine (1 g, 8 mmol). The orange solution was stirred at room temperature for 18 hours. The LC/MS showed the desired product as one of the major peaks. The deep orange solution was concentrated and the remaining residue was filtered. The filtrate was purified by silica gel chromatography (10-50% ethyl acetate/hexanes) to afford 4-isothiocyanato-6-methoxypyrimidine (0.72 g, 4.3 mmol, 54 % yield) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.49 (1 H, d, J=5.79 Hz), 6.95 (1 H, d, J=5.79 Hz), 3.92 (3 H, s). MS (LC/MS) R.T. = 3.15; $[M+H]^+$ = 168.1.

Step B: (R)-N-(6-Methoxypyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

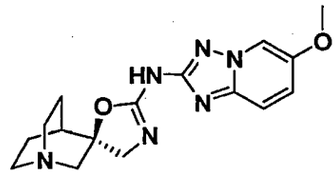


To (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (from Step B of Example 21) (0.34 g, 1.49 mmol) in N,N-dimethylformamide (15 mL) was added Cs_2CO_3 (1.22 g, 3.74 mmol) and 4-isothiocyanato-6-methoxypyrimidine (0.25 g, 1.5 mmol). The suspension was stirred at room temperature for 30 minutes. N,N'-diisopropylcarbodiimide (0.7 mL, 4.5 mmol) was then added and the mixture was

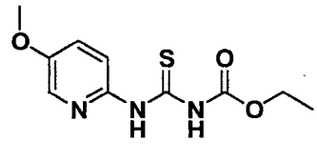
stirred at room temperature for 18 hours. The mixture was concentrated and purified by silica gel chromatography (5-15 % [9:1 methanol:ammonium hydroxide]/chloroform) to afford (R)-N-(6-methoxypyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.21 g, 0.72 mmol, 48.2% yield) as a white solid. M.P. 186-8 °C. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.40 (1 H, s), 6.17 (1 H, br. s.), 3.92 - 4.04 (1 H, m), 3.89 (3 H, s), 3.68 (1 H, d, *J*=10.32 Hz), 3.12 - 3.23 (1 H, m), 2.98 - 3.12 (1 H, m), 2.67 - 2.97 (4 H, m), 2.11 (2 H, br. s.), 1.48 - 1.82 (3 H, m). MS (LC/MS) R.T. = 0.82; $[M+H]^+$ = 290.3.

EXAMPLE 24

(R)-N-(6-Methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

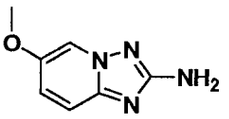


Step A: 5-Methoxypyridin-2-amine ethoxycarbonyl thiourea



To 5-methoxypyridin-2-amine (5g, 40 mmol) in dioxane (40 mL) was added ethoxycarbonyl isothiocyanate (5.23 mL, 44.3 mmol). The reaction mixture was stirred at room temperature overnight. The mixture was concentrated *in vacuo* to afford 5-methoxypyridin-2-amine ethoxycarbonyl thiourea (10.28 g, 40.3 mmol, 100 % yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 12.03 (1 H, br. s.), 11.37 (1 H, br. s.), 8.53 (1 H, br. s.), 8.11 (1 H, d, *J*=2.93 Hz), 7.50 (1 H, dd, *J*=8.97, 3.11 Hz), 4.22 (2 H, q, *J*=7.07 Hz), 3.84 (3 H, s), 1.26 (3 H, t, *J*=7.14 Hz). MS (LC/MS) R.T. = 2.40; $[M+H]^+$ = 256.1.

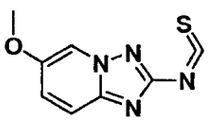
Step B: 6-Methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-amine



To 5-methoxypyridin-2-amine ethoxycarbonyl thiourea (10.21 g, 40 mmol) in ethanol (57 mL) and methanol (57 mL) was added hydroxylamine hydrochloride (14 g, 200 mmol) and Hunig's Base (21 mL, 120 mmol). The mixture was stirred at room temperature for 2 hours, and then heated at 60 °C for 4 hours. The reaction was cooled to room temperature and filtered to remove solids. It was concentrated *in vacuo* and then suspended in chloroform. The solids were filtered off to yield 6-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-amine (6.05 g, 33.2 mmol, 83 % yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.30 (1 H, d, *J*=1.83 Hz), 7.24 - 7.32 (1 H, m), 7.16 - 7.23 (1 H, m), 5.82 (2 H, br. s.), 3.78 (3 H, s). MS (LC/MS) R.T. = 0.53; $[M+H]^+$ = 165.2.

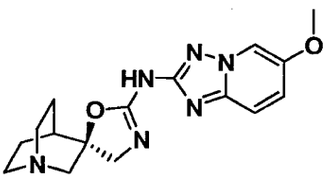
Two grams of 6-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-amine were purified via flash chromatography (2-20% [10% ammonium hydroxide/methanol]/chloroform) to afford 6-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-amine (1.35 g, 8.22 mmol, 67.5 % yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.29 (1 H, d, *J*=2.20 Hz), 7.24 - 7.30 (1 H, m), 7.15 - 7.22 (1 H, m), 5.79 (2 H, s), 3.78 (3 H, s).

Step C: 2-Isothiocyanato-6-methoxy-[1,2,4]triazolo[1,5-a]pyridine



To 6-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.3 g, 1.8 mmol) in dichloromethane (15 mL) was added 1,1'-thiocarbonyldi-2(1H)-pyridone (0.51 g, 2.2 mmol). The reaction was stirred at room temperature overnight, concentrated *in vacuo* and purified via flash chromatography yielding 2-isothiocyanato-6-methoxy-[1,2,4]triazolo[1,5-a]pyridine (166 mg, 0.8 mmol, 44 % yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.03 (1 H, d, *J*=2.20 Hz), 7.54 (1 H, d, *J*=9.88 Hz), 7.34 (1 H, dd, *J*=9.51, 2.56 Hz), 3.88 (3 H, s).

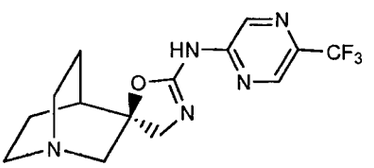
Step D: (R)-N-(6-Methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



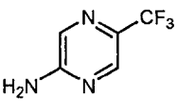
To 2-isothiocyanato-6-methoxy-[1,2,4]triazolo[1,5-a]pyridine (160 mg, 0.78 mmol) in N,N-dimethylformamide (5ml) was added (S)-3-(aminomethyl)quinuclidin-3-ol, 2 HCl (178 mg, 0.78 mmol) and triethylamine (0.32 ml, 2.33 mmol). The reaction was stirred at 70 °C for 1 hour. N,N'-Diisopropylcarbodiimide (0.36 ml, 2.33 mmol) was then added to the reaction mixture. The mixture was heated at 70 °C for 4 hours, then cooled and poured into aqueous sodium bicarbonate/chloroform. The product was extracted (3x) with chloroform. The combined organics were washed with water (3x), dried over sodium sulfate, filtered, and concentrated *in vacuo*, then purified via flash chromatography (2-20% [10% ammonium hydroxide:methanol]/chloroform) to yield (R)-N-(6-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-yl)-4H-1'-azaspiro-[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (114.5 mg, 0.33 mmol, 42 % yield) as a white powder. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.51 (1 H, br. s.), 8.08 (1 H, d, *J*=2.44 Hz), 7.35 (1 H, d, *J*=9.77 Hz), 7.18 (1 H, dd, *J*=9.46, 2.44 Hz), 3.92 (1 H, d, *J*=8.85 Hz), 3.84 (3 H, s), 3.58 (1 H, d, *J*=8.85 Hz), 3.36 - 3.41 (1 H, m), 2.72 - 3.05 (4 H, m), 2.18 - 2.26 (1 H, m, *J*=13.26, 9.98, 3.66, 3.49, 3.49 Hz), 2.13 (1 H, br. s.), 1.79 (1 H, br. s.), 1.67 - 1.76 (1 H, m, *J*=13.96, 9.84, 4.27, 4.27 Hz), 1.45 - 1.63 (2 H, m). MS (LC/MS) R.T. = 0.86; $[M+H]^+$ = 329.2.

EXAMPLE 25

(R)-N-(5-(Trifluoromethyl)pyrazin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

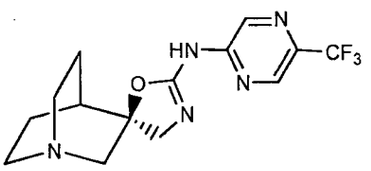


Step A: 5-(Trifluoromethyl)pyrazin-2-amine



To an ice bath-cooled solution of 5,6-diaminopyrimidin-4-ol (18 g, 143 mmol) in 3M sodium hydroxide (180 mL, 540 mmol), was added 3,3-dibromo-1,1,1-trifluoropropan-2-one (25.2 g, 93 mmol). The reaction was stirred for 3 days at ambient temperature. The solids were filtered, dissolved in 60% sulfuric acid (140 mL), and stirred at 135 °C for 8 h. The reaction was cooled, poured over ice and allowed to sit for 16 hours. The solution was neutralized to pH 8 with conc. ammonium hydroxide and extracted with ethyl acetate (5 X 100 mL), dried over sodium sulfate, filtered and concentrated. The solid residue was recrystallized from benzene/hexane to afford 5-(trifluoromethyl)pyrazin-2-amine (2.28 g, 14 mmol, 15 % yield). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 8.32 (1 H, s), 7.99 (1 H, d, *J*=1.26 Hz), 5.02 (2 H, br. s.). MS (LC/MS) R.T. = 1.56; $[M+H]^+$ = 164.03.

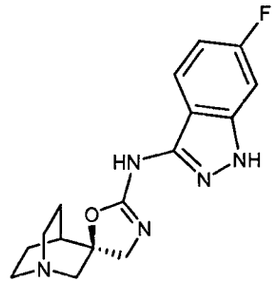
Step B: (R)-N-(5-(Trifluoromethyl)pyrazin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



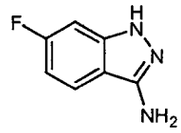
(R)-N-(5-(trifluoromethyl)pyrazin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was prepared by following the general procedures of **Example 23, Steps A-B** and using 5-(trifluoromethyl)pyrazin-2-amine **(from Step A above)** as the starting material. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 9.08 (1 H, br. s.), 8.35 (1 H, s), 8.32 (1 H, s), 3.95 (1 H, d, *J*=9.57 Hz), 3.61 (1 H, d, *J*=9.57 Hz), 3.30 (1 H, dd, *J*=14.86, 1.76 Hz), 2.65 - 2.99 (5 H, m), 2.05 - 2.16 (2 H, m), 1.64 - 1.74 (1 H, m), 1.42 - 1.57 (2 H, m). MS (LC/MS) R.T. = 1.06; $[M+H]^+$ = 328.30.

EXAMPLE 26

(R)-N-(6-Fluoro-1H-indazol-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

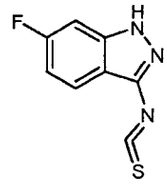


Step A: 6-Fluoro-1H-indazol-3-amine



To 2,4-difluorobenzonitrile (1.21 g, 8.70 mmol) was added hydrazine monohydrate (8.46 mL, 174 mmol). The mixture was heated to reflux for 5 hours and then poured onto ice. The solution was extracted with ethyl acetate, dried with magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography (25-100% ethyl acetate/hexane) to afford 6-fluoro-1H-indazol-3-amine (0.5 g, 3.3 mmol, 38 % yield) as light yellow powder. ^{1}H NMR (500 MHz, *DMSO-D6*) δ ppm 11.42 (s, 1 H), 7.70 (dd, *J*=8.55, 5.49 Hz, 1 H), 6.97 (dd, *J*=10.07, 1.83 Hz, 1 H), 6.72 - 6.79 (m, 1 H), 5.40 (s, 2 H). MS (LC/MS) R.T. = 0.61; $[M+H]^+$ = 152.11.

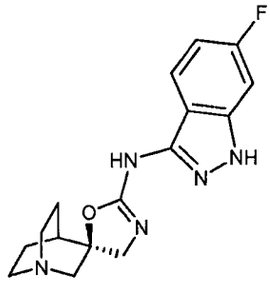
Step B: 6-Fluoro-3-isothiocyanato-1H-indazole



To 6-fluoro-1H-indazol-3-amine (0.32 g, 2.1 mmol) in dichloromethane (15 mL) was added 1,1'-thiocarbonyldipyridin-2(1H)-one (0.53 g, 2.30 mmol). The reaction was stirred at 50 °C for 3 hours. The reaction was cooled to room temperature and the crude product was purified by column chromatography (25%

ethyl acetate/hexanes) to afford 6-fluoro-3-isothiocyanato-1H-indazole (0.30 g, 1.53 mmol, 73.0 % yield) as a light yellow powder. ^{1}H NMR (500 MHz, *DMSO-D6*) δ ppm 13.39 (s, 1 H), 7.78 (dd, *J*=8.85, 4.88 Hz, 1 H), 7.41 (dd, *J*=9.31, 1.68 Hz, 1 H), 7.14 (td, *J*=9.16, 1.83 Hz, 1 H). MS (LC/MS) R.T. = 3.69; $[M+H]^+$ = 194.07.

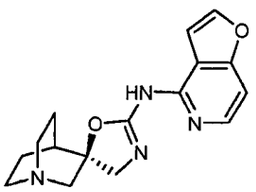
Step C: (R)-N-(6-Fluoro-1H-indazol-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



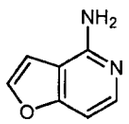
To 6-fluoro-3-isothiocyanato-1H-indazole (0.20 g, 1.04 mmol) in DMF (15 mL) was added triethylamine (0.43 mL, 3.11 mmol) and (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (0.26 g, 1.14 mmol) at room temperature. The reaction was stirred at 70 °C for 2 hours. The reaction was cooled to room temperature and treated with N,N'-diisopropylcarbodiimide (0.48 mL, 3.11 mmol). The reaction was then heated to 70 °C for 2 hours. The reaction was cooled to ambient temperature and concentrated. The crude product was purified by column chromatography (85% chloroform, 14% methanol, 1% ammonium hydroxide) to afford (R)-N-(6-fluoro-1H-indazol-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.22 g, 0.66 mmol, 64 % yield) as a white powder. ^{1}H NMR (500 MHz, *DMSO-D6*) δ ppm 12.16 (s, 1 H), 8.00 (s, 1 H), 7.59 - 7.67 (m, 1 H), 7.09 (dd, *J*=9.77, 2.14 Hz, 1 H), 6.81 - 6.88 (m, 1 H), 3.81 (d, *J*=9.16 Hz, 1 H), 3.56 (d, *J*=8.85 Hz, 1 H), 3.00 (s, 2 H), 2.78 (s, 2 H), 2.67 (t, *J*=7.32 Hz, 2 H), 2.01 (d, *J*=2.44 Hz, 1 H), 1.92 (s, 1 H), 1.59 (d, *J*=5.80 Hz, 2 H), 1.46 (s, 1 H). MS (LC/MS) R.T. = 1.44; $[M+H]^+$ = 316.16.

EXAMPLE 27

(R)-N-(Furo[3,2-c]pyridin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

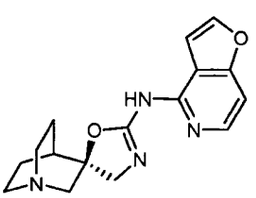


Step A: Furo[3,2-c]pyridin-4-amine



To 4-chlorofuro[3,2-c]pyridine (1 g, 6.5 mmol) in toluene under nitrogen was added racemic BINAP (0.243 g, 0.4 mmol) , $Pd_2(dba)_3$ (0.12 g, 0.13 mmol) and sodium *tert*-butoxide (0.88 g, 9.1 mmol). Benzophenoneimine (1.3 mL, 7.81 mmol) was added and the mixture was heated to 80 ° C for 3 h and cooled to room temperature. The reaction mixture was diluted with ether, filtered through Celite, and washed with ether. The filtrate was concentrated and the deep orange residue was taken up in methanol (90 ml) and treated with hydroxylamine (1.2 mL, 19.5 mmol). The mixture was stirred at ambient temperature for 18 h and concentrated. The residue was purified by column chromatography (95-100 % ethyl acetate/hexanes) to afford furo[3,2-c]pyridin-4-amine (776 mg, 5.79 mmol, 89 % yield) as a deep orange solid. MS (LC/MS) R.T. = 0.51; $[M+H]^+$ = 135.02.

Step B: (R)-N-(Furo[3,2-c]pyridin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

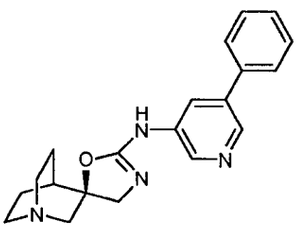


(R)-N-(Furo[3,2-c]pyridin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was prepared by following the general procedures of **Example 23, Steps A-B** using furo[3,2-c]pyridin-4-amine **(Step A above)** as the

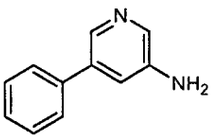
starting material. ^{1}H NMR (400 MHz, *MeOD*) δ ppm 8.08 (1 H, d, *J*=5.79 Hz), 7.69 (1 H, d, *J*=2.01 Hz), 6.99 - 7.13 (2 H, m), 4.00 (1 H, d, *J*=10.07 Hz), 3.69 (1 H, d, *J*=10.07 Hz), 3.19 - 3.26 (1 H, m), 3.05 - 3.13 (1 H, m), 2.93 (2 H, t, *J*=7.43 Hz), 2.73 - 2.87 (2 H, m), 2.08 - 2.24 (2 H, m), 1.52 - 1.82 (3 H, m). MS (LC/MS) R.T. = 0.68; $[M+H]^+$ = 299.19.

EXAMPLE 28

(R)-N-(5-Phenylpyridin-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

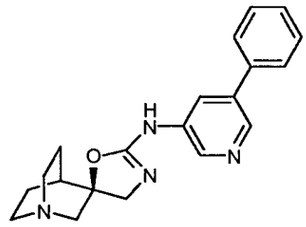


Step A: 5-Phenylpyridin-3-amine



A mixture of 5-bromopyridin-3-amine (248 mg, 1.43 mmol), $Pd(PPh_3)_4$ (50.4 mg, 0.04 mmol), toluene (3 mL), sodium carbonate (2 M, 3 mL, 6 mmol), and phenylboronic acid (195 mg, 1.60 mmol) dissolved in ethanol (3 mL) was heated for 4 hours in an oil bath at 90 °C and allowed to cool to room temperature for 16 hours. The reaction mixture was transferred to a separatory funnel and partitioned between ethyl acetate and water. The aqueous phase was washed once more with ethyl acetate, and the combined organic phases were washed with brine and dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (80% ethyl acetate/hexanes) to afford 5-phenylpyridin-3-amine (31.9 mg, 0.19 mmol, 13 % yield) as a white solid. ^{1}H NMR (500 MHz, *CDCl*$_3$) δ ppm 8.17 - 8.42 (m, 1 H), 8.02 - 8.20 (m, 1 H), 7.32 - 7.62 (m, 4 H), 7.25 (s, 1 H), 7.06 - 7.20 (m, 1 H). MS (LC/MS) R.T. = 0.91; $[M+H]^+$ = 171.09.

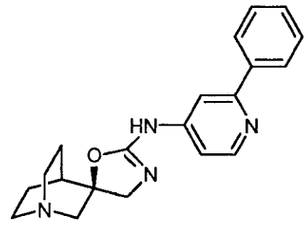
Step B: (R)-N-(5-Phenylpyridin-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



(R)-N-(5-Phenylpyridin-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was prepared by following the general procedures of **Example 23, Steps A-B** using 5-phenylpyridin-3-amine **(from Step A above)** as the starting material. ^{1}H NMR (500 MHz, *MeOD-d$_4$*) δ ppm 8.40 (br. s., 2 H), 7.66 (d, *J*=7.32 Hz, 2 H), 7.46 - 7.56 (m, 3 H), 7.43 (d, *J*=7.32 Hz, 1 H), 3.79 - 4.02 (m, 1 H), 3.51 - 3.68 (m, 1 H), 3.22 (d, *J*=14.95 Hz, 1 H), 3.02 - 3.15 (m, 1 H), 2.72 - 2.99 (m, 3 H), 2.14 (br. s., 2 H), 1.76 (dd, *J*=9.31, 4.12 Hz, 3 H), 1.12 - 1.35 (m, 1 H). MS (LC/MS) R.T. = 0.90; $[M+H]^+$ = 335.17.

EXAMPLE 29

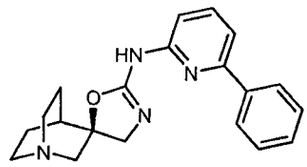
(R)-N-(2-Phenylpyridin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



(R)-N-(2-Phenylpyridin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was prepared from 2-bromopyridin-4-amine by following the general procedures of **Example 28, Steps A-B.** ^{1}H NMR (500 MHz, *MeOD*) δ ppm 8.38 (d, *J*=5.49 Hz, 1 H), 7.88 (d, *J*=7.93 Hz, 2 H), 7.71 - 7.84 (m, 1 H), 7.48 (d, *J*=7.63 Hz, 3 H), 7.19 - 7.36 (m, 1 H), 3.94 - 4.09 (m, 1 H), 3.61 - 3.79 (m, 1 H), 3.17 - 3.27 (m, 1 H), 3.00 - 3.14 (m, 1 H), 2.74 - 3.00 (m, 4 H), 2.05 - 2.23 (m, 2 H), 1.55 - 1.86 (m, 3 H). MS (LC/MS) R.T. = 0.86; $[M+H]^+$ = 335.23.

EXAMPLE 30

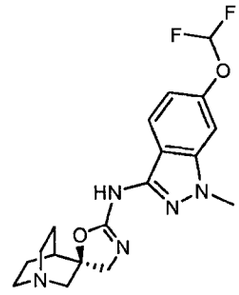
(R)-N-(6-Phenylpyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



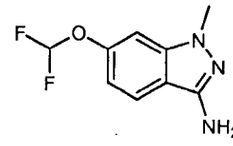
(R)-N-(6-Phenylpyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was prepared from 6-bromopyridin-2-amine by following the general procedures of **Example 28, Steps A-B**. ^{1}H NMR (500 MHz, *MeOD-d4*) δ ppm 7.91 (d, *J*=7.63 Hz, 2 H), 7.71 (t, *J*=7.78 Hz, 1 H), 7.32 - 7.55 (m, 5 H), 4.04 (d, *J*=10.07 Hz, 1 H), 3.72 (d, *J*=9.77 Hz, 1 H), 3.23 (d, *J*=1.22 Hz, 1 H), 3.12 (s, 1 H), 2.95 (s, 2 H), 2.84 (s, 2 H), 2.16 (br. s., 2 H), 1.58 - 1.85 (m, 3 H). MS (LC/MS) R.T. = 0.75; $[M+H]^+$ = 335.23.

EXAMPLE 31

(R)-N-(6-(Difluoromethoxy)-1-methyl-1H-indazol-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



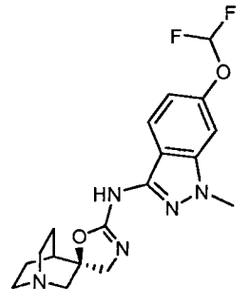
Step A: 6-(Difluoromethoxy)-1-methyl-1H-indazol-3-amine



To 4-(difluoromethoxy)-2-fluorobenzonitrile (1 g, 5.3 mmol) was added methylhydrazine (4.92 g, 107 mmol). The mixture was heated to 50 °C for 5 hours and then cooled to room temperature. The crude product was purified by column chromatography (40-100% ethyl acetate/hexanes) to afford 6-(difluoromethoxy)-1-

methyl-1H-indazol-3-amine (0.5 g, 2.35 mmol, 44 % yield) as a white powder. ^{1}H NMR (500 MHz, *DMSO-d$_6$*) δ ppm 7.70 (d, *J*=8.55 Hz, 1 H), 7.14 (s, 1 H), 6.73 (d, *J*=8.55 Hz, 1 H), 5.49 (s, 1 H), 3.70 (s, 3 H).

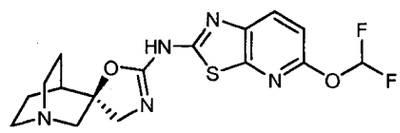
Step B: (R)-N-(6-(Difluoromethoxy)-1-methyl-1H-indazol-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



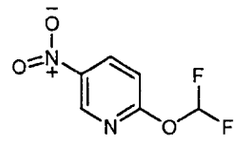
(R)-N-(6-(difluoromethoxy)-1-methyl-1H-indazol-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was prepared by following the general procedures of **Example 23, Steps A-B** using 6-(difluoromethoxy)-1-methyl-1H-indazol-3-amine **(Step A)** as the starting material. ^{1}H NMR (500 MHz, *DMSO-d$_6$*) δ ppm 7.64 (d, *J*=8.55 Hz, 1 H), 7.28 (d, *J*=5.19 Hz, 1 H), 6.83 (dd, *J*=8.55, 1.83 Hz, 1 H), 3.88 (s, 3 H), 3.77 - 3.84 (m, 1 H), 3.51 - 3.64 (m, 1 H), 3.00 (s, 2 H), 2.72 - 2.84 (m, 2 H), 2.67 (t, *J*=7.48 Hz, 2 H), 2.02 (br. s., 1 H), 1.85 - 1.98 (m, 1 H), 1.59 (d, *J*=5.80 Hz, 2 H), 1.36 - 1.53 (m, 1 H), 1.09 (d, *J*=6.41 Hz, 1 H). MS (LC/MS) R.T. = 1.04; $[M+H]^+$ = 378.19.

EXAMPLE 32

(R)-N-(5-(Difluoromethoxy)thiazolo[5,4-b]pyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

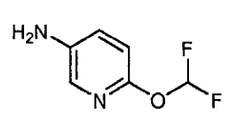


Step A: 2-(Difluoromethoxy)-5-nitropyridine



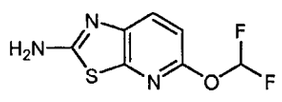
To 2-hydroxy-5-nitropyridine (7 g, 50 mmol) in acetonitrile (500 mL) was added sodium sulfate (1.5 g, 10.6 mmol), and 2,2-difluoro-2-(fluorosulfonyl)acetic acid (6.2 mL, 60 mmol) and the reaction was allowed to stir at room temperature for 16 hours. The reaction was quenched with saturated aqueous sodium bicarbonate and the acetonitrile was removed *in vacuo*. The remaining aqueous component was extracted with ethyl acetate, washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The pale brown oily solid was triturated with ether/hexanes, filtered and the filtrate concentrated to afford 2-(difluoromethoxy)-5-nitropyridine (4.7 g, 24.7 mmol, 49 % yield) as a yellow oil. ^{1}H NMR (400 MHz, *DMSO-d$_6$*) δ ppm 9.14 (d, *J*=2.76 Hz, 1 H), 8.68 (dd, *J*=9.03, 2.76 Hz, 1 H), 7.98 (s, 0.5 H), 7.62 (s, 0.5 H), 7.34 (d, *J*=9.03 Hz, 1 H).

Step B: 6-(Difluoromethoxy)pyridin-3-amine



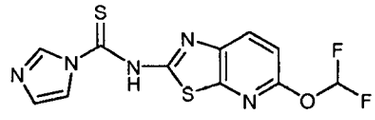
To 2-(difluoromethoxy)-5-nitropyridine (4.7 g, 24.7 mmol) in degassed methanol (100 mL) was added 10% palladium on carbon (500 mg, 0.47 mmol) and the reaction was hydrogenated at atmospheric pressure for 1 hour. To this was added acetic acid (2.83 mL, 49.4 mmol) and the reaction was filtered through Celite and concentrated *in vacuo* to afford 6-(difluoromethoxy)pyridin-3-amine (6.33 g, 25.9 mmol, 105 % yield) as an olive green liquid. ^{1}H NMR (400 MHz, *MeOD-d$_4$*) δ ppm 7.60 (d, *J*=2.76 Hz, 1 H), 7.37 (s, 0.5 H), 7.15 (dd, *J*=8.66, 2.89 Hz, 1 H), 7.00 (s, 0.5 H), 6.71 (d, *J*=8.78 Hz, 1 H).

Step C: 5-(Difluoromethoxy)thiazolo[5,4-b]pyridin-2-amine



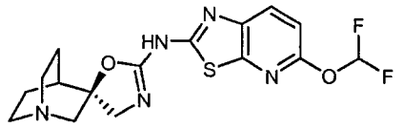
To acetic acid (10 mL) cooled in an ice bath was added potassium thiocyanate (3.18 g, 32.8 mmol) and 6-(difluoromethoxy)pyridin-3-amine (1 g, 4.1 mmol). The reaction was cooled in an ice-salt bath until the reaction temperature reached <0°C. A solution of bromine (0.65 mL, 12.7 mmol) in acetic acid (3 mL) was added dropwise over 2 hours at a rate that maintained the reaction temperature <0°C. This gave a very thick mixture. After the addition was complete, the mixture was left to stir and allowed to slowly warm to room temperature overnight. After stirring overnight, water (5 mL) was added and the mixture was heated to 85°C in an oil bath. This mixture was then filtered while still hot. The yellow filter cake was returned to the reaction flask, and an additional 5 mL acetic acid was added. The mixture was heated again to 85°C, and then filtered while still hot. The combined filtrates were cooled in an ice bath and neutralized to pH 8 with concentrated ammonium hydroxide. A yellow precipitate formed which was then collected by filtration. This crude material was purified by column chromatography (12-100% ethyl acetate/hexanes) to afford 5-(difluoromethoxy)thiazolo[5,4-b]pyridin-2-amine (321 mg, 1.48 mmol, 36.1 % yield) as a yellow solid. ^{1}H NMR (400 MHz, *DMSO-d_6*) δ ppm 7.64 - 7.81 (m, 2 H), 6.92 (d, *J*=8.53 Hz, 1 H). MS (LC/MS) R.T. = 1.66; $[M+H]^+$ = 218.10.

Step D: N-(5-(Difluoromethoxy)thiazolo[5,4-b]pyridin-2-yl)-1H-imidazole-1-carbothioamide



5-(Difluoromethoxy)thiazolo[5,4-b]pyridin-2-amine (310 mg, 1.43 mmol) and di(1H-imidazol-1-yl)methanethione (311 mg, 1.75 mmol) were dissolved in acetonitrile (5 mL) and heated to 70 °C in a sealed vial for 10 hours. The vial was then stored in the freezer for 16 hours. The solids were collected by filtration and washed with acetonitrile to afford N-(5-(difluoromethoxy)thiazolo[5,4-b]pyridin-2-yl)-1H-imidazole-1-carbothioamide (296 mg, 0.72 mmol, 51 % yield). ^{1}H NMR (400 MHz, *DMSO-d_6*) δ ppm 8.77 (d, *J*=4.77 Hz, 1 H), 8.06 (d, *J*=8.53 Hz, 1 H), 8.01 (s, 1 H), 7.72 (s, 1 H), 7.54 (s, 1 H), 6.94 - 7.13 (m, 1 H).

Step E: (R)-N-(5-(Difluoromethoxy)thiazolo[5,4-b]pyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

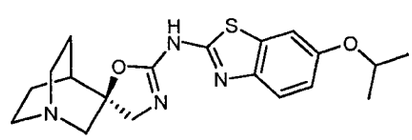


To N-(5-(difluoromethoxy)thiazolo[5,4-b]pyridin-2-yl)-1H-imidazole-1-carbothioamide (296 mg, 0.72 mmol) in N,N-dimethylformamide (4 mL) in a sealed vial was added (S)-3-(aminomethyl)quinuclidin-3-ol, 2 HCl (175 mg, 0.76 mmol) and triethylamine (0.3 ml, 2.2 mmol) and the mixture was heated to 70 °C overnight.

To this was added N,N'-diisopropylcarbodiimide (350 µl, 2.25 mmol) and the reaction was heated to 70 ° C for 6 hours. It was cooled to ambient temperature and poured into water/chloroform, extracted with additional chloroform and concentrated *in vacuo*. The residue was then taken up in toluene and washed with water to remove the residual N,N-dimethylformamide. The residue was purified by column chromatography (2%-20% (10% ammonium hydroxide/methanol)/chloroform) to afford (R)-N-(5-(difluoromethoxy)thiazolo[5,4-b]pyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (104 mg, 0.27 mmol, 37 % yield) as a pale cream colored solid. ^{1}H NMR (400 MHz, *DMSO-d$_6$*) δ ppm 7.99 (d, *J*=8.78 Hz, 1 H), 7.68 (s, 1 H), 7.03 (d, *J*=8.53 Hz, 1 H), 3.87 (d, *J*=10.04 Hz, 1 H), 3.62 (d, *J*=10.04 Hz, 1 H), 3.03 (d, *J*=5.02 Hz, 2 H), 2.80 (d, *J*=9.03 Hz, 2 H), 2.65 (t, *J*=7.65 Hz, 2 H), 2.08 (br. s., 1 H), 1.83 - 1.99 (m, 1 H), 1.43 - 1.68 (m, 3 H). MS (LC/MS) R.T. = 1.73; $[M+H]^+$ = 382.20.

EXAMPLE 33

(R)-N-(6-Isopropoxybenzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

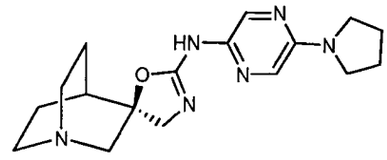


(R)-N-(6-Isopropoxybenzo[d]thiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was prepared from 4-isopropoxyaniline by following the general procedures of **Example 32, Steps C-E**. ^{1}H NMR (400 MHz, *DMSO-d$_6$*) δ ppm 7.49 (d, *J*=8.78 Hz, 1 H), 7.38 (d, *J*=2.51 Hz, 1 H), 6.90 (dd, *J*=8.78, 2.51 Hz,

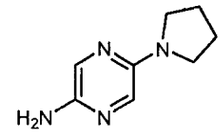
1 H), 4.50 - 4.68 (m, 1 H), 3.87 (d, *J*=10.04 Hz, 1 H), 3.62 (d, *J*=9.79 Hz, 1 H), 2.79 (d, *J*=9.03 Hz, 2 H), 2.66 (t, *J*=7.78 Hz, 2 H), 2.06 (br. s., 1 H), 1.85 - 1.96 (m, 1 H), 1.42 - 1.67 (m, 3 H), 1.17 - 1.34 (m, 6 H), 0.96 - 1.19 (m, 2 H).

EXAMPLE 34

(R)-N-(5-(Pyrrolidin-1-yl)pyrazin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

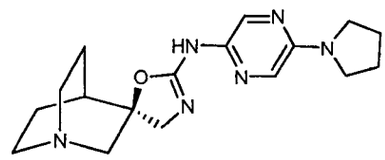


Step A: 5-(Pyrrolidin-1-yl)pyrazin-2-amine



A mixture of 5-bromopyrazin-2-amine (1.2 g, 6.9 mmol) and pyrrolidine (4 mL, 48 mmol) was microwaved at 180 ° C, 200 W for 2 h. The reaction was diluted into 125 mL ethyl acetate and extracted with water (3 x 50 mL) and brine (50 mL). It was dried over sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (0 to 3% methanol/methylene chloride) to afford 5-(pyrrolidin-1-yl)pyrazin-2-amine (495 mg, 3. mmol, 43.7 % yield). ^{1}H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 7.52 (1 H, d, *J*=1.51 Hz), 7.36 (1 H, d, *J*=1.76 Hz), 5.21 (2 H, s), 3.24 - 3.29 (4 H, m), 1.90 (4 H, ddd, *J*=6.48, 3.53, 3.34 Hz). MS (LC/MS) R.T. = 0.52; $[M+H]^+$ = 165.29.

Step B: (R)-N-(5-(Pyrrolidin-1-yl)pyrazin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

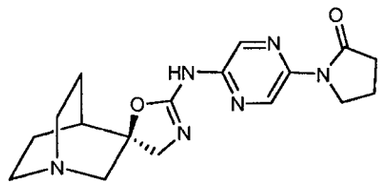


(R)-N-(5-(Pyrrolidin-1-yl)pyrazin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was prepared from 5-(pyrrolidin-1-yl)pyrazin-2-amine

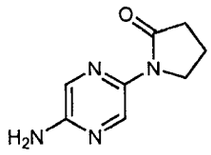
by following the general procedures of **Example 23, Steps A-B.** ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 8.51 (1 H, br. s.), 8.02 (1 H, s), 7.44 (1 H, d, *J*=0.92 Hz), 3.84 (1 H, d, *J*=9.16 Hz), 3.51 (1 H, d, *J*=8.85 Hz), 3.39 - 3.45 (4 H, m), 3.31 (1 H, dd, *J*=14.80, 1.07 Hz), 2.69 - 3.04 (5 H, m), 2.15 - 2.25 (1 H, m), 2.09 (1 H, br. s.), 1.98 - 2.02 (4 H + HOD, m), 1.64 - 1.74 (1 H, m), 1.42 - 1.61 (2 H, m). MS (LC/MS) R.T. = 0.76; $[M+H]^+$ = 329.40.

EXAMPLE 35

(R)-1-(5-(4H-1'-Azaspiro[oxazole-5,3'-bicyclo[2.2.2]octane]-2-ylamino)pyrazin-2-yl)pyrrolidin-2-one

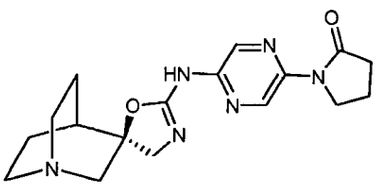


Step A: 1-(5-Aminopyrazin-2-yl)pyrrolidin-2-one



A mixture of 5-bromopyrazin-2-amine (5 g, 29 mmol), pyrrolidin-2-one (11 mL, 144 mmol), copper (I) iodide (1.1 g, 5.75 mmol), potassium carbonate (7.94 g, 57.5 mmol), and (1R,2R)-cyclohexane-1,2-diamine (1.38 mL, 11.49 mmol) was refluxed under nitrogen in dioxane (100 mL) for 18 h. After cooling, 200 mL ethyl acetate and 20 mL methanol were added to the reaction. This was filtered through celite, concentrated, and absorbed onto sodium sulfate for purification by column chromatography (0-5% methanol/methylene chloride). The purified product was recrystallized from ether/ethyl acetate to afford 1-(5-aminopyrazin-2-yl)pyrrolidin-2-one (1.57 g, 8.81 mmol, 30.7 % yield). ^{1}H NMR (400 MHz, *DMSO-d$_6$*) δ ppm 8.74 (1 H, d, *J*=1.51 Hz), 7.69 (1 H, d, *J*=1.51 Hz), 6.20 (2 H, s), 3.84 (2 H, t, *J*=7.05 Hz), 2.49 (2 H, t, *J*=7.93 Hz), 2.04 (2 H, dq, *J*=7.68, 7.51 Hz). MS (LC/MS) R.T. = 0.48; $[M+H]^+$ = 179.27.

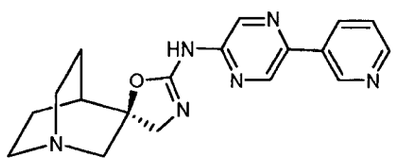
Step B: (R)-1-(5-(4H-1'-Azaspiro[oxazole-5,3'-bicyclo[2.2.2]octane]-2-ylamino)pyrazin-2-yl)pyrrolidin-2-one



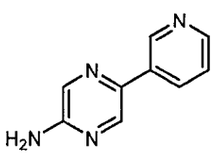
(R)-1-(5-(4H-1'-Azaspiro[oxazole-5,3'-bicyclo[2.2.2]octane]-2-ylamino)pyrazin-2-yl)pyrrolidin-2-one was prepared from 1-(5-Aminopyrazin-2-yl)pyrrolidin-2-one by following the general procedures of **Example 23, Steps A-B.** ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 9.20 (1 H, d, *J*=1.22 Hz), 8.91 (1 H, br. s.), 8.13 (1 H, s), 4.02 (2 H, t, *J*=7.02 Hz), 3.92 (1 H, d, *J*=9.46 Hz), 3.58 (1 H, d, *J*=9.16 Hz), 3.33 (1 H, dd, *J*=14.95, 1.53 Hz), 2.71 - 3.01 (5 H, m), 2.63 (2 H, t, *J*=8.09 Hz), 2.08 - 2.23 (4 H, m), 1.66 - 1.76 (1 H, m), 1.42 - 1.61 (2 H, m). MS (LC/MS) R.T. = 0.67; $[M+H]^+$ = 343.30.

EXAMPLE 36

(R)-N-(5-(Pyridin-3-yl)pyrazin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



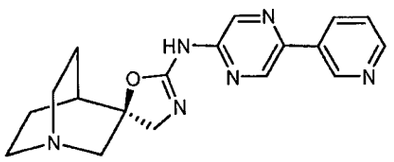
Step A: 5-(Pyridin-3-yl)pyrazin-2-amine



Pyridin-3-ylboronic acid (307 mg, 2.50 mmol), 5-bromopyrazin-2-amine (391 mg, 2.25 mmol) and dichlorobis(triphenylphosphine)-palladium(II) (88 mg, 0.13 mmol) were added to degassed dioxane (12 mL) and the mixture was stirred for 30 min. Then sodium carbonate (795 mg, 7.50 mmol) and degassed water (8 mL) were added and the reaction was heated in a closed reaction vial at 100 °C for 8 h. The reaction was allowed to stand at ambient temperature over the weekend. It was

diluted into ethyl acetate (100 mL) and extracted with brine (3 x 25 mL). The organic layers were dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by column chromatography (0 to 5% methanol/ethyl acetate) to afford 5-(pyridin-3-yl)pyrazin-2-amine (235 mg, 1.37 mmol, 54.6 % yield). ^{1}H NMR (400 MHz, *Acetone*) δ ppm 9.13 (1 H, d, *J*=1.51 Hz), 8.54 (1 H, d, *J*=1.26 Hz), 8.50 (1 H, dd, *J*=4.78, 1.51 Hz), 8.22 - 8.28 (1 H, m), 8.07 (1 H, d, *J*=1.26 Hz), 7.39 (1 H, ddd, *J*=7.87, 4.72, 0.76 Hz), 6.05 (2 H, br. s.). MS (LC/MS) R.T. = 0.58; $[M+H]^+$ = 173.20.

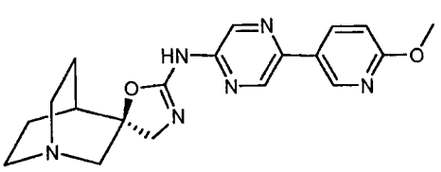
Step B: (R)-N-(5-(Pyridin-3-yl)pyrazin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



(R)-N-(5-(Pyridin-3-yl)pyrazin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was prepared from 5-(pyridin-3-yl)pyrazin-2-amine by following the general procedures of **Example 23, Steps A-B.** ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 9.12 (1 H, dd, *J*=2.27, 0.76 Hz), 9.08 (1 H, br. s.), 8.59 (1 H, dd, *J*=4.78, 1.76 Hz), 8.55 (1 H, d, *J*=1.51 Hz), 8.45 (1 H, d, *J*=1.26 Hz), 8.25 (1 H, dt, *J*=7.99, 1.92 Hz), 7.38 (1 H, ddd, *J*=8.06, 4.78, 0.76 Hz), 3.97 (1 H, d, *J*=9.57 Hz), 3.63 (1 H, d, *J*=9.32 Hz), 3.36 (1 H, dd, *J*=14.86, 1.76 Hz), 2.69 - 3.06 (5 H, m), 2.14 - 2.24 (1 H, m), 2.12 (1 H, br. s.), 1.66 - 1.77 (1 H, m, *J*=13.94, 9.66, 4.31, 4.31 Hz), 1.44 - 1.62 (2 H, m). MS (LC/MS) R.T. = 0.65; $[M+H]^+$ = 337.30.

Example 37

(R)-N-(5-(6-Methoxypyridin-3-yl)pyrazin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

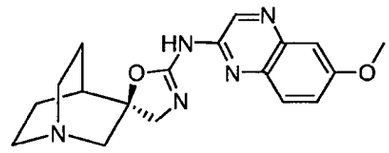


(R)-N-(5-(6-Methoxypyridin-3-yl)pyrazin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was prepared from 5-bromopyrazin-2-amine by

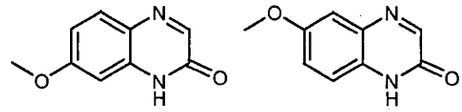
following the general procedures of **Example 36, Steps A-B.** ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 9.04 (1 H, br. s.), 8.66 (1 H, d, *J*=2.01 Hz), 8.46 (1 H, d, *J*=1.51 Hz), 8.41 (1 H, d, *J*=1.01 Hz), 8.15 (1 H, dd, *J*=8.81, 2.52 Hz), 6.82 (1 H, d, *J*=8.31 Hz), 3.97 (3 H, s), 3.95 (1 H, d, *J*=9.57 Hz), 3.61 (1 H, d, *J*=9.32 Hz), 3.35 (1 H, dd, *J*=14.86, 1.51 Hz), 2.68 - 3.07 (5 H, m), 2.14 - 2.24 (1 H, m, *J*=13.27, 9.93, 3.53, 3.38, 3.38 Hz), 2.11 (1 H, br. s.), 1.67 - 1.77 (1 H, m), 1.45 - 1.61 (2 H, m). MS (LC/MS) R.T. = 0.81; $[M+H]^+$ = 367.40.

EXAMPLE 38

(R)-N-(6-Methoxyquinoxalin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

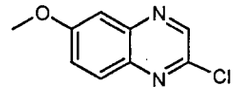


Step A: 7-Methoxyquinoxalin-2(1H)-one and 6-methoxyquinoxalin-2(1H)-one



A 50% solution of ethyl 2-oxoacetate (18.47 mL, 93 mmol) in toluene was added to a solution of 4-methoxybenzene-1,2-diamine (10.73 g, 78 mmol) in ethanol (100 mL) at ambient temperature and the reaction was refluxed for 2 h. The reaction was concentrated *in vacuo* and crystallized from ethanol to afford a mixture of 6-methoxyquinoxalin-2(1H)-one and 7-methoxyquinoxalin-2(1H)-one (5.73 g, 32.50 mmol, 42 % yield). MS (LC/MS) R.T. = 0.68; $[M+H]^+$ = 177.10.

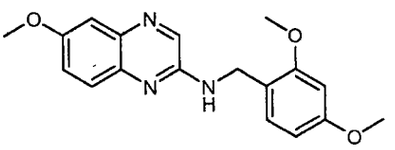
Step B: 2-Chloro-6-methoxyquinoxaline



A mixture of 6-methoxyquinoxalin-2(1H)-one and 7-methoxyquinoxalin-2(1H)-one (5.67 g, 32.20 mmol) was refluxed in phosphorus oxychloride (120 mL) for 1 h. The reaction was concentrated and quenched by addition of ice, then basified

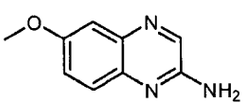
with sodium carbonate, and extracted with ethyl acetate (3 x 200 mL). The organic layers were combined and concentrated *in vacuo*. The crude product was absorbed onto sodium sulfate and purified by column chromatography (0 to 5% ethyl acetate/hexanes) to afford 2-chloro-6-methoxyquinoxaline (2.21 g, 11.36 mmol, 35% yield). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 8.69 (s, 1 H), 7.88 (d, *J*=9.32 Hz, 1 H), 7.43 (dd, *J*=9.32, 2.77 Hz, 1 H), 7.37 (d, *J*=2.77 Hz, 1 H), 3.95 (s, 3 H).

Step C: N-(2,4-Dimethoxybenzyl)-6-methoxyquinoxalin-2-amine



2-Chloro-6-methoxyquinoxaline (0.93 g, 4.77 mmol) and (2,4-dimethoxyphenyl)methanamine (2.2 ml, 14.64 mmol) were microwaved in dimethylsulfoxide (5 mL) for 30 min at 150 °C. The reaction was diluted into ethyl acetate (250 mL) and extracted with brine (3 x 100 mL). The crude product was purified by column chromatography (20 to 80% ethyl acetate/hexanes) to afford N-(2,4-dimethoxybenzyl)-6-methoxyquinoxalin-2-amine (1.46 g, 87% yield). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 8.13 (1 H, s), 7.59 - 7.63 (1 H, m), 7.30 (1 H, d, *J*=8.31 Hz), 7.21 - 7.24 (2 H, m), 6.47 (1 H, d, *J*=2.27 Hz), 6.42 (1 H, dd, *J*=8.31, 2.27 Hz), 5.10 (1 H, t, *J*=5.92 Hz), 4.61 (2 H, d, *J*=5.79 Hz), 3.88 (3 H, s), 3.84 (3 H, s), 3.78 (3 H, s). MS (LC/MS) R.T. = 1.95; $[M+H]^+$ = 326.23.

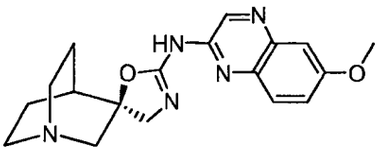
Step D: 6-Methoxyquinoxalin-2-amine



N-(2,4-Dimethoxybenzyl)-6-methoxyquinoxalin-2-amine (2.8 g, 8.61 mmol) was stirred in TFA (10 mL, 130 mmol) and dichloromethane (10 mL) at ambient temperature for 30 min. The solvents were removed *in vacuo*. Saturated aq. sodium hydrogen carbonate (200 mL) was added to the red residue, which then precipitated a yellow solid. The mixture was extracted extensively with dichloromethane. The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 6-methoxyquinoxalin-2-amine (1.50 g, 8.56 mmol, 99 % yield). ^{1}H NMR

(400 MHz, $CDCl_3$) δ ppm 8.27 (1 H, s), 7.54 - 7.58 (1 H, m), 7.25 - 7.29 (2 H, m), 4.71 (2 H, br. s.), 3.90 (3 H, s). MS (LC/MS) R.T. = 0.86; $[M+H]^+$ = 176.23.

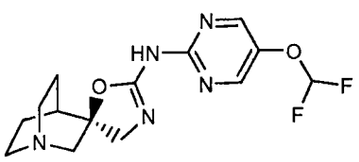
Step E: (R)-N-(6-Methoxyquinoxalin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



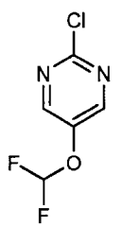
(R)-N-(6-Methoxyquinoxalin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was prepared from 6-methoxyquinoxalin-2-amine by following the general procedures of **Example 23, Steps A-B**. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 9.61 (1 H, br. s.), 8.57 (1 H, s), 7.62 (1 H, d, *J*=9.06 Hz), 7.23 - 7.32 (2 H, m), 4.01 (1 H, d, *J*=9.32 Hz), 3.90 (3 H, s), 3.66 (1 H, d, *J*=9.32 Hz), 3.37 (1 H, dd, *J*=14.86, 1.51 Hz), 2.68 - 3.08 (5 H, m), 2.15 - 2.25 (1 H, m), 2.10 - 2.14 (1 H, m), 1.67 - 1.77 (1 H, m), 1.42 - 1.63 (2 H, m). MS (LC/MS) R.T. = 0.81; $[M+H]^+$ = 340.30.

EXAMPLE 39

(R)-N-(5-(Difluoromethoxy)pyrimidin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



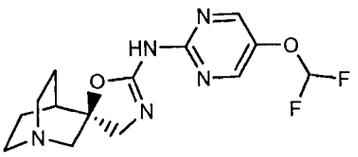
Step A: 2-Chloro-5-(Difluoromethoxy)pyrimidine



2-Chloropyrimidin-5-ol (1 g, 7.66 mmol) and sodium 2-chloro-2,2-difluoroacetate (3.50 g, 22.98 mmol) in N,N-dimethylformamide (20 mL) and water

(0.2 mL) were heated to 90 °C for 24 hours and concentrated *in vacuo*. The residue was purified by column chromatography (5-30 % ethyl acetate/hexanes) to afford 2-chloro-5-(difluoromethoxy)pyrimidine (549 mg, 3.04 mmol, 39.7 % yield) as a pale yellow oil. MS (LC/MS) R.T. = 1.32; $[M+H]^+$ = 181.14.

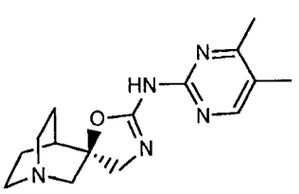
Step B: (R)-N-(5-(Difluoromethoxy)pyrimidin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



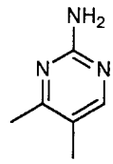
(R)-N-(5-(Difluoromethoxy)pyrimidin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was prepared from 2-chloro-5-(difluoromethoxy)pyrimidine by following the general procedures of **Example 23, Steps A-B**. ^{1}H NMR (400 MHz, *MeO-d$_4$*) δ ppm 8.46 (2 H, s), 6.85 (1 H, t), 4.02 (1 H, d, *J*=10.07 Hz), 3.73 (1 H, d, *J*=10.32 Hz), 3.28 (1 H, d, *J*=1.01 Hz), 3.16 (1 H, d), 2.81 - 3.05 (4 H, m), 2.08 - 2.25 (2 H, m), 1.46 - 1.89 (3 H, m). MS (LC/MS) R.T. = 0.53; $[M+H]^+$ = 326.30.

EXAMPLE 40

(R)-N-(4,5-Dimethylpyrimidin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

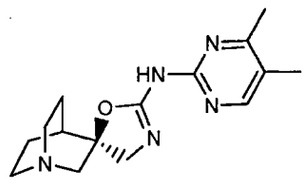


Step A: 4,5-Dimethylpyrimidin-2-amine



A solution of 4-chloro-5,6-dimethylpyrimidin-2-amine (0.35 g, 2.22 mmol) in 2M ammonia in methanol (100 ml) was flushed with nitrogen and palladium on carbon (0.035 g, 0.33 mmol) was added, flushed with nitrogen and the reaction was hydrogenated at 1 atm, ambient temperature for 18 h. The reaction mixture was flushed with nitrogen and filtered through celite and the celite pad washed with methanol. The filtrate was evaporated to dryness *in vacuo* to afford 4, 5-dimethylpyrimidin-2-amine (0.35 g, 2.56 mmol, 90 % yield) which was used without further purification. ^{1}H NMR (400 MHz, *DMSO-d_6*) δ ppm 7.89 (1 H, s), 6.19 (2 H, s), 2.18 (3 H, s), 1.99 (3 H, s). MS (LC/MS) R.T. = 0.56; $[M+H]^+$ = 124.20.

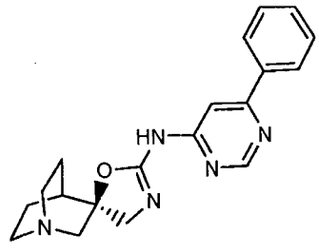
Step B: (R)-N-(4,5-Dimethylpyrimidin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



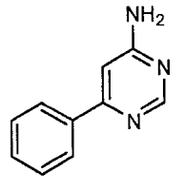
(R)-N-(4,5-Dimethylpyrimidin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was prepared from 4,5-dimethylpyrimidin-2-amine by following the general procedures of **Example 23, Steps A-B**. ^{1}H NMR (400 MHz, *MeOD-d_4*) δ ppm 8.22 (1 H, s), 4.01 (1 H, d, *J*=10.07 Hz), 3.73 (1 H, d, *J*=10.32 Hz), 3.40 (1 H, d), 3.25 (1 H, d), 2.91 - 3.12 (4 H, m), 2.41 (3 H, s), 2.09 - 2.28 (5 H, m), 1.62 - 1.97 (3 H, m). MS (LC/MS) R.T. = 0.47; $[M+H]^+$ = 288.31.

EXAMPLE 41

(R)-N-(6-Phenylpyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

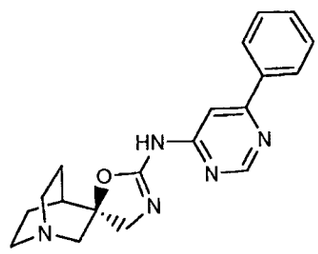


Step A: 6-Phenylpyrimidin-4-amine



A mixture of 6-chloropyrimidin-4-amine (0.32 g, 2.5 mmol), phenylboronic acid (0.38 g, 3.13 mmol), saturated aqueous sodium carbonate (0.80 g, 7.50 mmol) and bis(triphenylphosphine)palladium(II) chloride (0.035 g, 0.05 mmol) were suspended in a mixture of dimethoxyethane (15 mL)/ethanol (2 mL)/water (2mL). The mixture was heated in the microwave at 125 °C for 20 min then concentrated *in vacuo*. The residue was purified by column chromatography (10-60 % ethyl acetate/hexanes) to afford 6-phenylpyrimidin-4-amine (167 mg, 0.98 mmol, 39 %yield) as an off-white solid. MS (LC/MS) R.T. = 0.99; $[M+H]^+$ = 172.23.

Step B: (R)-N-(6-Phenylpyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

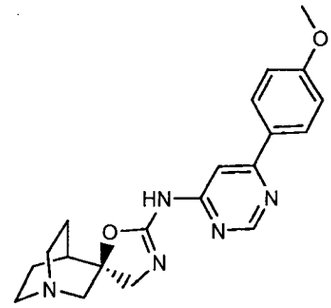


(R)-N-(6-Phenylpyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-aminewas prepared from 6-phenylpyrimidin-4-amine by

following the general procedures of **Example 23, Steps A-B**. ^{1}H NMR (400 MHz, *MeOD-d$_4$*) δ ppm 9.54 (1 H, d, *J*=1.01 Hz), 8.75 - 8.86 (2 H, m), 8.18 - 8.28 (3 H, m), 8.00 (1 H, br. s.), 4.70 (1 H, d, *J*=10.32 Hz), 4.43 (1 H, d, *J*=10.58 Hz), 3.72 - 3.88 (2 H, m), 3.41 - 3.63 (4 H, m), 2.63 - 2.87 (2 H, m), 2.18 - 2.48 (3 H, m). MS (LC/MS) R.T. = 1.36; $[M+H]^+$ = 336.24.

EXAMPLE 42

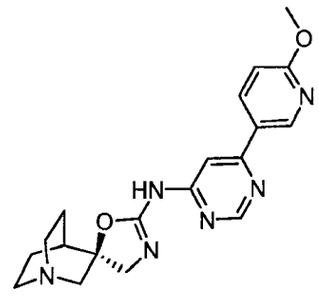
(R)-N-(6-(4-Methoxyphenyl)pyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



(R)-N-(6-(4-Methoxyphenyl)pyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was prepared from 6-chloropyrimidin-4-amine by following the general procedures of **Example 41, Steps A-B**. ^{1}H NMR (400 MHz, *MeOD-d$_4$*) δ ppm 8.72 (1 H, d, *J*=1.26 Hz), 7.90 - 8.00 (2 H, m), 7.16 (1 H, br. s.), 6.96 - 7.05 (2 H, m), 4.04 (1 H, d, *J*=10.07 Hz), 3.84 (3 H, s), 3.73 (1 H, d, *J*=10.07 Hz), 3.22 (1 H, d), 3.09 (1 H, d), 2.73 - 2.98 (4 H, m), 2.02 - 2.21 (2 H, m), 1.51 - 1.85 (3 H, m). MS (LC/MS) R.T. = 1.44; $[M+H]^+$ = 366.28.

EXAMPLE 43

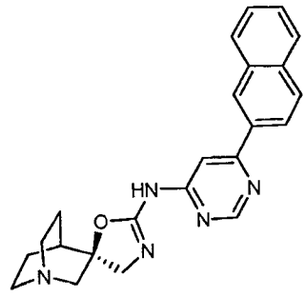
(R)-N-(6-(6-Methoxypyridin-3-yl)pyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



(R)-N-(6-(6-Methoxypyridin-3-yl)pyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was prepared from 6-chloropyrimidin-4-amine by following the general procedures of **Example 41, Steps A-B**. ^{1}H NMR (400 MHz, *MeOD-d$_4$*) δ ppm 8.79 (2 H, dd, *J*=19.01, 1.89 Hz), 8.27 (1 H, dd, *J*=8.56, 2.52 Hz), 7.18 (1 H, br. s.), 6.89 (1 H, d, *J*=8.81 Hz), 4.05 (1 H, d, *J*=10.32 Hz), 3.96 (3 H, s), 3.74 (1 H, d, *J*=10.32 Hz), 3.23 (1 H, d), 3.10 (1 H, d), 2.73 - 2.99 (4 H, m), 2.02 - 2.21 (2 H, m), 1.53 - 1.84 (3 H, m). MS (LC/MS) R.T. = 1.34; $[M+H]^+$ = 367.25.

EXAMPLE 44

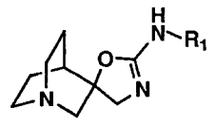
(R)-N-(6-(Naphthalen-2-yl)pyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

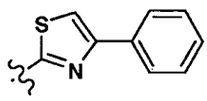
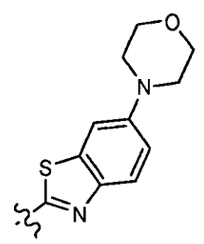


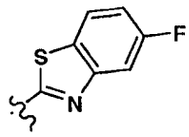
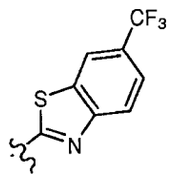
(R)-N-(6-(Naphthalen-2-yl)pyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was prepared from 6-chloropyrimidin-4-amine by following the general procedures of **Example 41, Steps A-B**. ^{1}H NMR (400 MHz, *MeOD-d$_4$*) δ ppm 8.83 (1 H, s), 8.56 (1 H, s), 7.83 - 8.13 (4 H, m), 7.49 - 7.58 (2 H, m), 7.37 (1 H, br. s.), 4.06 (1 H, d, *J*=10.32 Hz), 3.76 (1 H, d, *J*=10.32 Hz), 3.23 (1 H, s), 3.12 (1 H, d), 2.75 - 3.00 (4 H, m), 2.02 - 2.24 (2 H, m), 1.56 - 1.84 (3 H, m). MS (LC/MS) R.T. = 1.93; $[M+H]^+$ = 386.31.

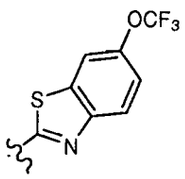
The compounds in Table 2 were synthesized according to the method of Example 1 using the appropriate commercially available isothiocyanate or amine. Amide-containing intermediates were obtained by the procedures described in Example 3.

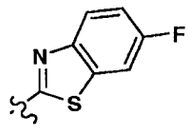
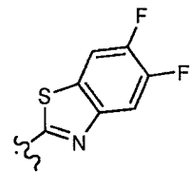
Table 2.

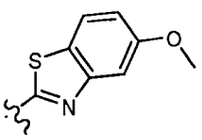
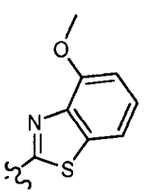


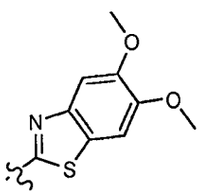
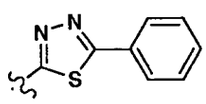
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^{1}H NMR
45		1.48	341.3	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.60 (1 H, br. s.), 7.94 (2 H, d, *J*=7.63 Hz), 7.43 (1 H, s), 7.39 (2 H, t, *J*=7.78 Hz), 7.28 (1 H, t, *J*=7.32 Hz), 3.86 (1 H, d, *J*=9.77 Hz), 3.60 (1 H, d, *J*=9.77 Hz), 2.98 - 3.06 (2 H, m), 2.71 - 2.85 (2 H, m), 2.66 (2 H, t, *J*=7.78 Hz), 2.05 (1 H, br. s.), 1.91 (1 H, br. s.), 1.53 - 1.64 (2 H, m), 1.48 (1 H, td, *J*=9.99, 7.78 Hz)
46		1.41	400.4	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.86 (1 H, br. s.), 7.47 (1 H, d, *J*=8.85 Hz), 7.33 (1 H, d, *J*=2.44 Hz), 7.01 (1 H, dd, *J*=8.85, 2.75 Hz), 3.87 (1 H, d, *J*=10.07 Hz), 3.71 - 3.77 (4 H, m), 3.61 (1 H, d, *J*=9.77 Hz), 3.06 - 3.12 (4 H, m), 3.01 (2 H, s), 2.72 - 2.86 (2 H, m), 2.66 (2 H, t, *J*=7.63 Hz), 2.05 (1 H, br. s.), 1.91 (1 H, br. s.), 1.53 - 1.64 (2 H, m), 1.43 - 1.52 (1 H, m)

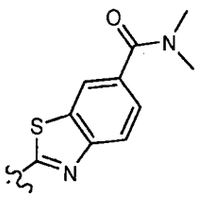
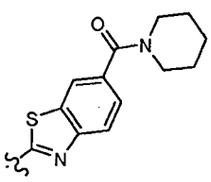
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^{1}H NMR
47		1.31	333.3	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.03 (1 H, br. s.), 7.80 (1 H, dd, *J*=8.70, 5.65 Hz), 7.37 (1 H, dd, *J*=10.38, 2.44 Hz), 7.04 (1 H, td, *J*=9.08, 2.59 Hz), 3.89 (1 H, d, *J*=10.07 Hz), 3.64 (1 H, d, *J*=10.07 Hz), 3.03 (2 H, d, *J*=2.75 Hz), 2.74 - 2.85 (2 H, m), 2.62 - 2.70 (2 H, m), 2.07 (1 H, d, *J*=2.44 Hz), 1.90 (1 H, d, *J*=8.85 Hz), 1.54 - 1.64 (2 H, m), 1.43 - 1.53 (1 H, m)
48		2.07	383.3	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.00 (1 H, s), 7.41 - 7.54 (2 H, m), 3.89 (1 H, d, *J*=11.29 Hz), 3.57 (1 H, d, *J*=11.60 Hz), 2.96 - 3.03 (1 H, m), 2.88 - 2.93 (1 H, m), 2.73 - 2.81 (2 H, m), 2.64 (2 H, dd, *J*=8.85, 5.19 Hz), 1.93 (2 H, br. s.), 1.56 (2 H, br. s.), 1.38 - 1.50 (1 H, m)

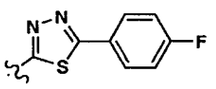
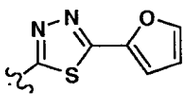
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M + H]^+$	^{1}H NMR
49		2.15	399.4	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.03 (1 H, br. s.), 7.91 (1 H, br. s.), 7.65 (1 H, d, *J*=8.85 Hz), 7.30 (1 H, d, *J*=7.63 Hz), 3.89 (1 H, d, *J*=10.07 Hz), 3.64 (1 H, d, *J*=10.07 Hz), 2.97 - 3.09 (2 H, m), 2.80 (2 H, d, *J*=8.55 Hz), 2.66 (2 H, t, *J*=7.48 Hz), 2.08 (1 H, br. s.), 1.93 (1 H, br. s.), 1.54 - 1.66 (2 H, m), 1.44 - 1.54 (1 H, m)
50		1.89	333.1	^{1}H NMR (500 MHz, MeOD) δ ppm 7.51 - 7.58 (1 H, m), 7.17 - 7.25 (1 H, m), 7.08 - 7.16 (1 H, m), 4.04 - 4.13 (1 H, m), 3.72 - 3.82 (1 H, m), 3.30 (1 H, br. s.), 3.17 (1 H, d, *J*=14.95 Hz), 3.01 (2 H, t, *J*=7.48 Hz), 2.80 - 2.92 (2 H, m), 2.12 - 2.27 (2 H, m), 1.66 - 1.88 (3 H, m)

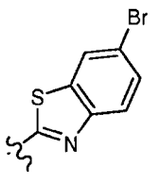
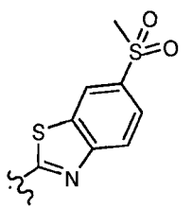
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M + H]^+$	^1H NMR
51		1.24	333.4	^1H NMR (500 MHz, DMSO-d_6) δ ppm 8.95 (1 H, br. s.), 7.66 - 7.77 (1 H, m), 7.52 - 7.63 (1 H, m), 7.08 - 7.24 (1 H, m), 3.88 (1 H, d, *J*=9.77 Hz), 3.63 (1 H, d, *J*=9.77 Hz), 3.03 (2 H, br. s.), 2.78 (2 H, br. s.), 2.66 (2 H, t, *J*=7.17 Hz), 2.06 (1 H, br. s.), 1.91 (1 H, br. s.), 1.39 - 1.67 (3 H, m)
52		2.05	351.2	^1H NMR (500 MHz, DMSO-d_6)δppm 9.01 (1 H, br. s.), 7.88 - 8.00 (1 H, m), 7.53 - 7.64 (1 H, m), 3.88 (1 H, d, *J*=10.07 Hz), 3.63 (1 H, d, *J*=10.07 Hz), 2.98 - 3.08 (2 H, m), 2.72 - 2.87 (2 H, m), 2.66 (2 H, t, *J*=7.17 Hz), 2.07 (1 H, br. s.), 1.92 (1 H, br. s.), 1.42 - 1.65 (3 H, m)

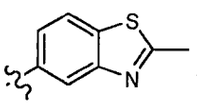
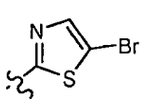
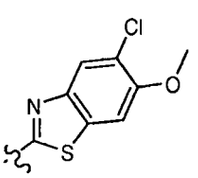
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M + H]^+$	^{1}H NMR
53		1.80	345.3	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.03 (s, 1 H), 7.65 (d, *J*=8.55 Hz, 1 H), 7.19 (d, *J*=2.44 Hz, 1 H), 6.82 (dd, *J*=8.70, 2.59 Hz, 1 H), 3.90 (d, *J*=10.07 Hz, 1 H), 3.79 (s, 3 H), 3.64 (d, *J*=10.07 Hz, 1 H), 3.04 (d, *J*=2.44 Hz, 2 H), 2.75 - 2.84 (m, 2 H), 2.67 (t, *J*=7.78 Hz, 2 H), 2.07 (s, 1 H), 1.92 (s, 1 H), 1.55 - 1.63 (m, 2 H), 1.49 (dd, *J*=9.77, 2.75 Hz, 1 H)
54		1.23	345.2	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.83 (s, 1 H), 7.37 (d, *J*=7.94 Hz, 1 H), 7.14 (t, *J*=7.93 Hz, 1 H), 6.92 (d, *J*=7.93 Hz, 1 H), 3.89 - 3.95 (m, 4 H), 3.66 (d, *J*=10.07 Hz, 1 H), 3.00 - 3.08 (m, 2 H), 2.76 - 2.85 (m, 2 H), 2.67 (t, *J*=7.78 Hz, 2 H), 2.08 (s, 1 H), 1.93 (d, *J*=3.66 Hz, 1 H), 1.60 (ddd, *J*=15.26, 6.87, 3.20 Hz, 2 H), 1.50 (ddd, *J*=7.48, 5.19, 2.59 Hz, 1 H)

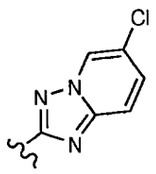
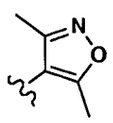
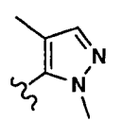
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^{1}H NMR
55		1.72	375.2	^{1}H NMR (500 MHz, DMSO-d_6) δppm 8.89 (s, 1 H), 7.40 (s, 1 H), 7.22 (s, 1 H), 3.87 (d, J=10.07 Hz, 1 H), 3.79 (d, J=8.55 Hz, 6 H), 3.62 (d, J=10.07 Hz, 1 H), 2.99 - 3.07 (m, 2 H), 2.75 - 2.84 (m, 2 H), 2.67 (t, J=7.63 Hz, 2 H), 2.06 (s, 1 H), 1.93 (s, 1 H), 1.56 - 1.64 (m, 2 H), 1.46 - 1.55 (m, 1 H)
56		2.14	342.1	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.75 (s, 1 H), 7.84 (dd, J=7.93, 1.53 Hz, 3 H), 7.46 - 7.53 (m, 5 H), 3.85 (d, J=9.77 Hz, 2 H), 3.60 (d, J=10.07 Hz, 2 H), 3.01 - 3.09 (m, 3 H), 2.84 (t, J=7.78 Hz, 3 H), 2.67 (t, J=7.78 Hz, 3 H), 2.09 (s, 2 H), 1.91 - 1.99 (m, 2 H), 1.53 - 1.62 (m, 3 H)

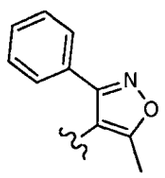
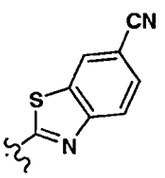
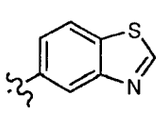
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M + H]^+$	^{1}H NMR
57		1.04	386.2	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.05 (1 H, br. s.), 7.86 (1 H, d, *J*=1.51 Hz), 7.60 (1 H, d, *J*=8.06 Hz), 7.36 (1 H, dd, *J*=8.31, 1.76 Hz), 3.90 (1 H, d, *J*=10.07 Hz), 3.65 (1 H, d, *J*=10.07 Hz), 3.03 (2 H, s), 2.97 (6 H, s), 2.72 - 2.87 (2 H, m), 2.66 (2 H, t, *J*=7.68 Hz), 2.07 (1 H, br. s.), 1.92 (1 H, br. s.), 1.55 - 1.64 (2 H, m), 1.44 - 1.54 (1 H, m)
58		1.57	426.2	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.06 (1 H, br. s.), 7.83 (1 H, d, *J*=1.51 Hz), 7.61 (1 H, d, *J*=8.31 Hz), 7.32 (1 H, dd, *J*=8.31, 1.76 Hz), 3.90 (1 H, d, *J*=10.07 Hz), 3.65 (1 H, d, *J*=10.07 Hz), 3.37 - 3.57 (4 H, m), 3.04 (2 H, d, *J*=1.76 Hz), 2.73 - 2.86 (2 H, m), 2.66 (2 H, t, *J*=7.68 Hz), 2.07 (1 H, d, *J*=2.52 Hz), 1.92 (1 H, dd, *J*=8.18, 5.67 Hz), 1.43 - 1.67 (9 H, m)

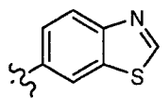
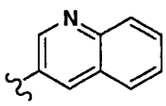
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M + H]^+$	^{1}H NMR
59		2.17	360.1	^{1}H NMR (500 MHz, *DMSO-D6*) δ ppm 8.74 (s, 1 H), 7.86 - 7.92 (m, 2 H), 7.31 - 7.37 (m, 2 H), 3.85 (d, *J*=9.77 Hz, 1 H), 3.60 (d, *J*=9.77 Hz, 1 H), 3.00 - 3.09 (m, 2 H), 2.84 (t, *J*=7.48 Hz, 2 H), 2.67 (t, *J*=7.32 Hz, 2 H), 2.09 (d, *J*=1.83 Hz, 1 H), 1.89 - 1.98 (m, 1 H), 1.55 - 1.61 (m, 2 H), 1.51 - 1.54 (m, *J*=11.29 Hz, 1 H)
60		1.67	332.2	^{1}H NMR (500 MHz, *DMSO-D6*) δ ppm 7.87 (s, 1 H), 7.01 (d, *J*=3.05 Hz, 1 H), 6.68 (dd, *J*=3.51, 1.68 Hz, 1 H), 3.84 (d, *J*=10.38 Hz, 1 H), 3.58 (d, *J*=10.07 Hz, 1 H), 3.03 (d, *J*=11.29 Hz, 2 H), 2.78 - 2.86 (m, 2 H), 2.66 (t, *J*=7.48 Hz, 2 H), 2.06 (s, 1 H), 1.87 - 1.96 (m, 1 H), 1.55 - 1.61 (m, 2 H), 1.51 - 1.54 (m, 1 H)

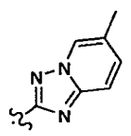
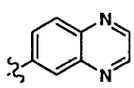
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M + H]^+$	^1H NMR
61		1.83	393.0	^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.02 (1 H, br. s.), 8.04 (1 H, d, *J*=2.01 Hz), 7.49 - 7.53 (1 H, m), 7.43 - 7.47 (1 H, m), 3.88 (1 H, d, *J*=10.07 Hz), 3.63 (1 H, d, *J*=10.07 Hz), 3.02 (2 H, s), 2.74 - 2.84 (2 H, m), 2.65 (2 H, t, *J*=7.68 Hz), 2.06 (1 H, d, *J*=2.52 Hz), 1.89 (1 H, br. s.), 1.42 - 1.64 (3 H, m)
62		1.16	391.1	^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.21 (1 H, br. s.), 8.40 (1 H, d, *J*=1.51 Hz), 7.80 - 7.85 (1 H, m), 7.72 - 7.77 (1 H, m), 3.92 (1 H, d, *J*=10.32 Hz), 3.67 (1 H, d, *J*=10.07 Hz), 3.21 (3 H, s), 3.05 (2 H, d, *J*=4.03 Hz), 2.82 (2 H, d, *J*=6.80 Hz), 2.67 (2 H, t, *J*=7.43 Hz), 2.10 (1 H, br. s.), 1.94 (1 H, d, *J*=3.27 Hz), 1.45 - 1.66 (3 H, m)

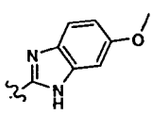
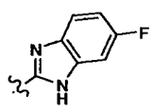
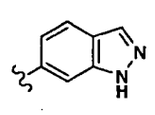
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^{1}H NMR
63		1.35	329.1	^{1}H NMR (500 MHz, *DMSO-D6*) δ ppm 8.54 (s, 1 H), 7.32 (s, 1 H), 3.79 (d, *J*=10.07 Hz, 1 H), 3.54 (d, *J*=10.07 Hz, 1 H), 2.98 - 3.05 (m, 2 H), 2.76 - 2.85 (m, 2 H), 2.66 (t, *J*=7.63 Hz, 2 H), 2.05 (s, 1 H), 1.87 - 1.95 (m, 1 H), 1.41 - 1.68 (m, 3 H)
64		1.02	349.9	^{1}H NMR (500 MHz, DMSO-d_6) δppm 8.54 (s, 1 H), 7.32 (s, 1 H), 3.67 (dd, *J*=126.04, 10.07 Hz, 2 H), 2.92 - 3.09 (m, 2 H), 2.72 - 2.91 (m, 2 H), 2.60 - 2.73 (m, *J*=7.63, 7.63 Hz, 2 H), 2.00 - 2.12 (m, 1 H), 1.81 - 1.99 (m, 1 H), 1.35 - 1.69 (m, 3 H)
65		2.14	380	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.93 (s, 1 H), 7.54 - 7.76 (m, *J*=10.53, 3.81 Hz, 2 H), 3.79 - 4.04 (m, 1 H), 3.56 - 3.72 (m, *J*=9.92, 3.20 Hz, 1 H), 3.26 - 3.45 (m, 2 H), 2.98 - 3.12 (m, 2 H), 2.75 - 2.90 (m, 2 H), 2.61 - 2.74 (m, *J*=1.22 Hz, 2 H), 2.09 (s, 1 H), 1.87 - 2.04 (m, 1 H), 1.42 - 1.76 (m, 3 H)

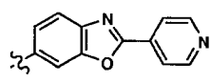
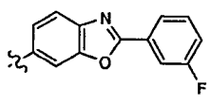
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^{1}H NMR
66		1.26	333.1	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.04 (1 H, d, *J*=1.22 Hz), 8.44 (1 H, br. s.), 7.52 - 7.69 (2 H, m), 3.77 - 3.82 (1 H, m), 3.68 (1 H, d, *J*=10.07 Hz), 3.05 - 3.12 (2 H, m), 2.94 - 3.04 (2 H, m), 2.80 - 2.91 (2 H, m), 2.19 (1 H, d, *J*=1.83 Hz), 2.01 (1 H, br. s.), 1.67 - 1.85 (3 H, m)
67		0.28	277.1	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 6.72 - 7.61 (m, 1 H), 3.49 - 3.70 (m, 1 H), 3.31 - 3.46 (m, 1 H), 2.86 - 3.06 (m, *J*=9.46 Hz, 2 H), 2.56 - 2.84 (m, 4 H), 2.10 - 2.31 (m, 3 H), 1.91 - 2.10 (m, 4 H), 1.70 (s, 1 H), 1.49 - 1.61 (m, 2 H), 1.36 - 1.49 (m, 1 H)
68		0.44	276.2	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.55 (s, 1 H), 5.63 (s, 1 H), 3.57 - 3.74 (m, *J*=8.55 Hz, 1 H), 3.48 (s, 3 H), 2.96 (s, 2 H), 2.72 - 2.88 (m, 2 H), 2.65 (s, 2 H), 1.93 - 2.17 (m, 4 H), 1.86 (s, 1 H), 1.57 (s, 3 H)

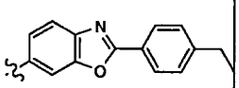
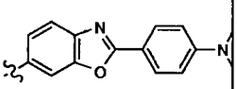
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^{1}H NMR
69		1.35	339.1	^{1}H NMR (500 MHz, DMSO-*d6*) δ ppm 7.87 (d, *J*=6.71 Hz, 1 H), 7.80 (d, *J*=7.02 Hz, 2 H), 7.42 - 7.48 (m, 4 H), 3.49 - 3.57 (m, 1 H), 3.25 - 3.33 (m, 4 H), 2.77 (t, *J*=15.41 Hz, 2 H), 2.59 - 2.68 (m, 1 H), 2.49 - 2.57 (m, 15 H), 2.24 - 2.31 (m, 2 H), 2.21 (s, 1 H), 1.94 (s, 1 H), 1.47 (s, 2 H)
70		0.73	340.1	^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 9.20 (1 H, br. s.), 8.29 - 8.42 (1 H, m), 7.63 - 7.76 (2 H, m), 3.91 (1 H, d, *J*=10.25 Hz), 3.66 (1 H, d, *J*=10.25 Hz), 3.05 (2 H, s), 2.74 - 2.90 (2 H, m), 2.66 (2 H, t, *J*=7.68 Hz), 2.09 (1 H, br. s.), 1.92 (1 H, d, *J*=4.03 Hz), 1.42 - 1.66 (3 H, m)
71		1.00	315.1	^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.92 (1 H, s), 8.00 (1 H, br. s.), 7.78 (1 H, d, J=8.56 Hz), 7.42 (1 H, d, J=8.06 Hz), 3.92 (1 H, d, J=11.08 Hz), 3.55 (1 H, d, J=10.83 Hz), 3.23 (1 H, d, J=14.86 Hz), 2.83 - 2.90 (2 H, m), 2.65 - 2.83 (2 H, m), 1.89 - 2.17 (3 H, m), 1.41 - 1.75 (3 H, m)

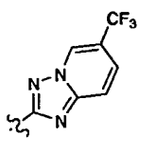
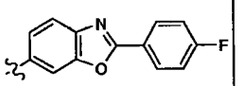
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^{1}H NMR
72		0.75	315.1	^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.82 (1 H, s), 8.22 (1 H, s), 7.98 (1 H, d, *J*=8.56 Hz), 7.21 - 7.25 (1 H, m), 6.37 (1 H, br. s.), 3.99 (1 H, d, *J*=11.58 Hz), 3.61 (1 H, d, *J*=11.58 Hz), 3.23 (1 H, d, *J*=14.86 Hz), 2.89 (2 H, t, *J*=7.68 Hz), 2.69 - 2.84 (2 H, m), 1.91 - 2.09 (2 H, m), 1.45 - 1.73 (4 H, m)
73		0.85	309.2	^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.70 (1 H, d, *J*=1.76 Hz), 8.09 (1 H, br. s.), 8.00 (1 H, d, *J*=8.31 Hz), 7.43 - 7.58 (2 H, m), 3.90 (1 H, d, *J*=10.58 Hz), 3.54 (1 H, d, *J*=10.32 Hz), 3.26 (1 H, d, *J*=14.60 Hz), 2.65 - 3.06 (5 H, m), 2.13 (1 H, br. s.), 2.00 (1 H, br. s.), 1.34 - 1.79 (5 H, m)

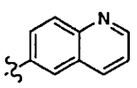
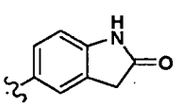
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M + H]^+$	^1H NMR
74		0.65	313.2	^1H NMR (500 MHz, MeOD) δ ppm 8.55 (1 H, s), 7.66 - 7.70 (1 H, m), 7.59 - 7.63 (1 H, m), 4.25 (1 H, d, *J*=10.99 Hz), 4.04 (1 H, d, *J*=10.68 Hz), 3.91 (1 H, d, *J*=14.95 Hz), 3.76 (1 H, dd, *J*=14.95, 2.44 Hz), 3.45 - 3.53 (1 H, m), 3.29 - 3.40 (3 H, m), 2.61 (1 H, d, *J*=2.14 Hz), 2.40 (3 H, s), 2.31 (1 H, tt, *J*=10.26, 3.47 Hz), 2.06 - 2.16 (1 H, m, *J*=14.23, 9.35, 4.54, 4.54 Hz), 1.92 - 2.06 (2 H, m)
75		1.24	310.1	^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.73 (1 H, d, *J*=1.76 Hz), 8.66 (1 H, d, *J*=2.01 Hz), 7.96 (1 H, d, *J*=9.07 Hz), 7.90 (1 H, br. s.), 7.68 (1 H, br. s.), 7.50 (1 H, br. s.), 3.93 (1 H, d, *J*=10.32 Hz), 3.56 (1 H, d, *J*=9.32 Hz), 3.29 (1 H, d, *J*=14.86 Hz), 2.97 (1 H, d, *J*=14.86 Hz), 2.88 - 2.94 (2 H, m), 2.69 - 2.87 (2 H, m), 2.12 (1 H, br. s.), 2.06 (1 H, br. s.), 1.64 - 1.73 (1 H, m), 1.46 - 1.64 (2 H, m)

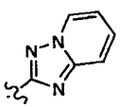
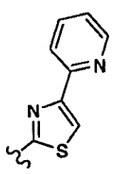
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^{1}H NMR
76		1.58	328.2	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.30 (s, 1 H), 9.16 (s, 1 H), 7.04 - 7.43 (m, 1 H), 6.70 - 7.03 (m, 1 H), 6.54 - 6.69 (m, 1 H), 3.89 (d, *J*=9.77 Hz, 1 H), 3.53 - 3.81 (m, 4 H), 3.01 (s, 2 H), 2.58 - 2.91 (m, 4 H), 2.03 (s, 1 H), 1.78 - 1.96 (m, 1 H), 1.32 - 1.73 (m, 3 H)
77		1.40	316.1	^{1}H NMR (500 MHz, *DMSO-D6*) δ ppm 11.53 (s, 1 H), 9.12 (s, 1 H), 6.94 - 7.46 (m, 2 H), 6.83 (s, 2 H), 3.90 (d, *J*=9.77 Hz, 1 H), 3.64 (d, *J*=9.77 Hz, 1 H), 2.90 - 3.09 (m, 2 H), 2.61 - 2.87 (m, 4 H), 1.95 - 2.10 (m, 1 H), 1.88 (d, *J*=3.05 Hz, 1 H), 1.33 - 1.70 (m, 3 H)
78		0.35	298.1	^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.94 (1 H, s), 7.80 (1 H, br. s.), 7.26 - 7.36 (1 H, m), 7.17 - 7.25 (1 H, m), 3.97 (1 H, d, *J*=11.33 Hz), 3.59 (1 H, d, *J*=11.58 Hz), 3.23 (1 H, d, *J*=14.60 Hz), 2.65 - 3.01 (5 H, m), 1.86 - 2.16 (2 H, m), 1.35 - 1.73 (3 H, m)

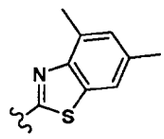
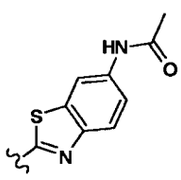
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M + H]^+$	^1H NMR
79		1.10	376.1	^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.78 (2 H, d, *J*=5.79 Hz), 8.03 (2 H, d, *J*=6.04 Hz), 7.73 (1 H, br. s.), 7.48 (1 H, d, *J*=8.56 Hz), 7.36 (1 H, br. s.), 3.92 (1 H, d, *J*=8.81 Hz), 3.55 (1 H, d, *J*=9.06 Hz), 3.24 (1 H, d, *J*=14.10 Hz), 2.57 - 3.06 (5 H, m), 1.86 - 2.20 (2 H, m), 1.30 - 1.80 (3 H, m)
80		2.36	393.1	^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.00 (1 H, d, *J*=7.81 Hz), 7.83 - 7.97 (1 H, m), 7.68 (1 H, br. s.), 7.39 - 7.55 (2 H, m), 7.35 (1 H, br. s.), 7.20 (2 H, td, *J*=8.31, 2.27 Hz), 3.93 (1 H, d, *J*=10.83 Hz), 3.56 (1 H, d, *J*=10.58 Hz), 3.24 (1 H, d, *J*=15.11 Hz), 2.62 - 3.05 (5 H, m), 1.88 - 2.22 (2 H, m), 1.34 - 1.79 (3 H, m)

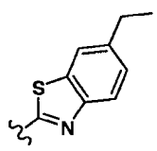
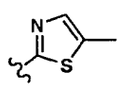
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M + H]^+$	^1H NMR
81		2.81	403.1	^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.12 (2 H, d, *J*=8.06 Hz), 7.64 (1 H, br. s.), 7.43 (1 H, d, *J*=8.56 Hz), 7.32 (3 H, d, *J*=8.06 Hz), 3.94 (1 H, d, *J*=10.07 Hz), 3.56 (1 H, d, *J*=9.57 Hz), 3.24 (1 H, d, *J*=13.60 Hz), 2.57 - 3.03 (7 H, m), 1.88 - 2.22 (2 H, m), 1.39 - 1.74 (3 H, m), 1.27 (3 H, t, *J*=7.68 Hz)
82		2.62	418.1	^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.06 (2 H, d, *J*=9.07 Hz), 7.56 (1 H, br. s.), 7.30 - 7.43 (2 H, m), 6.74 (2 H, d, *J*=9.07 Hz), 3.95 (1 H, d, *J*=11.58 Hz), 3.58 (1 H, d, *J*=11.83 Hz), 3.24 (1 H, d, *J*=14.10 Hz), 3.05 (6 H, s), 2.61 - 2.99 (5 H, m), 1.88 - 2.13 (2 H, m), 1.35 - 1.81 (4 H, m)

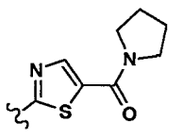
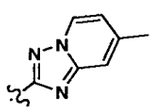
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M + H]^+$	^1H NMR
83		1.15	367.1	^1H NMR (500 MHz, MeOD) δ ppm 9.12 (1 H, s), 7.78 - 7.82 (1 H, m), 7.70 - 7.74 (1 H, m), 4.05 (1 H, d, *J*=9.77 Hz), 3.75 (1 H, d, *J*=9.77 Hz), 3.29 (1 H, d, *J*=14.65 Hz), 3.11 - 3.18 (1 H, m), 2.98 (2 H, t, *J*=7.93 Hz), 2.80 - 2.91 (2 H, m), 2.13 - 2.22 (2 H, m), 1.71 - 1.87 (2 H, m), 1.62 - 1.71 (1 H, m)
84		1.96	393.1	^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.18 - 8.26 (2 H, m), 7.66 (1 H, s), 7.44 (1 H, d, *J*=8.56 Hz), 7.32 (1 H, d, *J*=8.56 Hz), 7.16 - 7.23 (2 H, m), 3.95 (1 H, d, *J*=11.33 Hz), 3.57 (1 H, d, *J*=11.33 Hz), 3.25 (1 H, d, *J*=14.60 Hz), 2.69 - 3.04 (6 H, m), 2.09 (1 H, br. s.), 1.45 - 1.74 (4 H, m)

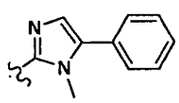
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M + H]^+$	^1H NMR
85		1.34	309.1	^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.75 (1 H, dd, *J*=4.15, 1.64 Hz), 8.04 (1 H, d, *J*=8.06 Hz), 7.98 (2 H, d, *J*=8.81 Hz), 7.49 (1 H, d, *J*=8.81 Hz), 7.31 (1 H, dd, *J*=8.31, 4.28 Hz), 6.71 (1 H, br. s.), 4.03 (1 H, d, *J*=11.83 Hz), 3.65 (1 H, d, *J*=12.09 Hz), 3.25 (1 H, d, *J*=14.86 Hz), 2.96 (1 H, d, *J*=14.86 Hz), 2.89 (2 H, t, *J*=7.55 Hz), 2.69 - 2.84 (2 H, m), 2.07 (1 H, br. s.), 1.98 (1 H, br. s.), 1.57 - 1.73 (2 H, m), 1.44 - 1.55 (1 H, m)
86		1.16	313.1	^1H NMR (400 MHz, $CDCl_3$) δ ppm 9.78 (1 H, br. s.), 7.19 (1 H, br. s.), 6.99 (1 H, d, *J*=6.80 Hz), 6.67 (1 H, d, *J*=8.31 Hz), 3.87 (1 H, d, *J*=10.32 Hz), 3.50 (1 H, d, *J*=11.08 Hz), 3.46 (2 H, s), 3.21 (1 H, d, *J*=14.60 Hz), 2.93 (1 H, d, *J*=15.11 Hz), 2.87 (2 H, t, *J*=7.68 Hz), 2.65 - 2.81 (2 H, m), 2.04 (1 H, br. s.), 1.96 (1 H, br. s.), 1.40 - 1.75 (3 H, m)

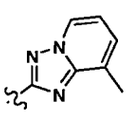
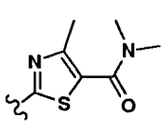
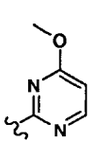
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M + H]^+$	^{1}H NMR
87		1.13	299.2	^{1}H NMR (500 MHz, MeOD) δ ppm 8.57 - 8.63 (1 H, m), 7.55 - 7.64 (2 H, m), 7.06 - 7.12 (1 H, m), 4.04 (1 H, dd, *J*=9.92, 1.98 Hz), 3.81 (1 H, dd, *J*=10.07, 2.14 Hz), 3.46 - 3.57 (1 H, m), 3.23 (2 H, d, *J*=10.68 Hz), 3.09 - 3.18 (2 H, m), 2.82 - 3.02 (1 H, m), 2.41 (1 H, br. s.), 2.28 - 2.37 (1 H, m), 1.99 - 2.07 (1 H, m), 1.86 - 1.97 (2 H, m)
88		1.26	342.1	^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ ppm 9.20 (s, 1 H), 8.64 (s, 1 H), 8.45 - 8.56 (m, *J*=4.58, 1.53 Hz, 1 H), 8.21 - 8.38 (m, *J*=7.63 Hz, 1 H), 7.62 (s, 1 H), 7.33 - 7.50 (m, *J*=7.93, 4.88 Hz, 1 H), 3.75 (dd, *J*=128.64, 9.92 Hz, 2 H), 2.95 - 3.14 (m, 2 H), 2.62 - 2.91 (m, 4 H), 2.06 (s, 1 H), 1.92 (s, 1 H), 1.42 - 1.70 (m, 3 H)

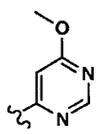
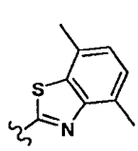
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M + H]^+$	^1H NMR
89		2.13	343.1	^1H NMR (500 MHz, DMSO-d_6) δ ppm 8.81 (s, 1 H), 7.39 (s, 1 H), 6.97 (s, 1 H), 3.78 (dd, *J*=130.16, 9.92 Hz, 2 H), 2.95 - 3.15 (m, 2 H), 2.74 - 2.90 (m, 2 H), 2.61 - 2.72 (m, *J*=7.78, 7.78 Hz, 2 H), 2.47 - 2.55 (m, *J*=3.66, 1.83 Hz, 3 H), 2.33 (s, 3 H), 2.07 (s, 1 H), 1.85 - 2.01 (m, 1 H), 1.41 - 1.70 (m, 3 H)
90		0.55	372.0	^1H NMR (300 MHz, DMSO-d_6) δ ppm 9.98 (1 H, s), 8.92 (1 H, br. s.), 8.11 (1 H, d, *J*=1.83 Hz), 7.48 - 7.53 (1 H, m), 7.34 - 7.40 (1 H, m), 3.88 (1 H, d, *J*=10.25 Hz), 3.62 (1 H, d, *J*=10.25 Hz), 3.02 (2 H, s), 2.74 - 2.83 (2 H, m), 2.66 (2 H, t, *J*=7.50 Hz), 2.04 (4 H, s), 1.90 (1 H, br. s.), 1.58 (3 H, br. s.)

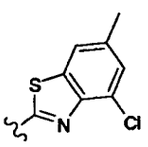
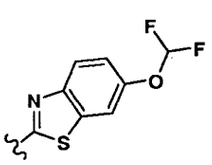
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M + H]^+$	^1H NMR
91		1.60	343.3	^1H NMR (300 MHz, DMSO-d_6) δ ppm 7.61 (1 H, s), 7.47 - 7.53 (1 H, m), 7.16 (1 H, d, *J*=8.05 Hz), 3.84 - 3.92 (1 H, m), 3.62 (1 H, d, *J*=10.25 Hz), 3.26 - 3.46 (3 H, m), 3.02 (1 H, s), 2.79 (1 H, d, *J*=6.95 Hz), 2.65 (2 H, q, *J*=7.32 Hz), 2.01 - 2.20 (1 H, m), 1.93 (2 H, d, *J*=9.88 Hz), 1.40 - 1.64 (2 H, m), 1.15 - 1.28 (3 H, m), 1.00 (1 H, d, *J*=6.59 Hz)
92		0.45	279.1	^1H NMR (500 MHz, *DMSO-D6*) δ ppm 8.34 - 8.83 (m, 1 H), 6.96 (s, 1 H), 3.79 (d, *J*=9.77 Hz, 2 H), 3.53 (d, *J*=9.77 Hz, 2 H), 2.89 - 3.06 (m, 2 H), 2.71 - 2.86 (m, 2 H), 2.60 - 2.70 (m, *J*=7.78, 7.78 Hz, 2 H), 2.29 (s, 3 H), 2.01 (s, 1 H), 1.90 (d, *J*=13.43 Hz, 2 H), 1.35 - 1.65 (m, 3 H)

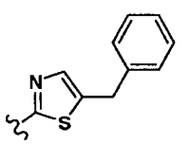
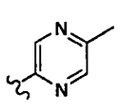
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M + H]^+$	^{1}H NMR
93		1.79	355.1	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.74 (s, 1 H), 7.62 - 7.88 (m, 1 H), 3.83 (d, *J*=10.07 Hz, 1 H), 3.63 - 3.76 (m, 2 H), 3.58 (d, *J*=10.07 Hz, 1 H), 3.40 - 3.53 (m, 2 H), 2.96 - 3.10 (m, 2 H), 2.73 - 2.90 (m, 2 H), 2.58 - 2.72 (m, *J*=7.63, 7.63 Hz, 2 H), 2.06 (s, 1 H), 1.75 - 1.99 (m, 5 H), 1.43 - 1.69 (m, 3 H)
94		1.53	313.1	^{1}H NMR (500 MHz, MeOD) δ ppm 8.63 (1 H, d, *J*=7.02 Hz), 7.55 (1 H, s), 7.19 - 7.23 (1 H, m), 4.27 (1 H, d, *J*=10.68 Hz), 4.06 (1 H, d, *J*=10.68 Hz), 3.94 (1 H, d, *J*=14.95 Hz), 3.76 - 3.83 (1 H, m), 3.54 (1 H, t, *J*=11.90 Hz), 3.36 - 3.48 (3 H, m), 2.64 (1 H, d, *J*=1.83 Hz), 2.56 (3 H, s), 2.34 - 2.42 (1 H, m, *J*=10.15, 10.15, 3.66, 3.51 Hz), 2.17 (1 H, dddd, *J*=14.19, 9.46, 4.58, 4.43 Hz), 1.97 - 2.11 (2 H, m)

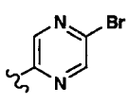
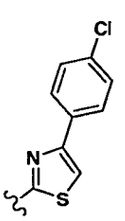
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M + H]^+$	^1H NMR
95		0.63	260.2	^1H NMR (400 MHz, $CDCl_3$) δ ppm 9.05 (1 H, br. s.), 8.34 (1 H, s), 8.04 (1 H, dd, *J*=2.77, 1.26 Hz), 8.00 (1 H, d, *J*=2.77 Hz), 3.91 (1 H, d, *J*=9.32 Hz), 3.57 (1 H, d, *J*=9.57 Hz), 3.31 (1 H, dd, *J*=14.98, 1.64 Hz), 2.65 - 3.02 (5 H, m), 2.10 - 2.20 (1 H, m), 2.05 - 2.09 (1 H, m), 1.63 - 1.75 (1 H, m), 1.40 - 1.60 (2 H, m)
96		1.88	338.1	^1H NMR (500 MHz, *DMSO-D6*) δ ppm 8.85 (s, 1 H), 7.41 - 7.47 (m, 4 H), 7.28 - 7.35 (m, 1 H), 6.85 (s, 1 H), 3.83 (d, *J*=9.77 Hz, 1 H), 3.57 (d, *J*=9.77 Hz, 1 H), 3.46 - 3.51 (m, 3 H), 3.00 (s, 2 H), 2.78 (t, *J*=7.78 Hz, 2 H), 2.67 (t, *J*=7.78 Hz, 2 H), 1.98 - 2.03 (m, 1 H), 1.85 - 1.93 (m, 1 H), 1.54 - 1.63 (m, *J*=8.16, 7.82, 7.82, 3.05 Hz, 2 H), 1.43 - 1.51 (m, 1 H)

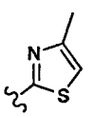
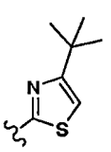
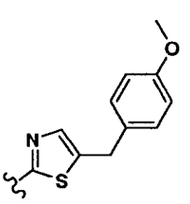
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M + H]^+$	^1H NMR
97		1.57	313.1	^1H NMR (500 MHz, MeOD) δ ppm 8.61 (1 H, d, *J*=6.71 Hz), 7.65 (1 H, d, *J*=7.32 Hz), 7.25 (1 H, t, *J*=7.02 Hz), 4.32 (1 H, d, *J*=10.99 Hz), 4.11 (1 H, d, *J*=10.68 Hz), 3.98 (1 H, dd, *J*=14.80, 1.68 Hz), 3.82 (1 H, dd, *J*=14.95, 2.14 Hz), 3.52 - 3.61 (1 H, m), 3.35 - 3.47 (3 H, m), 2.66 - 2.71 (1 H, m), 2.62 (3 H, s), 2.34 - 2.44 (1 H, m), 2.14 - 2.24 (1 H, m), 1.99 - 2.13 (2 H, m)
98		0.57	350.1	^1H NMR (500 MHz, *DMSO-D6*) δ ppm 8.64 (s, 1 H), 3.82 (d, *J*=10.07 Hz, 1 H), 3.57 (d, *J*=9.77 Hz, 1 H), 3.02 (s, 2 H), 2.97 (s, 6 H), 2.79 (s, 2 H), 2.67 (t, *J*=7.63 Hz, 2 H), 2.19 (s, 3 H), 2.04 (s, 1 H), 1.85 - 1.94 (m, 1 H), 1.58 (s, 2 H), 1.49 (d, *J*=6.71 Hz, 1 H)
99		0.87	290.1	^1H NMR (400 MHz, MeOD) δ ppm 8.20 (1 H, d, *J*=5.79 Hz), 6.34 (1 H, d, *J*=5.79 Hz), 3.94 - 4.04 (1 H, m), 3.91 (3 H, s), 3.55 - 3.76 (1 H, m), 3.00 - 3.28 (2 H, m), 2.63 - 2.97 (4 H, m), 1.99 - 2.21 (2 H, m), 1.44 - 1.85 (3 H, m)

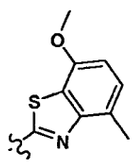
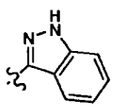
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M + H]^+$	^1H NMR
100		0.91	290.1	^1H NMR (400 MHz, MeOD) δ ppm 8.39 (1 H, s), 6.21 (1 H, d, *J*=6.04 Hz), 3.98 (1 H, d, *J*=10.32 Hz), 3.89 (3 H, s), 3.67 (1 H, d, *J*=10.32 Hz), 3.01 - 3.24 (2 H, m), 2.65 - 2.97 (4 H, m), 1.96 - 2.17 (2 H, m), 1.43 - 1.81 (3 H, m)
101		1.18	260.1	^1H NMR (400 MHz, MeOD) δ ppm 8.56 (2 H, d, *J*=4.78 Hz), 6.94 - 6.99 (1 H, m), 3.98 - 4.04 (1 H, m), 3.78 (1 H, d, *J*=10.32 Hz), 3.45 - 3.52 (1 H, m), 3.35 (1 H, s), 3.15 - 3.22 (2 H, m), 3.05 - 3.12 (2 H, m), 2.22 - 2.38 (2 H, m), 1.95 - 2.03 (1 H, m), 1.80 - 1.92 (2 H, m)
102		2.19	343.4	^1H NMR (500 MHz, DMSO-d_6) δ ppm 8.87 (1 H, br. s.), 7.06 (1 H, d, *J*=7.63 Hz), 6.91 (1 H, d, *J*=7.63 Hz), 3.92 (1 H, d, *J*=10.07 Hz), 3.66 (1 H, d, *J*=10.07 Hz), 3.03 (2 H, s), 2.72 - 2.85 (2 H, m), 2.64 - 2.70 (2 H, m), 2.51 (3 H, s), 2.35 (3 H, s), 2.07 (1 H, br. s.), 1.91 (1 H, br. s.), 1.55 - 1.65 (2 H, m), 1.44 - 1.53 (1 H, m)

Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^{1}H NMR
103		2.48	363.3	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.84 (1 H, br. s.), 7.71 (1 H, d, *J*=1.83 Hz), 7.18 (1 H, s), 3.90 (1 H, d, *J*=10.07 Hz), 3.64 (1 H, d, *J*=10.07 Hz), 3.03 (2 H, s), 2.72 - 2.85 (2 H, m), 2.66 (2 H, t, *J*=7.63 Hz), 2.53 (3 H, s), 2.07 (1 H, br. s.), 1.88 - 1.96 (1 H, m), 1.55 - 1.63 (2 H, m), 1.44 - 1.53 (1 H, m)
104		1.45	381.0	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.99 (1 H, br. s.), 7.69 (1 H, d, *J*=2.44 Hz), 7.61 (1 H, d, *J*=8.55 Hz), 7.01 - 7.34 (2 H, m), 3.89 (1 H, d, *J*=10.07 Hz), 3.64 (1 H, d, *J*=10.07 Hz), 3.03 (2 H, d, *J*=2.44 Hz), 2.72 - 2.86 (2 H, m), 2.66 (2 H, t, *J*=7.78 Hz), 2.07 (1 H, br. s.), 1.88 - 1.96 (1 H, m), 1.55 - 1.64 (2 H, m), 1.45 - 1.53 (1 H, m)

Example Number	R_1	LCMS RT (min)	LCMS Ion $[M + H]^+$	^1H NMR
105		1.83	355.1	^1H NMR (500 MHz, *DMSO-D6*) δ ppm 8.57 (s, 1 H), 7.31 (t, *J*=7.32 Hz, 2 H), 7.20 - 7.26 (m, 3 H), 7.08 (s, 1 H), 4.01 (s, 2 H), 3.78 (d, *J*=9.77 Hz, 1 H), 3.53 (d, *J*=10.07 Hz, 1 H), 2.97 (s, 2 H), 2.70 - 2.78 (m, 2 H), 2.64 (t, *J*=7.78 Hz, 2 H), 1.99 (s, 1 H), 1.81 - 1.90 (m, 1 H), 1.52 - 1.60 (m, 2 H), 1.41 - 1.49 (m, *J*=6.90, 2.90, 2.67, 2.48 Hz, 1 H)
106		0.71	274.2	^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.87 (1 H, br. s.), 8.23 (1 H, s), 7.88 (1 H, s), 3.85 (1 H, d, *J*=9.32 Hz), 3.51 (1 H, d, *J*=9.32 Hz), 3.27 (1 H, dd, *J*=14.98, 1.64 Hz), 2.60 - 2.97 (5 H, m), 2.37 (3 H, s), 2.06 - 2.16 (1 H, m, *J*=13.25, 9.85, 3.46, 3.46, 3.46 Hz), 1.99 - 2.05 (1 H, m), 1.57 - 1.70 (1 H, m), 1.36 - 1.54 (2 H, m)

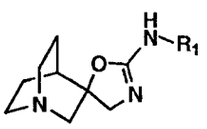
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M + H]^+$	^1H NMR
107		0.93	338.1	^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.71 (1 H, br. s.), 8.14 (1 H, d, *J*=1.26 Hz), 8.11 (1 H, d, *J*=1.26 Hz), 3.92 (1 H, d, *J*=9.32 Hz), 3.58 (1 H, d, *J*=9.57 Hz), 3.32 (1 H, dd, *J*=14.98, 1.89 Hz), 2.68 - 3.03 (5 H, m), 2.04 - 2.19 (2 H, m), 1.63 - 1.75 (1 H, m, *J*=14.01, 9.85, 4.31, 4.31 Hz), 1.42 - 1.59 (2 H, m)
108		2.34	375.0	^1H NMR (500 MHz, *DMSO-D6*) δ ppm 8.58 (s, 1 H), 7.98 (d, *J*=8.24 Hz, 2 H), 7.51 (s, 1 H), 7.45 (d, *J*=8.54 Hz, 2 H), 3.87 (d, *J*=10.07 Hz, 1 H), 3.62 (d, *J*=9.77 Hz, 1 H), 3.04 (s, 2 H), 2.75 - 2.87 (m, 2 H), 2.68 (t, *J*=7.63 Hz, 2 H), 2.07 (s, 1 H), 1.92 (s, 1 H), 1.40 - 1.68 (m, 3 H)

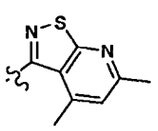
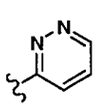
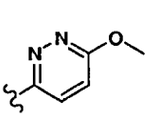
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M + H]^+$	^{1}H NMR
109		0.73	279.3	^{1}H NMR (400 MHz, *DMSO-D6*) δ ppm 8.61 (s, 1 H), 6.54 (d, *J*=1.01 Hz, 1 H), 3.80 (d, *J*=10.07 Hz, 1 H), 3.54 (d, *J*=9.82 Hz, 1 H), 2.98 (s, 2 H), 2.70 - 2.81 (m, 2 H), 2.65 (t, *J*=7.81 Hz, 2 H), 2.20 (s, 3 H), 1.95 - 2.05 (m, 1 H), 1.88 (s, 1 H), 1.50 - 1.61 (m, 2 H), 1.41 - 1.50 (m, 1 H)
110		1.76	321.4	^{1}H NMR (400 MHz, *DMSO-D6*) δ ppm 8.24 - 8.82 (m, 1 H), 6.51 (s, 1 H), 3.83 (d, *J*=9.57 Hz, 1 H), 3.57 (d, *J*=9.32 Hz, 1 H), 2.98 (s, 2 H), 2.70 - 2.82 (m, 2 H), 2.65 (t, *J*=7.68 Hz, 2 H), 1.97 - 2.04 (m, 1 H), 1.88 (s, 1 H), 1.52 - 1.61 (m, 2 H), 1.46 (dd, *J*=9.69, 2.90 Hz, 1 H), 1.24 (s, 9 H)
111		1.64	312.3	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.55 (s, 1 H), 7.13 (d, *J*=8.56 Hz, 2 H), 7.04 (s, 1 H), 6.86 (d, *J*=8.56 Hz, 2 H), 3.92 (s, 2 H), 3.66 - 3.85 (m, 4 H), 3.45 - 3.60 (m, *J*=10.07 Hz, 1 H), 2.95 (s, 2 H), 2.57 - 2.86 (m, 4 H), 1.98 (s, 1 H), 1.84 (s, 1 H), 1.31 - 1.66 (m, 2 H)

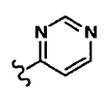
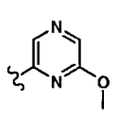
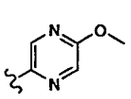
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M + H]^+$	^{1}H NMR
112		1.70	359.1	^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.83 (1 H, d, *J*=1.83 Hz), 7.08 (1 H, d, *J*=8.42 Hz), 6.71 (1 H, d, *J*=8.05 Hz), 3.87 - 3.94 (1 H, m), 3.85 (3 H, s), 3.65 (1 H, d, *J*=9.88 Hz), 3.04 (2 H, s), 2.61 - 2.85 (4 H, m), 2.47 (3 H, s), 2.08 (1 H, d, *J*=2.20 Hz), 1.82 - 1.99 (1 H, m), 1.41 - 1.66 (3 H, m)
113		1.48	298.3	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.09 (s, 1 H), 8.02 (s, 1 H), 7.63 (d, *J*=7.32 Hz, 1 H), 7.33 - 7.36 (m, 1 H), 7.30 (d, *J*=5.80 Hz, 1 H), 6.99 (t, *J*=7.02 Hz, 1 H), 3.82 (d, *J*=8.24 Hz, 1 H), 3.57 (s, 1 H), 3.00 (s, 2 H), 2.79 (s, 2 H), 2.67 (s, 2 H), 1.99 - 2.04 (m, 1 H), 1.93 (s, 1 H), 1.58 (s, 2 H), 1.47 (s, 1 H)

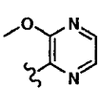
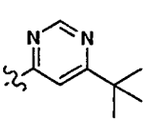
The compounds in Table 3 were synthesized according to the method of Example 21, steps C-D using the appropriate isothiocyanate or amine and racemic 3-(aminomethyl)quinuclidin-3-ol, 2 HCl.

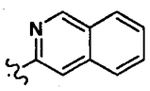
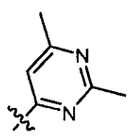
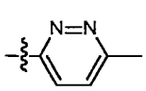
Table 3.



Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^{1}H NMR
114		2.06	344.3	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.02 (1 H, s), 7.10 (1 H, s), 3.67 - 3.88 (2 H, m), 3.07 - 3.30 (2 H, m), 2.80 - 3.05 (4 H, m), 2.78 (3 H, s), 2.55 (3 H, s), 2.22 (1 H, br. s.), 2.00 (1 H, d, *J*=12.09 Hz), 1.55 - 1.88 (3 H, m)
115		1.19	260.3	^{1}H NMR (400 MHz, MeOD) δ ppm 8.70 (1 H, dd, *J*=4.41, 1.39 Hz), 7.51 (1 H, dd, *J*=8.81, 4.53 Hz), 7.15 (1 H, d, *J*=7.81 Hz), 4.03 (1 H, d, *J*=10.07 Hz), 3.72 (1 H, d, *J*=10.07 Hz), 3.14 - 3.26 (1 H, m), 3.03 - 3.14 (1 H, m), 2.85 - 2.99 (2 H, m), 2.69 - 2.84 (2 H, m), 2.00 - 2.26 (2 H, m), 1.51 - 1.87 (3 H, m)
116		0.73	290.3	^{1}H NMR (400 MHz, MeOD) δ ppm 6.99 - 7.12 (2 H, m), 3.95 - 4.02 (4 H, m), 3.68 (1 H, d, *J*=10.07 Hz), 3.20 (1 H, dd), 3.08 (1 H, dd), 2.84 - 2.95 (2 H, m), 2.69 - 2.84 (2 H, m), 1.99 - 2.21 (2 H, m), 1.47 - 1.87 (3 H, m)

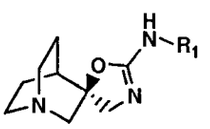
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M + H]^+$	^1H NMR
117				^1H NMR (400 MHz, MeOD) δ ppm 8.71 (1 H, s), 8.33 (1 H, d, *J*=5.54 Hz), 6.84 (1 H, br. s.), 4.04 (1 H, d, *J*=10.32 Hz), 3.73 (1 H, d, *J*=10.32 Hz), 3.17 - 3.25 (1 H, m), 3.04 - 3.13 (1 H, m), 2.70 - 3.00 (4 H, m), 2.02 - 2.18 (2 H, m), 1.51 - 1.81 (3 H, m)
118		0.83	290.3	^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.48 (1 H, br. s.), 7.96 (1 H, br. s.), 7.71 (1 H, s), 3.91 (1 H, d, *J*=9.32 Hz), 3.87 (3 H, s), 3.57 (1 H, d, *J*=9.32 Hz), 3.30 (1 H, d, *J*=14.86 Hz), 2.62 - 3.03 (5 H, m), 2.09 - 2.21 (1 H, m), 2.08 (1 H, br. s.), 1.61 - 1.78 (1 H, m), 1.39 - 1.60 (2 H, m)
119		0.84	290.3	^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.56 (1 H, br. s.), 7.96 (1 H, d, *J*=1.26 Hz), 7.79 (1 H, d, *J*=1.51 Hz), 3.89 (3 H, s), 3.85 (1 H, s), 3.53 (1 H, d, *J*=9.06 Hz), 3.31 (1 H, d, *J*=14.86 Hz), 2.65 - 3.04 (5 H, m), 2.11 - 2.23 (1 H, m, *J*=9.85, 9.85, 6.74, 3.53 Hz), 2.08 (1 H, br. s.), 1.62 - 1.75 (1 H, m), 1.40 - 1.61 (2 H, m)

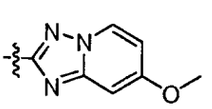
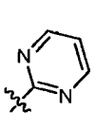
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M + H]^+$	^1H NMR
120		0.75	290.3	^1H NMR (400 MHz, $CDCl_3$) δ ppm 9.30 (1 H, br. s.), 7.58 (1 H, d, *J*=3.02 Hz), 7.52 (1 H, d, *J*=3.02 Hz), 3.92 (3 H, s), 3.88 (1 H, d, *J*=9.32 Hz), 3.54 (1 H, d, *J*=9.32 Hz), 3.28 (1 H, dd, *J*=14.86, 1.51 Hz), 2.63 - 2.96 (5 H, m), 2.07 - 2.22 (1 H, m), 2.02 (1 H, br. s.), 1.57 - 1.71 (1 H, m), 1.33 - 1.55 (2 H, m)
121		1.15	316.4	^1H NMR (400 MHz, MeOD) δ ppm 8.65 (1 H, d, *J*=3.02 Hz), 6.82 (1 H, br. s.), 4.02 (1 H, dd, *J*=10.32, 3.02 Hz), 3.71 (1 H, dd, *J*=10.32, 3.02 Hz), 2.98 - 3.26 (2 H, m), 2.66 - 2.96 (4 H, m), 1.97 - 2.18 (2 H, m), 1.48 - 1.86 (3 H, m), 1.29 (9 H, s)

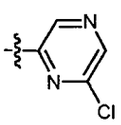
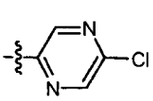
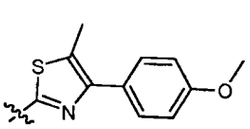
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M + H]^+$	^{1}H NMR
122		1.73	309.3	^{1}H NMR (400 MHz, MeOD) δ ppm 8.99 (1 H, s), 7.90 (1 H, d, *J*=8.31 Hz), 7.70 (1 H, d, *J*=8.31 Hz), 7.57 (1 H, t, *J*=7.55 Hz), 7.39 (1 H, t, *J*=7.55 Hz), 7.30 (1 H, br. s.), 3.94 (1 H, d, *J*=9.82 Hz), 3.63 (1 H, d, *J*=10.07 Hz), 3.14 - 3.24 (1 H, m), 3.00 - 3.10 (1 H, m), 2.68 - 2.98 (4 H, m), 2.01 - 2.24 (2 H, m), 1.45 - 1.87 (3 H, m)
123		0.79	288.30	^{1}H NMR (400 MHz, MeOD-*d*$_4$) δ ppm 6.51 (1 H, br. s.), 4.03 (1 H, d, *J*=10.32 Hz), 3.71 (1 H, d, *J*=10.32 Hz), 3.12 - 3.24 (1 H, m), 3.01 - 3.12 (1 H, m), 2.72 - 3.00 (4 H, m), 2.52 (3 H, s), 2.33 (3 H, s), 1.98 - 2.20 (2 H, m), 1.51 - 1.87 (3 H, m)
124		0.72	274.30	^{1}H NMR (400 MHz, MeOD-*d*$_4$) δ ppm 7.42 (1 H, d, *J*=9.07 Hz), 7.07 (1 H, d, *J*=8.06 Hz), 4.02 (1 H, d, *J*=10.07 Hz), 3.71 (1 H, d, *J*=10.07 Hz), 3.15 - 3.25 (1 H, m), 3.04 - 3.14 (1 H, m), 2.69 - 2.98 (4 H, m), 2.55 (3 H, s), 1.99 - 2.21 (2 H, m), 1.47 - 1.89 (3 H, m)

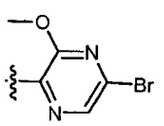
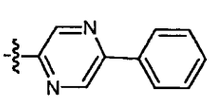
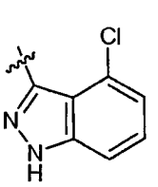
The compounds in Table 3 were synthesized according to the method of Example 21, steps C-D using the appropriate isothiocyanate or amine and (S)-3-(aminomethyl)quinuclidin-3-ol, 2 HCl.

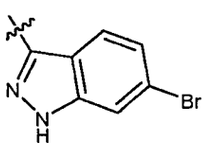
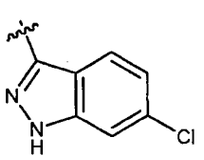
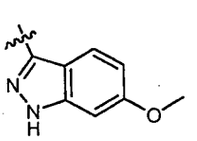
Table 3.

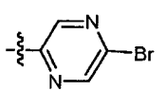
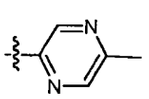
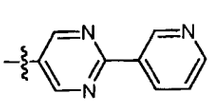


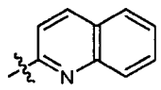
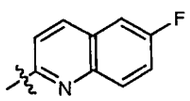
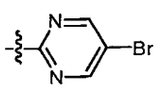
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^1H NMR
125		2.06	329.11	^1H NMR (500 MHz, MeOD-d_4) δppm 8.37 (d, *J*=7.32 Hz, 1 H), 6.92 (d, *J*=2.75 Hz, 1 H), 6.65 - 6.75 (m, 1 H), 4.01 (d, *J*=9.77 Hz, 1 H), 3.86 - 3.95 (m, 3 H), 3.70 (d, *J*=9.77 Hz, 1 H), 3.26 (d, *J*=14.95 Hz, 2 H), 3.12 (d, *J*=14.95 Hz, 1 H), 2.96 (t, *J*=7.32 Hz, 2 H), 2.76 - 2.89 (m, 2 H), 2.06 - 2.26 (m, 2 H), 1.58 - 1.86 (m, 3 H)
126		0.56	260.30	^1H NMR (400 MHz, *CDCl*$_3$) δ ppm 8.52 (2 H, d, *J*=4.78 Hz), 6.83 (1 H, t, *J*=4.78 Hz), 3.94 - 4.10 (2 H, m), 3.87 (1 H, d, *J*=14.60 Hz), 3.62 (1 H, dd, *J*=14.48, 1.89 Hz), 3.41 - 3.56 (1 H, m), 3.29 (2 H, t, *J*=8.44 Hz), 3.04 - 3.18 (1 H, m), 2.27 - 2.50 (2 H, m), 1.88 - 2.06 (2 H, m), 1.71 - 1.87 (1 H, m)

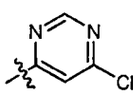
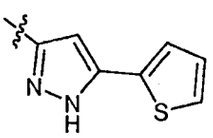
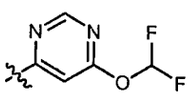
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^1H NMR
127		0.88	294.20	^1H NMR (400 MHz, *CDCl$_3$*) δ ppm 8.58 (1 H, br. s.), 8.18 (1 H, s), 7.97 (1 H, s), 3.93 (1 H, d, *J*=9.32 Hz), 3.58 (1 H, d, *J*=9.57 Hz), 3.28 (1 H, dd, *J*=14.86, 1.51 Hz), 2.64 - 2.98 (5 H, m), 2.02 - 2.15 (2 H, m), 1.60 - 1.73 (1 H, m), 1.38 - 1.56 (2 H, m)
128		0.86	294.20	^1H NMR (400 MHz, *CDCl$_3$*) δ ppm 8.72 (1 H, br. s.), 8.12 (1 H, d, *J*=0.76 Hz), 8.06 (1 H, d, *J*=1.26 Hz), 3.93 (1 H, d, *J*=9.32 Hz), 3.59 (1 H, d, *J*=9.32 Hz), 3.32 (1 H, dd, *J*=14.98, 1.38 Hz), 2.68 - 3.02 (5 H, m), 2.05 - 2.21 (2 H, m), 1.64 - 1.76 (1 H, m), 1.42 - 1.59 (2 H, m). M.P.. 185-8 °C
129		2.04	385.28	^1H NMR (500 MHz, *DMSO-D$_6$*) δ ppm 8.48 (s, 1 H), 7.58 (d, *J*=8.24 Hz, 2 H), 6.98 (d, *J*=8.55 Hz, 2 H), 3.73 - 3.87 (m, 4 H), 3.56 (d, *J*=9.16 Hz, 1 H), 3.00 (s, 2 H), 2.72 - 2.87 (m, 2 H), 2.61 - 2.72 (m, *J*=7.63, 7.63 Hz, 2 H), 2.38 (s, 3 H), 2.03 (s, 1 H), 1.91 (s, 1 H), 1.37 - 1.70 (m, 3 H)

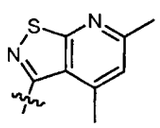
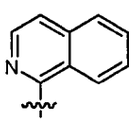
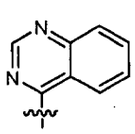
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^1H NMR
130		1.10	368.20	^1H NMR (400 MHz, *CDCl3*) δ ppm 8.97 (1 H, br. s.), 7.67 (1 H, s), 3.94 (3 H, s), 3.89 (1 H, d, *J*=9.57 Hz), 3.55 (1 H, d, *J*=9.57 Hz), 3.28 (1 H, dd, *J*=14.86, 1.76 Hz), 2.63 - 2.95 (5 H, m), 2.08 - 2.19 (1 H, m), 1.99 - 2.06 (1 H, m), 1.60 - 1.70 (1 H, m, *J*=14.01, 9.85, 4.31, 4.31 Hz), 1.35 - 1.55 (2 H, m)
131		1.19	336.30	^1H NMR (400 MHz, *CDCl3*) δ ppm 9.06 (1 H, br. s.), 8.52 (1 H, d, *J*=1.51 Hz), 8.44 (1 H, d, *J*=1.26 Hz), 7.89 - 7.93 (2 H, m), 7.40 - 7.47 (2 H, m), 7.33 - 7.39 (1 H, m), 3.94 (1 H, d, *J*=9.32 Hz), 3.60 (1 H, d, *J*=9.32 Hz), 3.34 (1 H, dd, *J*=14.86, 1.76 Hz), 2.69 - 3.05 (5 H, m), 2.13 - 2.23 (1 H, m), 2.07 - 2.12 (1 H, m), 1.65 - 1.76 (1 H, m), 1.44 - 1.60 (2 H, m)
132		1.35	332.23	^1H NMR (500 MHz, *DMSO-D6*) δ ppm 12.40 (s, 1 H), 7.95 (s, 1 H), 7.30 (d, *J*=8.24 Hz, 1 H), 7.22 (t, *J*=7.78 Hz, 2 H), 6.97 (d, *J*=7.02 Hz, 1 H), 3.79 (d, *J*=6.71 Hz, 1 H), 3.53 (s, 1 H), 3.18 (d, *J*=4.58 Hz, 3 H), 3.00 (s, 2 H), 2.79 (d, *J*=2.14 Hz, 2 H), 2.74 (s, 1 H), 2.66 (d, *J*=7.93 Hz, 3 H), 1.96 - 2.04 (m, 2 H), 1.91 (s, 1 H), 1.59 (s, 3 H), 1.46 (s, 1 H)

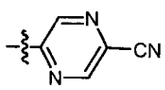
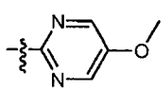
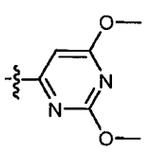
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^1H NMR
133		1.94	378.16	^1H NMR (500 MHz, *DMSO-D6*) δ ppm 12.22 (s, 1 H), 8.32 (s, 1 H), 8.01 (s, 1 H), 7.58 (d, *J*=8.24 Hz, 1 H), 7.55 (s, 1 H), 7.08 - 7.14 (m, 1 H), 3.82 (d, *J*=9.77 Hz, 1 H), 3.56 (d, *J*=9.16 Hz, 1 H), 2.96 - 3.04 (m, 2 H), 2.73 - 2.82 (m, 2 H), 2.67 (t, *J*=7.48 Hz, 2 H), 2.00 - 2.05 (m, 1 H), 1.91 (s, 1 H), 1.54 - 1.63 (m, 2 H), 1.45 (s, 1 H)
134		1.86	332.16	^1H NMR (500 MHz, *DMSO-D6*) δ ppm 12.22 (s, 1 H), 8.00 (s, 1 H), 7.63 (d, *J*=8.55 Hz, 1 H), 7.40 (s, 1 H), 7.00 (d, *J*=7.93 Hz, 1 H), 3.82 (d, *J*=9.46 Hz, 1 H), 3.56 (d, *J*=9.16 Hz, 1 H), 3.00 (s, 2 H), 2.78 (s, 2 H), 2.67 (t, *J*=7.32 Hz, 2 H), 2.02 (s, 1 H), 1.91 (s, 1 H), 1.58 (s, 2 H), 1.45 (s, 1 H)
135		1.51	328.28	^1H NMR (500 MHz, *DMSO-D6*) δ ppm 11.88 (s, 2 H), 8.01 (s, 1 H), 7.48 (d, *J*=8.55 Hz, 2 H), 6.73 (s, 2 H), 6.62 (dd, *J*=8.70, 1.68 Hz, 2 H), 3.77 - 3.83 (m, 7 H), 3.55 (d, *J*=8.85 Hz, 2 H), 2.97 - 3.05 (m, 4 H), 2.80 (s, 3 H), 2.65 - 2.72 (m, 4 H), 1.98 - 2.04 (m, 3 H), 1.92 (s, 2 H), 1.60 (d, *J*=2.14 Hz, 2 H), 1.59 (s, 2 H), 1.47 (s, 2 H)

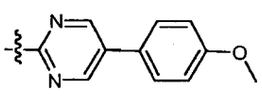
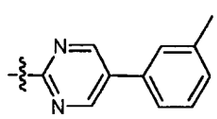
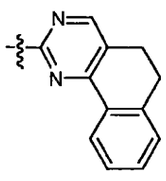
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^1H NMR
136		0.91	338.20	^1H NMR (400 MHz, *CDCl$_3$*) δ ppm 8.69 (1 H, br. s.), 8.12 (1 H, d, *J*=1.51 Hz), 8.08 (1 H, d, *J*=1.26 Hz), 3.91 (1 H, d, *J*=9.57 Hz), 3.57 (1 H, d, *J*=9.32 Hz), 3.29 (1 H, dd, *J*=14.86, 1.51 Hz), 2.62 - 3.01 (5 H, m), 2.01 - 2.18 (2 H, m), 1.61 - 1.76 (1 H, m), 1.39 - 1.59 (2 H, m)
137		0.77	274.30	^1H NMR (400 MHz, *CDCl$_3$*) δ ppm 8.92 (1 H, br. s.), 8.27 (1 H, s), 7.92 (1 H, s), 3.90 (1 H, d, *J*=9.32 Hz), 3.56 (1 H, d, *J*=9.32 Hz), 3.32 (1 H, dd, *J*=14.86, 1.76 Hz), 2.67 - 3.02 (5 H, m), 2.42 (3 H, s), 2.10 - 2.21 (1 H, m, *J*=13.17, 9.84, 3.49, 3.49, 3.49 Hz), 2.04 - 2.10 (1 H, m), 1.64 - 1.74 (1 H, m), 1.39 - 1.59 (2 H, m)
138		0.84	337.40	^1H NMR (400 MHz, *MeOD-d$_4$*) d ppm 9.39 (1 H, s), 8.57 - 8.73 (2 H, m), 8.52 (1 H, d, *J*=5.79 Hz), 7.56 (1 H, dd, *J*=8.06, 5.04 Hz), 6.54 - 7.00 (1 H, m), 4.11 (1 H, d, *J*=10.32 Hz), 3.79 (1 H, d, *J*=10.58 Hz), 3.02 - 3.29 (2 H, m), 2.72 - 3.02 (4 H, m), 2.01 - 2.25 (2 H, m), 1.47 - 1.89 (3 H, m)

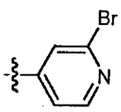
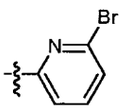
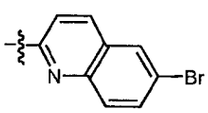
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^1H NMR
139		1.15	309.30	^1H NMR (500 MHz, *MeOD-d_4*) δ ppm 8.07 (1 H, d, *J*=8.85 Hz), 7.88 (1 H, d, *J*=8.24 Hz), 7.75 (1 H, d, *J*=7.93 Hz), 7.56 - 7.66 (1 H, m), 7.39 (1 H, t, *J*=7.48 Hz), 7.06 (1 H, d, *J*=8.85 Hz), 4.09 (1 H, d, *J*=10.07 Hz), 3.78 (1 H, d, *J*=10.07 Hz), 3.27 (1 H, d, *J*=14.95 Hz), 3.06 - 3.18 (1 H, m), 2.93 - 3.01 (2 H, m), 2.75 - 2.93 (2 H, m), 2.07 - 2.29 (2 H, m), 1.57 - 1.88 (3 H, m)
140		1.26	327.30	^1H NMR (500 MHz, *MeOD-d_4*) δ ppm 8.05 (1 H, d, *J*=8.85 Hz), 7.92 (1 H, dd, *J*=9.00, 5.34 Hz), 7.35 - 7.49 (2 H, m), 7.08 (1 H, d, *J*=8.24 Hz), 4.09 (1 H, d, *J*=10.07 Hz), 3.78 (1 H, d, *J*=10.07 Hz), 3.22 - 3.30 (1 H, m), 3.09 - 3.18 (1 H, m), 2.91 - 3.04 (2 H, m), 2.71 - 2.91 (2 H, m), 2.06 - 2.30 (2 H, m), 1.56 - 1.90 (3 H, m)
141		0.80	339.40	^1H NMR (400 MHz, *MeOD-d_4*) δ ppm 8.58 (2 H, s), 3.99 (1 H, d, *J*=10.07 Hz), 3.69 (1 H, d, *J*=10.07 Hz), 3.16 - 3.24 (1 H, m), 3.03 - 3.12 (1 H, m), 2.85 - 2.95 (2 H, m), 2.70 - 2.85 (2 H, m), 1.96 - 2.21 (2 H, m), 1.42 - 1.87 (3 H, m)

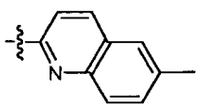
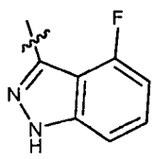
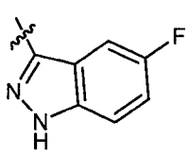
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^{1}H NMR
142		0.80	294.40	^{1}H NMR (400 MHz, *MeOD-d4*) δppm 8.54 (1 H, d, *J*=1.01 Hz), 6.83 (1 H, br. s.), 4.04 (1 H, d, *J*=10.32 Hz), 3.73 (1 H, d, *J*=10.32 Hz), 3.04 - 3.25 (2 H, m), 2.69 - 2.97 (4 H, m), 1.96 - 2.18 (2 H, m), 1.43 - 1.84 (3 H, m)
143		1.60	330.28	^{1}H NMR (500 MHz, *DMSO-D6*) δ ppm 11.95 (s, 1 H), 7.54 (s, 1 H), 7.35 (s, 1 H), 7.22 (s, 1 H), 7.04 (s, 1 H), 6.09 (s, 1 H), 3.66 (s, 1 H), 3.39 (d, *J*=7.02 Hz, 1 H), 3.04 (s, 1 H), 2.99 (s, 1 H), 2.84 (s, 2 H), 2.67 (s, 3 H), 2.02 (s, 1 H), 1.92 (s, 1 H), 1.59 (s, 2 H), 1.51 (s, 1 H)
144		1.00	326.30	^{1}H NMR (400 MHz, *MeOD-d4*) δppm 8.47 (1 H, s), 7.30 - 7.79 (1 H, m), 6.28 (1 H, br. s.), 4.02 (1 H, d, *J*=10.32 Hz), 3.71 (1 H, d, *J*=10.32 Hz), 3.16 - 3.25 (1 H, m), 3.04 - 3.13 (1 H, m), 2.85 - 2.99 (2 H, m), 2.70 - 2.86 (2 H, m), 1.94 - 2.20 (2 H, m), 1.49 - 1.84 (3 H, m). M.P. 185-90 °C

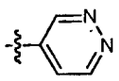
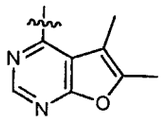
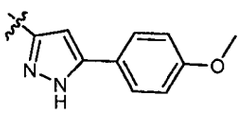
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^1H NMR
145		1.16	344.30	^1H NMR (400 MHz, *MeOD-d4*) δ ppm 7.06 (1 H, s), 3.96 (1 H, d, *J*=9.82 Hz), 3.65 (1 H, d, *J*=10.07 Hz), 3.18 - 3.26 (1 H, m), 3.05 - 3.13 (1 H, m), 2.87 - 2.98 (2 H, m), 2.70 - 2.86 (5 H, m), 2.57 (3 H, s), 2.03 - 2.20 (2 H, m), 1.51 - 1.85 (3 H, m)
146		1.20	309.30	^1H NMR (400 MHz, *MeOD-d4*) δ ppm 8.46 (1 H, d, *J*=8.31 Hz), 8.06 (1 H, d, *J*=6.04 Hz), 7.58 - 7.78 (2 H, m), 7.51 (1 H, td, *J*=7.68, 1.26 Hz), 7.25 (1 H, d, *J*=6.04 Hz), 3.99 (1 H, d, *J*=9.82 Hz), 3.67 (1 H, d, *J*=9.82 Hz), 3.23 (1 H, s), 3.04 - 3.13 (1 H, m), 2.89 - 2.99 (2 H, m), 2.71 - 2.88 (2 H, m), 2.04 - 2.27 (2 H, m), 1.46 - 1.85 (3 H, m)
147		0.98	310.30	^1H NMR (400 MHz, *MeOD-d4*) δ ppm 8.72 (1 H, s), 8.46 (1 H, d, *J*=7.81 Hz), 7.72 - 7.88 (2 H, m), 7.56 (1 H, ddd, *J*=8.25, 6.86, 1.26 Hz), 4.11 (1 H, d, *J*=10.32 Hz), 3.80 (1 H, d, *J*=10.32 Hz), 3.09 - 3.17 (1 H, m), 2.97 (2 H, t, *J*=7.43 Hz), 2.76 - 2.89 (2 H, m), 2.04 - 2.26 (2 H, m), 1.50 - 1.87 (3 H, m)

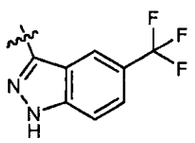
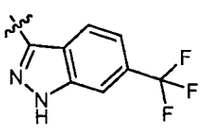
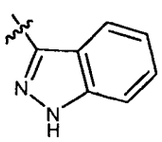
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^1H NMR
148		0.81	285.30	^1H NMR (400 MHz, *MeOD-d_4*) δ ppm 8.64 (1 H, d, *J*=1.26 Hz), 8.28 (1 H, d, *J*=1.26 Hz), 4.19 (1 H, d, *J*=10.83 Hz), 3.97 (1 H, d, *J*=11.08 Hz), 3.86 (1 H, dd, *J*=14.60, 1.51 Hz), 3.72 (1 H, dd, *J*=14.86, 2.52 Hz), 3.44 - 3.56 (1 H, m), 3.31 - 3.43 (3 H, m), 2.49 - 2.58 (1 H, m), 2.28 - 2.42 (1 H, m, J=13.53, 10.07, 3.56, 3.56, 3.27 Hz), 1.91 - 2.18 (3 H, m)
149		0.73	290.30	^1H NMR (400 MHz, *MeOD-d_4*) δ ppm 8.28 (2 H, s), 3.95 (1 H, d, *J*=9.82 Hz), 3.86 (3 H, s), 3.65 (1 H, d, *J*=9.82 Hz), 3.15 - 3.24 (1 H, m), 3.03 - 3.11 (1 H, m), 2.68 - 2.96 (4 H, m), 1.97 - 2.19 (2 H, m), 1.49 - 1.85 (3 H, m)
150		0.90	320.40	^1H NMR (400 MHz, *MeOD-d_4*) δ ppm 5.87 (1 H, br. s.), 3.99 (1 H, d, *J*=10.32 Hz), 3.92 (3 H, s), 3.88 (3 H, s), 3.67 (1 H, d, *J*=10.32 Hz), 3.14 - 3.22 (1 H, m), 3.01 - 3.10 (1 H, m), 2.70 - 2.94 (4 H, m), 1.98 - 2.16 (2 H, m), 1.51 - 1.82 (3 II, m)

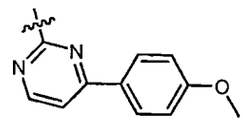
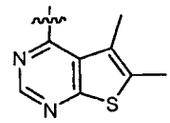
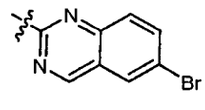
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^1H NMR
151		1.15	366.30	^1H NMR (400 MHz, *MeOD-d4*) δ ppm 8.74 (2 H, s), 7.53 (2 H, d, *J*=8.81 Hz), 7.02 (2 H, d, *J*=8.81 Hz), 4.01 (1 H, d, *J*=10.07 Hz), 3.81 (3 H, s), 3.71 (1 H, d, *J*=10.07 Hz), 3.26 (1 H, s), 3.08 - 3.18 (1 H, m), 2.73 - 3.03 (4 H, m), 2.16 (2 H, br. s.), 1.51 - 1.90 (3 H, m)
152		1.27	350.40	^1H NMR (400 MHz, *MeOD-d4*) δ ppm 8.78 (2 H, s), 7.27 - 7.47 (3 H, m), 7.20 (1 H, d, *J*=7.30 Hz), 4.02 (1 H, d, *J*=10.07 Hz), 3.71 (1 H, d, *J*=10.07 Hz), 3.24 (1 H, d, *J*=15.11 Hz), 3.03 - 3.14 (1 H, m), 2.70 - 3.00 (4 H, m), 2.40 (3 H, s), 2.03 - 2.22 (2 H, m), 1.53 - 1.84 (3 H, m)
153		2.13	362.28	^1H NMR (400 MHz, *MeOD-d4*) δ ppm 8.37 (1 H, s), 8.24 (1 H, dd, *J*=7.55, 1.51 Hz), 7.88 (1 H, s), 7.19 - 7.44 (3 H, m), 4.02 (1 H, d, *J*=10.07 Hz), 3.71 (1 H, d, *J*=10.07 Hz), 3.24 (1 H, d, *J*=16.87 Hz), 3.05 - 3.12 (1 H, m), 2.70 - 2.99 (8 H, m), 2.05 - 2.21 (2 H, m), 1.48 - 1.84 (3 H, m)

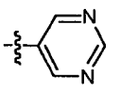
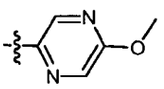
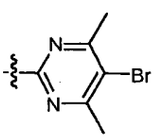
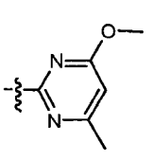
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^1H NMR
154		0.57	339.10	^1H NMR (500 MHz, *MeOD-d_4*) δ ppm 8.07 (d, *J*=5.49 Hz, 1 H), 7.47 - 7.71 (m, 1 H), 7.13 - 7.34 (m, 1 H), 3.91 - 4.06 (m, 1 H), 3.56 - 3.73 (m, 1 H), 3.14 - 3.24 (m, 1 H), 3.02 - 3.14 (m, 1 H), 2.73 - 3.01 (m, 4 H), 1.98 - 2.21 (m, 2 H), 1.58 - 1.85 (m, 3 H)
155		0.64	339.04	^1H NMR (500 MHz, *MeOD-d_4*) δ ppm 7.45 - 7.58 (m, 1 H), 7.04 - 7.16 (m, 1 H), 6.90 (d, *J*=7.32 Hz, 1 H), 3.95 - 4.09 (m, 1 H), 3.67 - 3.77 (m, 1 H), 3.18 - 3.28 (m, 1 H), 3.07 - 3.17 (m, 1 H), 2.76 - 3.05 (m, 4 H), 2.04 - 2.22 (m, 2 H), 1.50 - 1.89 (m, 3 H)
156		1.47	388.40	^1H NMR (500 MHz, *MeOD-d_4*) δ ppm 7.96 - 8.03 (1 H, m), 7.88 - 7.95 (1 H, m), 7.75 - 7.84 (1 H, m), 7.61 - 7.73 (1 H, m), 7.06 (1 H, d, *J*=8.55 Hz), 4.01 - 4.11 (1 H, m), 3.69 - 3.82 (1 H, m), 3.20 - 3.29 (1 H, m), 3.09 - 3.19 (1 H, m), 2.76 - 3.02 (4 H, m), 2.09 - 2.23 (2 H, m), 1.58 - 1.87 (3 H, m)

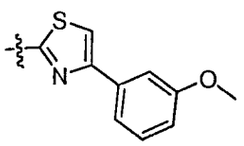
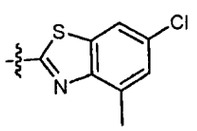
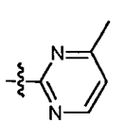
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^1H NMR
157		1.33	323.50	^1H NMR (500 MHz, *MeOD-d_4*) δ ppm 7.99 (1 H, d, *J*=8.55 Hz), 7.77 (1 H, d, *J*=8.55 Hz), 7.41 - 7.57 (2 H, m), 7.02 (1 H, d, *J*=8.55 Hz), 4.08 (1 H, d, *J*=9.77 Hz), 3.76 (1 H, d, *J*=9.77 Hz), 3.26 (1 H, d, *J*=14.95 Hz), 3.08 - 3.17 (1 H, m), 2.78 - 3.02 (4 H, m), 2.49 (3 H, s), 2.08 - 2.31 (2 H, m), 1.54 - 1.89 (3 H, m)
158		1.19	316.16	^1H NMR (500 MHz, *DMSO-D6*) δ ppm 12.36 (s, 1 H), 7.98 (s, 1 H), 7.19 - 7.27 (m, 1 H), 7.15 (d, *J*=8.24 Hz, 1 H), 6.64 - 6.71 (m, 1 H), 3.80 (d, *J*=7.63 Hz, 1 H), 3.54 (s, 1 H), 2.95 - 3.04 (m, 2 H), 2.78 (s, 2 H), 2.66 (s, 2 H), 2.01 (s, 1 H), 1.93 (s, 1 H), 1.58 (s, 2 H), 1.46 (s, 1 H)
159		1.40	316.16	^1H NMR (500 MHz, *DMSO-D6*) δ ppm 12.20 (s, 1 H), 7.98 (s, 1 H), 7.38 (dd, *J*=8.55, 3.36 Hz, 1 H), 7.32 (d, *J*=8.55 Hz, 1 H), 7.18 (t, *J*=8.85 Hz, 1 H), 3.81 (d, *J*=8.85 Hz, 1 H), 3.55 (d, *J*=8.55 Hz, 1 H), 2.97 - 3.05 (m, 2 H), 2.79 (s, 2 H), 2.68 (t, *J*=7.32 Hz, 3 H), 2.02 (s, 1 H), 1.92 (s, 1 H), 1.59 (d, *J*=6.41 Hz, 2 H), 1.47 (d, *J*=8.85 Hz, 1 H)

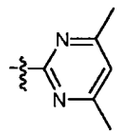
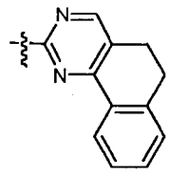
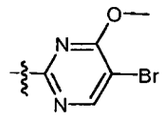
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^1H NMR
160		0.83	260.27	^1H NMR (400 MHz, *MeOD*) δ ppm 8.89 (1 H, br. s.), 8.80 (1 H, d, *J*=5.79 Hz), 7.53 (1 H, br. s.), 3.91 (1 H, d, *J*=10.83 Hz), 3.60 (1 H, d, *J*=10.83 Hz), 3.16 - 3.25 (1 H, m), 3.02 - 3.12 (1 H, m), 2.68 - 2.99 (4 H, m), 1.94 - 2.17 (2 H, m), 1.53 - 1.83 (3 H, m)
161		1.55	328.21	^1H NMR (400 MHz, *MeOD-d_4*) δ ppm 8.35 (1 H, s), 4.01 (1 H, d, *J*=10.07 Hz), 3.70 (1 H, d, *J*=10.07 Hz), 3.20 - 3.27 (1 H, m), 3.05 - 3.13 (1 H, m), 2.69 - 2.99 (4 H, m), 2.34 (3 H, s), 2.29 (3 H, s), 2.01 - 2.22 (2 H, m), 1.51 - 1.83 (3 H, m)
162		1.85	354.25	^1H NMR (500 MHz, *DMSO-D6*) δ ppm 11.75 - 12.09 (m, *J*=14.95 Hz, 1 H), 7.62 (d, *J*=7.93 Hz, 2 H), 7.38 - 7.54 (m, *J*=10.99 Hz, 1 H), 6.95 (d, *J*=6.71 Hz, 2 H), 6.13 (s, 1 H), 3.76 - 3.83 (m, 4 H), 3.74 (s, 1 H), 3.38 (d, *J*=2.75 Hz, 1 H), 2.98 (s, 1 H), 2.82 (s, 2 H), 2.62 - 2.71 (m, 2 H), 2.00 (s, 1 H), 1.92 (s, 1 H), 1.58 (s, 2 H), 1.50 (s, 1 H)

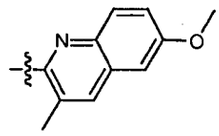
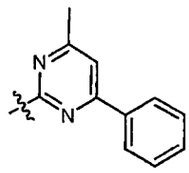
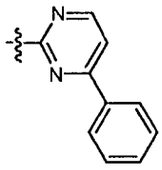
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^1H NMR
163		2.09	366.17	^1H NMR (500 MHz, *DMSO-D6*) δ ppm 12.54 (s, 1 H), 8.05 (s, 1 H), 7.97 (s, 1 H), 7.52 - 7.60 (m, 2 H), 3.82 (s, 1 H), 3.58 (s, 1 H), 3.01 (s, 2 H), 2.78 (s, 2 H), 2.64 - 2.70 (m, 2 H), 1.99 - 2.05 (m, 1 H), 1.92 (s, 1 H), 1.58 (s, 2 H), 1.47 (s, 1 H)
164		2.12	366.17	^1H NMR (500 MHz, *DMSO-D6*) δ ppm 12.54 (s, 1 H), 8.03 (s, 1 H), 7.85 (d, *J*=8.24 Hz, 1 H), 7.70 (s, 1 H), 7.26 (d, *J*=8.24 Hz, 1 H), 3.83 (d, *J*=9.46 Hz, 1 H), 3.57 (d, *J*=8.85 Hz, 1 H), 2.97 - 3.05 (m, 2 H), 2.79 (s, 2 H), 2.67 (t, *J*=7.48 Hz, 2 H), 2.03 (d, *J*=2.44 Hz, 1 H), 1.92 (s, 1 H), 1.59 (d, *J*=5.80 Hz, 2 H), 1.46 (s, 1 H)
165		1.24	298.16	^1H NMR (500 MHz, *DMSO-D6*) δ ppm 12.07 (s, 1 H), 8.02 (s, 1 H), 7.63 (d, *J*=7.63 Hz, 1 H), 7.27 - 7.36 (m, 2 H), 6.99 (t, *J*=7.32 Hz, 1 H), 3.82 (d, *J*=9.46 Hz, 1 H), 3.56 (d, *J*=8.85 Hz, 1 H), 3.00 (s, 2 H), 2.79 (s, 2 H), 2.67 (t, *J*=6.87 Hz, 2 H), 2.02 (d, *J*=2.75 Hz, 1 H), 1.93 (s, 1 H), 1.58 (s, 2 H), 1.47 (s, 1 H)

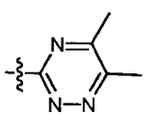
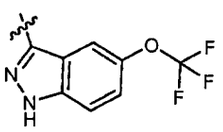
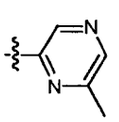
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^1H NMR
166		1.16	366.30	^1H NMR (500 MHz, *MeOD-d4*) δ ppm 8.53 (1 H, d, *J*=5.19 Hz), 8.02 - 8.15 (2 H, m), 7.39 (1 H, d, *J*=5.19 Hz), 7.01 - 7.11 (2 H, m), 4.06 (1 H, d, *J*=10.07 Hz), 3.89 (3 H, s), 3.74 (1 H, d, *J*=10.07 Hz), 3.28 (1 H, d, *J*=14.95 Hz), 3.13 (1 H, d, *J*=14.95 Hz), 2.73 - 3.02 (4 H, m), 2.07 - 2.25 (2 H, m), 1.54 - 1.86 (3 H, m)
167		1.25	344.40	^1H NMR (500 MHz, *MeOD-d4*) δ ppm 8.48 (1 H, s), 4.05 (1 H, d, *J*=10.07 Hz), 3.74 (1 H, d, *J*=10.07 Hz), 3.26 (1 H, s), 3.14 (1 H, d, *J*=14.65 Hz), 2.76 - 3.02 (4 H, m), 2.59 (3 H, s), 2.46 (3 H, s), 2.09 - 2.23 (2 H, m), 1.57 - 1.89 (3 H, m)
168		1.73	390.20	^1H NMR (500 MHz, *MeOD-d4*) δ ppm 9.27 (1 H, s), 8.14 (1 H, d, *J*=2.14 Hz), 7.93 (1 H, dd, *J*=8.85, 1.83 Hz), 7.78 (1 H, d, *J*=8.85 Hz), 4.11 (1 H, d, *J*=10.07 Hz), 3.80 (1 H, d, *J*=10.07 Hz), 3.28 (1 H, s), 3.15 (1 H, d, *J*=14.95 Hz), 2.78 - 3.02 (4 H, m), 2.05 - 2.25 (2 H, m), 1.52 - 1.88 (3 H, m)

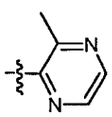
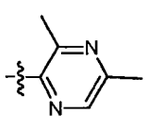
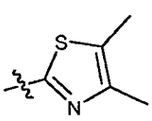
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^1H NMR
169		0.71	260.40	^1H NMR (500 MHz, *MeOD-d_4*) δ ppm 8.73 (1 H, s), 8.59 (2 H, br. s.), 3.86 (1 H, d, *J*=9.77 Hz), 3.56 (1 H, d, *J*=9.77 Hz), 3.18 - 3.26 (1 H, m), 3.05 - 3.12 (1 H, m), 2.72 - 2.99 (4 H, m), 2.17 (1 H, br. s.), 2.01 (1 H, br. s.), 1.54 - 1.86 (3 H, m)
170		0.78	290.30	^1H NMR (400 MHz, *$CDCl_3$*) δ ppm 8.57 (1 H, br. s.), 7.97 (1 H, d, *J*=1.51 Hz), 7.80 (1 H, d, *J*=1.26 Hz), 3.90 (3 H, s), 3.87 (1 H, d, *J*=9.06 Hz), 3.54 (1 H, d, *J*=9.06 Hz), 3.32 (1 H, dd, *J*=14.86, 1.76 Hz), 2.69 - 3.04 (5 H, m), 2.13 - 2.23 (1 H, m), 2.06 - 2.11 (1 H, m), 1.63 - 1.76 (1 H, m), 1.41 - 1.61 (2 H, m)
171		1.06	368.40	^1H NMR (400 MHz, *MeOD-d_4*) δ ppm 3.99 (1 H, d, *J*=10.07 Hz), 3.68 (1 H, d, *J*=10.07 Hz), 3.15 - 3.24 (1 H, m), 3.02 - 3.10 (1 H, m), 2.68 - 2.96 (4 H, m), 2.53 (6 H, s), 2.02 - 2.19 (2 H, m), 1.46 - 1.83 (3 II, m)
172		0.89	304.25	^1H NMR (400 MHz, *MeOD-d_4*) δ ppm 6.22 (1 H, s), 3.99 (1 H, d, *J*=10.07 Hz), 3.89 (3 H, s), 3.67 (1 H, d, *J*=10.07 Hz), 3.15 - 3.25 (1 H, m), 3.00 - 3.11 (1 H, m), 2.67 - 2.97 (4 H, m), 2.32 (3 H, s), 2.00 - 2.19 (2 H, m), 1.42 - 1.83 (3 H, m)

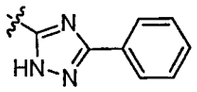
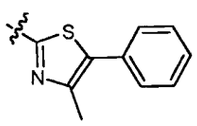
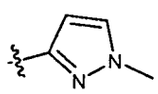
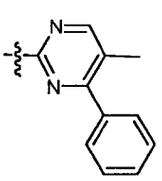
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^1H NMR
173		1.07	371.17	^1H NMR (500 MHz, *DMSO-D6*) δ ppm 8.57 (s, 1 H), 7.46 - 7.54 (m, 6 H), 7.31 (t, *J*=7.93 Hz, 2 H), 6.87 (dd, *J*=8.24, 2.44 Hz, 2 H), 3.87 (d, *J*=9.77 Hz, 2 H), 3.82 (s, 6 H), 3.61 (d, *J*=9.77 Hz, 2 H), 3.03 (s, 4 H), 2.75 - 2.84 (m, 4 H), 2.68 (t, *J*=7.63 Hz, 4 H), 2.06 (s, 2 H), 1.93 (s, 2 H), 1.56 - 1.64 (m, 4 H), 1.50 (dd, *J*=9.46, 2.44 Hz, 2 H)
174		1.32	363.44	^1H NMR (500 MHz, *DMSO-d_6*) δ ppm 8.73 - 8.93 (m, 1 H), 7.73 (s, 1 H), 7.20 (s, 1 H), 3.91 (d, *J*=9.77 Hz, 1 H), 3.66 (d, *J*=10.07 Hz, 1 H), 3.05 (s, 2 H), 2.74 - 2.89 (m, 1 H), 2.68 (t, *J*=7.63 Hz, 1 H), 2.54 (s, 3 H), 2.09 (br. s., 2 H), 1.83 - 1.98 (m, 1 H), 1.42 - 1.69 (m, 2 H)
175		0.40	274.26	^1H NMR (400 MHz, *MeOD-d_4*) δ ppm 8.36 (1 H, d, *J*=5.04 Hz), 6.82 (1 H, d, *J*=5.04 Hz), 3.98 (1 H, d, *J*=10.07 Hz), 3.67 (1 H, d, *J*=10.07 Hz), 3.17 - 3.25 (1 H, m), 3.03 - 3.10 (1 H, m), 2.70 - 2.96 (4 H, m), 2.41 (3 H, s), 1.98 - 2.22 (2 H, m), 1.44 - 1.87 (3 H, m)

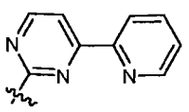
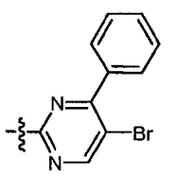
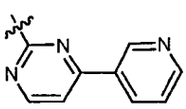
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^1H NMR
176		0.72	288.25	^1H NMR (400 MHz, *MeOD-d_4*) δ ppm 6.72 (1 H, s), 3.98 (1 H, d, *J*=10.07 Hz), 3.67 (1 H, d, *J*=9.82 Hz), 3.18 - 3.24 (1 H, m), 3.02 - 3.12 (1 H, m), 2.65 - 2.96 (4 H, m), 2.36 (6 H, s), 2.02 - 2.21 (2 H, m), 1.45 - 1.83 (3 H, m)
177		2.13	362.28	^1H NMR (400 MHz, *MeOD-d_4*) δ ppm 8.37 (1 H, s), 8.24 (1 H, dd, *J*=7.55, 1.51 Hz), 7.88 (1 H, s), 7.19 - 7.44 (3 H, m), 4.02 (1 H, d, *J*=10.07 Hz), 3.71 (1 H, d, *J*=10.07 Hz), 3.24 (1 H, d, *J*=16.87 Hz), 3.05 - 3.12 (1 H, m), 2.70 - 2.99 (8 H, m), 2.05 - 2.21 (2 H, m), 1.48 - 1.84 (3 H, m)
178		1.31	370.18	^1H NMR (400 MHz, *MeOD-d_4*) δ ppm 8.32 (1 H, s), 3.94 - 4.03 (4 H, m), 3.68 (1 H, d, *J*=10.07 Hz), 3.15 - 3.26 (1 H, m), 3.01 - 3.12 (1 H, m), 2.68 - 2.96 (4 H, m), 2.01 - 2.16 (2 H, m), 1.51 - 1.84 (3 H, m)

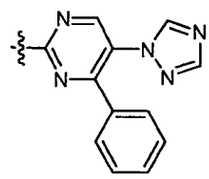
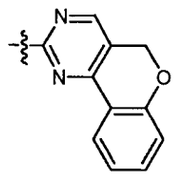
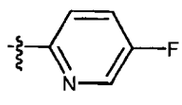
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^1H NMR
179		1.87	353.28	^1H NMR (500 MHz, *MeOD-d4*) δ ppm 7.83 (1 H, s), 7.63 - 7.76 (1 H, m), 7.19 (1 H, dd, *J*=9.00, 2.90 Hz), 7.09 (1 H, d, *J*=2.75 Hz), 3.93 - 4.02 (1 H, m), 3.84 - 3.93 (3 H, m), 3.69 (1 H, d, *J*=9.77 Hz), 3.26 (1 H, d, *J*=14.65 Hz), 3.11 (1 H, d, *J*=14.95 Hz), 2.70 - 3.01 (4 H, m), 2.39 (3 H, s), 2.06 - 2.27 (2 H, m), 1.57 - 1.85 (3 H, m)
180		1.94	350.30	^1H NMR (400 MHz, *MeOD-d4*) δ ppm 7.91 - 8.15 (2 H, m), 7.38 - 7.53 (3 H, m), 7.31 (1 H, s), 4.02 (1 H, d, *J*=10.07 Hz), 3.70 (1 H, d, *J*=10.07 Hz), 3.17 - 3.26 (1 H, m), 3.02 - 3.14 (1 H, m), 2.66 - 2.98 (4 H, m), 2.48 (3 H, s), 2.03 - 2.20 (2 H, m), 1.49 - 1.83 (3 H, m)
181		1.17	336.40	^1H NMR (400 MHz, *MeOD-d4*) δ ppm 8.55 (1 H, d, *J*=5.29 Hz), 8.08 (2 H, dd, *J*=6.67, 2.90 Hz), 7.44 - 7.53 (3 H, m), 7.40 (1 H, d, *J*=5.29 Hz), 4.01 (1 H, d, *J*=10.07 Hz), 3.70 (1 H, d, *J*=10.07 Hz), 3.20 - 3.28 (1 H, m), 3.04 - 3.14 (1 H, m), 2.67 - 2.99 (4 H, m), 2.05 - 2.24 (2 H, m), 1.49 - 1.85 (3 H, m)

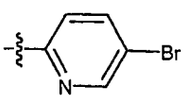
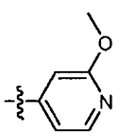
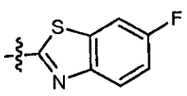
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^1H NMR
182		0.42	289.22	^1H NMR (400 MHz, *MeOD-d4*) δ ppm 4.02 (1 H, d, *J*=10.32 Hz), 3.71 (1 H, d, *J*=10.32 Hz), 3.23 (1 H, d, *J*=15.36 Hz), 3.03 - 3.13 (1 H, m), 2.69 - 2.98 (4 H, m), 2.54 (3 H, s), 2.48 (3 H, s), 2.01 - 2.21 (2 H, m), 1.41 - 1.85 (3 H, m)
183		1.19	382.19	^1H NMR (500 MHz, *DMSO-D6*) δ ppm 12.37 (s, 1 H), 8.01 (s, 1 H), 7.53 (s, 1 H), 7.45 (d, *J*=9.16 Hz, 1 H), 7.28 (d, *J*=8.85 Hz, 1 H), 3.82 (d, *J*=9.16 Hz, 1 H), 3.57 (d, *J*=9.46 Hz, 1 H), 3.00 (s, 2 H), 2.78 (s, 2 H), 2.67 (t, *J*=7.48 Hz, 2 H), 1.96 - 2.04 (m, 1 H), 1.91 (d, *J*=8.85 Hz, 1 H), 1.55 - 1.63 (m, 2 H), 1.47 (d, *J*=7.02 Hz, 1 H)
184		0.75	274.30	^1H NMR (400 MHz, *CDCl3*) δ ppm 9.08 (1 H, br. s.), 8.12 (1 H, s), 7.85 (1 H, s), 3.89 (1 H, d, *J*=9.32 Hz), 3.55 (1 H, d, *J*=9.32 Hz), 3.28 (1 H, dd, *J*=14.86, 1.26 Hz), 2.62 - 2.97 (5 H, m), 2.35 (3 H, s), 2.06 - 2.17 (1 H, m, *J*=13.13, 9.82, 3.53, 3.38, 3.38 Hz), 2.04 (1 H, br. s.), 1.59 - 1.73 (1 H, m), 1.37 - 1.57 (2 H, m)

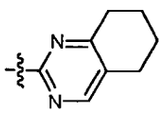
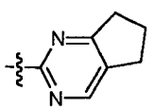
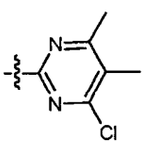
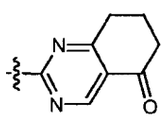
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^1H NMR
185		0.75	274.30	^1H NMR (400 MHz, *CDCl3*) δ ppm 9.29 (1 H, br. s.), 7.90 (2 H, br. s.), 3.90 (1 H, d, *J*=9.32 Hz), 3.55 (1 H, d, *J*=9.06 Hz), 3.35 (1 H, d, *J*=14.86 Hz), 2.65 - 3.08 (5 H, m), 2.56 (3 H, s), 2.12 - 2.27 (1 H, m), 2.08 (1 H, br. s.), 1.62 - 1.77 (1 H, m), 1.38 - 1.61 (2 H, m)
186		0.79	288.30	^1H NMR (400 MHz, *CDCl3*) δ ppm 9.16 (1 H, br. s.), 7.78 (1 H, s), 3.88 (1 H, d, *J*=9.06 Hz), 3.53 (1 H, d, *J*=9.32 Hz), 3.34 (1 H, dd, *J*=14.86, 2.01 Hz), 2.64 - 3.07 (5 H, m), 2.55 (3 H, s), 2.38 (3 H, s), 2.14 - 2.25 (1 H, m), 2.04 - 2.11 (1 H, m), 1.68 (1 H, dddd, *J*=13.94, 9.66, 4.53, 4.34 Hz), 1.41 - 1.61 (2 H, m)
187		0.58	293.06	^1H NMR (500 MHz, *DMSO-d6*) d ppm 3.73 - 3.87 (m, 1 H), 3.47 - 3.58 (m, 1 H), 2.98 (s, 2 H), 2.71 - 2.85 (m, 2 H), 2.65 (t, *J*=7.78 Hz, 2 H), 2.18 (s, 3 H), 2.11 (s, 3 H), 2.00 (br. s., 1 H), 1.80 - 1.96 (m, 1 H), 1.57 (dd, *J*=8.24, 2.75 Hz, 3 H)

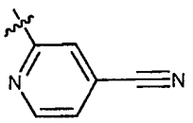
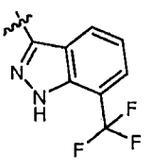
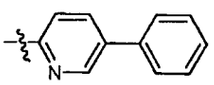
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^1H NMR
188		0.86	325.20	^1H NMR (500 MHz, *DMSO-d_6*) δ ppm 8.07 (d, *J*=7.32 Hz, 2 H), 7.42 (d, *J*=7.63 Hz, 3 H), 3.87 (s, 1 H), 3.55 - 3.70 (m, 1 H), 3.02 (s, 2 H), 2.72 - 2.88 (m, 2 H), 2.68 (s, 2 H), 1.98 - 2.10 (m, 1 H), 1.81 - 1.97 (m, 1 H), 1.40 - 1.68 (m, 3 H)
189		1.04	355.24	^1H NMR (500 MHz, *DMSO-d_6*) δ ppm 7.36 - 7.47 (m, 3 H), 7.24 - 7.34 (m, 2 H), 3.84 (d, *J*=10.07 Hz, 1 H), 3.58 (d, *J*=9.77 Hz, 1 H), 3.01 (s, 2 H), 2.71 - 2.87 (m, 2 H), 2.66 (t, *J*=7.63 Hz, 2 H), 2.32 (s, 3 H), 2.04 (br. s., 1 H), 1.83 - 1.98 (m, 1 H), 1.43 - 1.64 (m, 3 H)
190		0.26	262.11	^1H NMR (500 MHz, *DMSO-d_6*) d ppm 7.43 (br. s., 1 H), 5.56 - 5.76 (m, 1 H), 3.58 - 3.83 (m, 4 H), 3.37 - 3.52 (m, 1 H), 2.94 (s, 2 H), 2.68 - 2.88 (m, 2 H), 2.60 - 2.68 (m, 2 H), 1.94 (br. s., 2 H), 1.37 - 1.65 (m, 3 H)
191		1.65	350.30	^1H NMR (400 MHz, *MeOD*) δ ppm 8.43 (1 H, s), 7.58 (2 H, dd, *J*=7.55, 1.76 Hz), 7.39 - 7.52 (3 H, m), 3.96 (1 H, d, *J*=10.07 Hz), 3.66 (1 H, d, *J*=9.82 Hz), 3.25 (1 H, d, *J*=16.12 Hz), 3.05 - 3.14 (1 H, m), 2.88 - 2.98 (2 H, m), 2.68 - 2.87 (2 H, m), 2.24 (3 H, s), 2.03 - 2.17 (2 H, m), 1.45 - 1.84 (3 H, m)

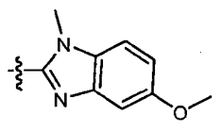
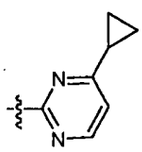
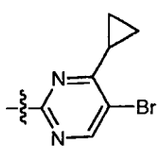
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^1H NMR
192		1.02	337.28	^1H NMR (400 MHz, *MeOD*) δ ppm 8.64 (2 H, d, *J*=5.29 Hz), 8.40 (1 H, d, *J*=7.81 Hz), 7.86 - 7.97 (1 H, m), 7.80 (1 H, d, *J*=5.04 Hz), 7.47 (1 H, dd, *J*=6.55, 5.04 Hz), 4.03 (1 H, d, *J*=10.07 Hz), 3.74 (1 H, d, *J*=10.07 Hz), 3.29 (1 H, d, *J*=1.51 Hz), 3.12 - 3.22 (1 H, m), 2.99 (2 H, t, *J*=7.68 Hz), 2.78 - 2.92 (2 H, m), 2.03 - 2.26 (2 H, m), 1.45 - 1.88 (3 H, m)
193		NA	NA	^1H NMR (400 MHz, *MeOD*) δ ppm 8.69 (1 H, s), 7.61 - 7.78 (2 H, m), 7.34 - 7.56 (3 H, m), 3.99 (1 H, d, *J*=10.07 Hz), 3.68 (1 H, d, *J*=10.32 Hz), 3.15 - 3.25 (1 H, m), 3.02 - 3.11 (1 H, m), 2.92 (2 H, t, *J*=7.55 Hz), 2.69 - 2.86 (2 H, m), 2.01 - 2.20 (2 H, m), 1.47 - 1.81 (3 H, m)
194		NA	NA	^1H NMR (400 MHz, *MeOD*) δ ppm 9.24 (1 H, d, *J*=1.51 Hz), 8.60 - 8.68 (2 H, m), 8.53 (1 H, dt, *J*=7.99, 1.92 Hz), 7.40 - 7.64 (2 H, m), 4.05 (1 H, d, *J*=10.32 Hz), 3.76 (1 H, d, *J*=10.07 Hz), 3.33 - 3.40 (1 H, m), 3.17 - 3.26 (1 H, m), 2.82 - 3.09 (4 H, m), 2.09 - 2.31 (2 H, m), 1.55 - 1.91 (3 H, m)

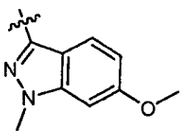
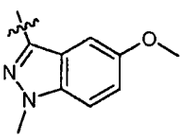
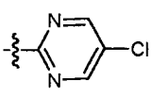
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^{1}H NMR
195		1.41	403.36	^{1}H NMR (400 MHz, *MeOD*) δ ppm 8.65 (1 H, s), 8.40 (1 H, s), 8.17 (1 H, s), 7.25 - 7.47 (5 H, m), 4.04 (1 H, d, *J*=10.32 Hz), 3.73 (1 H, d, *J*=10.32 Hz), 3.17 - 3.27 (1 H, m), 3.04 - 3.13 (1 H, m), 2.63 - 3.00 (4 H, m), 2.00 - 2.22 (2 H, m), 1.48 - 1.87 (3 H, m)
196		1.69	364.36	^{1}H NMR (400 MHz, *MeOD*) δ ppm 8.33 (1 H, s), 8.16 (1 H, dd, *J*=7.81, 1.51 Hz), 7.30 - 7.44 (1 H, m), 7.08 (1 H, t, *J*=7.55 Hz), 6.95 (1 H, d, *J*=8.31 Hz), 5.16 (2 H, s), 4.02 (1 H, d, *J*=9.82 Hz), 3.71 (1 H, d, *J*=10.07 Hz), 3.18 - 3.26 (1 H, m), 3.04 - 3.13 (1 H, m), 2.93 (2 H, t, *J*=7.68 Hz), 2.71 - 2.86 (2 H, m), 2.01 - 2.23 (2 H, m), 1.50 - 1.83 (3 H, m)
197		0.53	277.13	^{1}H NMR (500 MHz, *DMSO-D6*) δ ppm 8.76 (s, 1 H), 8.15 (d, *J*=2.44 Hz, 1 H), 7.55 (s, 1 H), 6.83 (s, 1 H), 3.79 (s, 1 H), 3.54 (d, *J*=10.07 Hz, 1 H), 2.92 - 3.00 (m, 3 H), 2.70 - 2.80 (m, 3 H), 2.66 (t, *J*=7.78 Hz, 3 H), 1.97 (s, 1 H), 1.88 (s, 1 H), 1.53 - 1.61 (m, 3 H), 1.41 - 1.49 (m, 1 H)

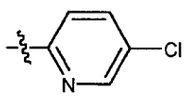
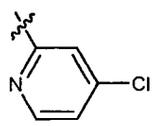
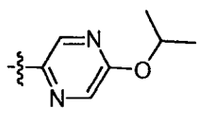
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^1H NMR
198		0.77	337.07	^1H NMR (500 MHz, *DMSO-d_6*) δ ppm 8.26 (br. s., 1 H), 7.76 (br. s., 1 H), 6.75 (br. s., 1 H), 3.81 (br. s., 1 H), 3.56 (d, *J*=9.46 Hz, 1 H), 2.85 - 3.10 (m, 2 H), 2.56 - 2.85 (m, 4 H), 1.97 (br. s., 2 H), 1.36 - 1.67 (m, 3 H)
199		0.16	289.19	^1H NMR (500 MHz, *MeOD*) δ ppm 7.90 (d, *J*=6.10 Hz, 1 H), 6.74 - 7.00 (m, 2 H), 3.93 - 4.09 (m, 1 H), 3.88 (s, 3 H), 3.61 - 3.71 (m, 1 H), 3.14 - 3.25 (m, 1 H), 3.06 (d, *J*=1.83 Hz, 1 H), 2.69 - 2.99 (m, 3 H), 2.07 (br. s., 2 H), 1.74 (d, *J*=8.24 Hz, 3 H), 1.18 (d, *J*=6.41 Hz, 1 H)
200		0.82	332.97	^1H NMR (400 MHz, *DMSO-d_6*) δ ppm 7.71 (dd, *J*=8.78, 2.76 Hz, 1 H), 7.59 (dd, *J*=8.91, 4.89 Hz, 1 H), 7.17 (td, *J*=9.03, 2.76 Hz, 1 H), 3.89 (d, *J*=10.04 Hz, 1 H), 3.64 (d, *J*=10.04 Hz, 1 H), 2.97 - 3.13 (m, 2 H), 2.75 - 2.88 (m, 2 H), 2.67 (t, *J*=7.65 Hz, 2 H), 2.02 - 2.12 (m, 1 H), 1.81 - 1.98 (m, 1 H), 1.36 - 1.69 (m, 3 H)

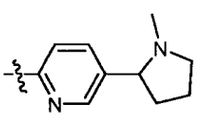
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^1H NMR
201		1.16	314.35	^1H NMR (400 MHz, *MeOD*) δ ppm 8.20 (1 H, s), 3.96 (1 H, d, *J*=10.07 Hz), 3.65 (1 H, d, *J*=9.82 Hz), 3.20 (1 H, d), 3.06 (1 H, d), 2.91 (2 H, t, *J*=7.43 Hz), 2.71 - 2.84 (4 H, m), 2.66 (2 H, t, *J*=6.04 Hz), 1.98 - 2.21 (2 H, m), 1.43 - 1.94 (7 H, m)
202		0.69	300.29	^1H NMR (400 MHz, *MeOD*) δ ppm 8.30 (1 H, s), 3.97 (1 H, d, *J*=9.82 Hz), 3.66 (1 H, d, *J*=10.07 Hz), 3.21 (1 H, d), 3.06 (1 H, d), 2.74 - 2.97 (8 H, m), 2.11 (4 H, dq, *J*=7.68, 7.51 Hz), 1.39 - 1.85 (3 H, m)
203		1.19	322.25	^1H NMR (400 MHz, *MeOD*) δ ppm 4.00 (1 H, d, *J*=10.07 Hz), 3.69 (1 H, d, *J*=10.07 Hz), 3.22 (1 H, d, *J*=14.60 Hz), 3.03 - 3.14 (1 H, m), 2.69 - 2.97 (4 H, m), 2.46 (3 H, s), 2.26 (3 H, s), 2.03 - 2.17 (2 H, m), 1.51 - 1.84 (3 H, m)
204		0.67	328.28	^1H NMR (400 MHz, *MeOD*) δ ppm 8.92 (1 H, s), 4.05 (1 H, d, *J*=10.32 Hz), 3.75 (1 H, d, *J*=10.32 Hz), 3.24 (1 H, d, *J*=1.26 Hz), 3.06 - 3.17 (1 H, m), 2.75 - 3.03 (6 H, m), 2.56 - 2.68 (2 H, m), 2.13 (4 H, ddd, *J*=12.72, 6.30, 6.17 Hz), 1.54 - 1.84 (3 H, m)

Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^1H NMR
205		0.15	284.10	^1H NMR (500 MHz, *DMSO-D6*) δ ppm 9.01 (s, 1 H), 8.40 (d, *J*=4.88 Hz, 1 H), 7.21 (s, 1 H), 7.16 (s, 1 H), 3.84 (s, 1 H), 3.59 (d, *J*=10.07 Hz, 1 H), 2.94 - 3.02 (m, 3 H), 2.70 - 2.79 (m, 3 H), 2.62 - 2.68 (m, 3 H), 1.99 (s, 1 H), 1.87 (s, 1 H), 1.57 (d, *J*=3.05 Hz, 2 H), 1.56 (s, 1 H), 1.41 - 1.49 (m, 1 H)
206		0.78	366.10	^1H NMR (500 MHz, *DMSO-D6*) δ ppm 12.63 (s, 1 H), 7.95 (d, *J*=7.63 Hz, 2 H), 7.68 (d, *J*=6.71 IIz, 1 II), 7.16 (t, *J*=7.32 Hz, 1 H), 3.84 (s, 1 H), 3.60 (s, 1 H), 3.03 (s, 2 H), 2.80 (s, 2 H), 2.64 - 2.72 (m, 2 H), 2.05 (s, 1 H), 1.92 (s, 1 H), 1.60 (d, *J*=8.24 Hz, 2 H), 1.48 (s, 1 H)
207		0.77	335.17	^1H NMR (500 MHz, *DMSO-D6*) δ ppm 9.05 (s, 1 H), 8.52 (d, *J*=2.44 Hz, 1 H), 7.91 (s, 1 H), 7.66 (d, *J*=7.63 Hz, 2 H), 7.47 (t, *J*=7.63 Hz, 2 H), 7.36 (t, *J*=7.32 Hz, 1 H), 6.87 (s, 1 H), 3.84 (s, 1 H), 3.59 (d, *J*=10.07 Hz, 1 H), 2.99 (s, 2 H), 2.72 - 2.81 (m, 2 H), 2.63 - 2.71 (m, 3 H), 1.99 (s, 1 H), 1.90 (s, 1 H), 1.59 (s, 2 H), 1.42 - 1.50 (m, 1 H)

Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^{1}H NMR
208		0.63	342.25	^{1}H NMR (500 MHz, *DMSO-D6*) δ ppm 9.30 (s, 1 H), 7.19 (d, *J*=8.55 Hz, 1 H), 6.94 (d, *J*=2.44 Hz, 1 H), 6.69 (dd, *J*=8.55, 2.14 Hz, 1 H), 3.92 (d, *J*=10.07 Hz, 1 H), 3.75 (s, 3 H), 3.66 (d, *J*=9.77 Hz, 1 H), 3.54 (s, 3 H), 2.99 - 3.07 (m, 2 H), 2.79 (t, *J*=7.78 Hz, 2 H), 2.68 (t, *J*=7.78 Hz, 2 H), 2.02 - 2.07 (m, 1 H), 1.89 (dd, *J*=6.41, 3.36 Hz, 1 H), 1.56 - 1.64 (m, 2 H), 1.44 - 1.52 (m, 1 H)
209		0.96	300.34	^{1}H NMR (400 MHz, *MeOD*) d ppm 8.27 (1 H, d, *J*=5.04 Hz), 6.78 (1 H, d, *J*=5.29 Hz), 3.98 (1 H, d, *J*=10.07 Hz), 3.66 (1 H, d, *J*=10.07 Hz), 3.21 (1 H, d), 3.06 (1 H, d), 2.64 - 2.99 (4 H, m), 2.02 - 2.17 (2 H, m), 1.92 - 2.05 (1 H, m), 1.54 - 1.82 (3 H, m), 0.92 - 1.11 (4 H, m)
210		1.64	378.23	^{1}H NMR (400 MHz, *MeOD*) d ppm 8.42 (1 H, s), 3.97 (1 H, d, *J*=10.07 Hz), 3.66 (1 H, d, *J*=10.07 Hz), 3.20 (1 H, d), 3.06 (1 H, d), 2.63 - 2.97 (4 H, m), 2.35 - 2.50 (1 H, m), 1.99 - 2.16 (2 H, m), 1.50 - 1.83 (3 H, m), 0.98 - 1.24 (4 H, m)

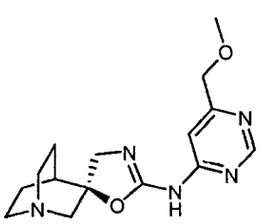
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^{1}H NMR
211		0.64	342.18	^{1}H NMR (500 MHz, *DMSO-D6*) δ ppm 7.98 (s, 1 H), 7.46 (t, *J*=7.93 Hz, 1 H), 6.91 (d, *J*=5.49 Hz, 1 H), 6.59 - 6.65 (m, 1 H), 3.82 - 3.88 (m, 6 H), 3.82 (s, 2 H), 3.55 (s, 1 H), 3.00 (s, 2 H), 2.78 (s, 2 H), 2.67 (d, *J*=6.71 Hz, 2 H), 2.01 (s, 1 H), 1.91 (s, 1 H), 1.59 (s, 2 H), 1.46 (s, 1 H)
212		0.63	342.25	^{1}H NMR (500 MHz, *DMSO-D6*) δ ppm 7.94 (s, 1 H), 7.37 (d, *J*=9.16 Hz, 1 H), 7.02 (d, *J*=9.46 Hz, 1 H), 6.99 (d, *J*=1.83 Hz, 1 H), 3.87 (s, 3 H), 3.82 (d, *J*=9.46 Hz, 1 H), 3.78 (s, 3 H), 3.56 (d, *J*=9.16 Hz, 1 H), 3.00 (s, 2 H), 2.78 (s, 2 H), 2.63 - 2.70 (m, 2 H), 2.01 (s, 1 H), 1.91 (s, 1 H), 1.58 (s, 2 H), 1.46 (s, 1 H)
213		0.35	294.25	^{1}H NMR (400 MHz, *MeOD*) d ppm 8.51 (2 H, s), 4.00 (1 H, d, *J*=10.32 Hz), 3.69 (1 H, d, *J*=10.32 Hz), 3.22 (1 H, d), 3.08 (1 H, d), 2.70 - 2.98 (4 H, m), 2.01 - 2.21 (2 H, m), 1.50 - 1.84 (3 H, m)

Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^1H NMR
214		0.36	293.14	^1H NMR (500 MHz, *DMSO-D6*) δ ppm 8.80 (s, 1 H), 8.19 (s, 1 H), 7.66 (s, 1 H), 6.80 (s, 1 H), 3.81 (s, 1 H), 3.56 (d, *J*=10.07 Hz, 1 H), 2.92 - 3.01 (m, 2 H), 2.70 - 2.79 (m, 2 H), 2.62 - 2.68 (m, 2 H), 1.97 (s, 1 H), 1.87 (s, 1 H), 1.57 (d, *J*=7.32 Hz, 2 H), 1.40 - 1.49 (m, 1 H)
215		0.35	293.14	^1H NMR (500 MHz, *DMSO-D6*) δ ppm 9.01 (s, 1 H), 8.17 (d, *J*=5.49 Hz, 2 H), 6.97 (s, 2 H), 6.83 (s, 1 H), 3.83 (s, 2 H), 3.57 (d, *J*=10.38 Hz, 2 H), 2.93 - 3.01 (m, 3 H), 2.74 - 2.82 (m, 3 H), 2.73 (s, 1 H), 2.66 (t, *J*=7.63 Hz, 3 H), 1.98 (s, 2 H), 1.87 (s, 2 H), 1.53 - 1.62 (m, 3 H), 1.41 - 1.49 (m, 2 H)
216		0.82	318.30	^1H NMR (400 MHz, *$CDCl_3$*) δ ppm 8.56 (1 H, br. s.), 7.94 (1 H, d, *J*=1.26 Hz), 7.72 (1 H, d, *J*=1.26 Hz), 5.14 (1 H, spt, *J*=6.13 Hz), 3.85 (1 H, d, *J*=9.06 Hz), 3.52 (1 H, d, *J*=9.06 Hz), 3.30 (1 H, dd, *J*=14.86, 1.51 Hz), 2.67 - 3.03 (5 H, m), 2.11 - 2.26 (1 H, m, *J*=13.17, 9.84, 3.65, 3.42, 3.42 Hz), 2.07 (1 H, br. s.), 1.62 - 1.75 (1 H, m), 1.41 - 1.59 (2 H, m), 1.30 (6 H, d, *J*=6.30 Hz)

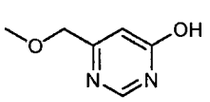
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^1H NMR
217		0.18	342.19	^1H NMR (400 MHz, *DMSO-D6*) δ ppm 8.09 (s, 1 H), 7.53 (s, 1 H), 3.80 (s, 1 H), 3.54 (d, *J*=10.32 Hz, 1 H), 3.07 - 3.18 (m, 1 H), 2.91 - 3.01 (m, 3 H), 2.75 (d, *J*=8.31 Hz, 2 H), 2.60 - 2.71 (m, 2 H), 2.19 (q, *J*=8.90 Hz, 1 H), 2.01 - 2.12 (m, 4 H), 1.94 (s, 1 H), 1.83 (d, *J*=15.11 Hz, 2 H), 1.56 (s, 3 H), 1.43 (s, 1 H)

EXAMPLE 218

(R)-N-(6-(methoxymethyl)pyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

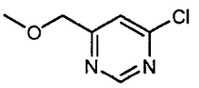


Step A: 6-(Methoxymethyl)pyrimidin-4-ol



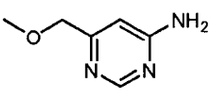
To a solution of methyl 4-methoxy-3-oxobutanoate (3.54 mL, 26.5 mmol) in methanol (30 ml) was added formamidine acetate (3.07 g, 29.2 mmol) and sodium methoxide (13 mL, 58.4 mmol). The mixture was then heated to reflux for 18 hours and cooled to ambient temperature, then concentrated. The residue was taken up in water and the pH adjusted to 7 with 1N HCl. The aqueous mixture was extracted with chloroform. The combined organic layers were dried over magnesium sulfate, filtered and concentrated to afford 6-(methoxymethyl)pyrimidin-4-ol (1.38 g, 9.85 mmol, 37.1 % yield). MS (LC/MS) R.T. = 0.19; $[M+H]^+$ = 141.20.

Step B: 4-Chloro-6-(methoxymethyl)pyrimidine



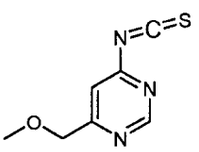
6-(Methoxymethyl)pyrimidin-4-ol (1.38 g, 9.85 mmol) was taken up in dichloromethane (14 ml) and phosphorous oxychloride (9 mL, 97 mmol) was added at ambient temperature. The mixture was stirred at ambient for 18 h and concentrated. The residue was taken up in ice-water and the pH was adjusted to 7 with 1N sodium hydroxide. The mixture was extracted with chloroform and dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (5 -10 % ethyl acetate/chloroform) to afford 4-chloro-6-(methoxymethyl)pyrimidine (1.2 g, 7.57 mmol, 77 % yield) as a pale yellow oil, which solidified on standing. 1H NMR (400 MHz, *CDCl*$_3$) δ ppm 8.88 (1 H, d, *J*=1.01 Hz), 7.52 (1 H, d, *J*=1.01 Hz), 4.53 (2 H, s), 3.50 (3 H, s). MS (LC/MS) R.T. = 0.98; $[M+H]^+$ = 159.10.

Step C: 6-(Methoxymethyl)pyrimidin-4-amine



A mixture of 4-chloro-6-(methoxymethyl)pyrimidine (1.2 g, 7.57 mmol) and ammonium hydroxide (20 ml) was heated in a sealed tube for 3 hours. The mixture was cooled to ambient temperature and concentrated. The residue was triturated with ether to afford 6-(methoxymethyl)pyrimidin-4-amine (0.50 g, 3.59 mmol, 48 % yield) as a pale yellow solid. ^{1}H NMR (400 MHz, *CDCl*$_3$) δ ppm 8.47 (1 H, s), 6.55 (1 H, s), 5.12 (2 H, br. s.), 4.38 (2 H, s), 3.45 (3 H, s). MS (LC/MS) R.T. = 0.42; $[M+H]^+$ = 140.20.

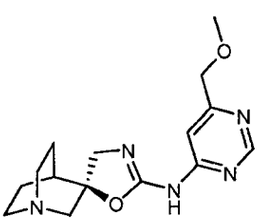
Step D: 4-Isothiocyanato-6-(methoxymethyl)pyrimidine



To a bright orange solution of 1,1'-thiocarbonyldipyridin-2(1H)-one (0.84 g, 3.59 mmol) was in dichloromethane at ambient temperature was added 6-

(methoxymethyl)pyrimidin-4-amine (0.5 g, 3.59 mmol). The orange solution was stirred at ambient temperature for 18 h. The solution was purified by column chromatography (0-40 % ethyl acetate/hexanes) to afford 4-isothiocyanato-6-(methoxymethyl)pyrimidine (0.32 g, 1.77 mmol, 49 % yield) as a yellow solid. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 8.91 (1 H, d, *J*=1.26 Hz), 7.19 (1 H, d, *J*=1.01 Hz), 4.52 (2 H, s), 3.49 (3 H, s). MS (LC/MS) R.T. = 1.39; $[M+H]^+$ = 182.10.

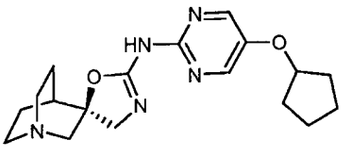
Step E: (R)-N-(6-(Methoxymethyl)pyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



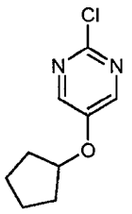
To (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (0.39 g, 1.71 mmol) in dimethylformamide was added cesium carbonate (1.39 g, 4.28 mmol) and 4-isothiocyanato-6-(methoxymethyl)pyrimidine (0.31 g, 1.71 mmol). The suspension was stirred at ambient temperature for 15 min. To the reaction mixture was added N,N'-diisopropylcarbodiimide (0.80 mL, 5.13 mmol) and the mixture was stirred overnight then concentrated. The residue was purified by column chromatography (5-25% 9:1 methanol/ammonium hydroxide in ethyl acetate) to afford (R)-N-(6-(methoxymethyl)pyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.18 g, 0.58 mmol, 34 % yield) as a yellow solid. ^{1}H NMR (400 MHz, *MeOD-d$_4$*) δ ppm 8.65 (1 H, d, *J*=1.01 Hz), 6.92 (1 H, br. s.), 4.40 (3 H, s), 4.03 (1 H, d, *J*=10.32 Hz), 3.72 (1 H, d, *J*=10.32 Hz), 3.44 (2 H, s), 3.18 - 3.26 (1 H, m), 3.06 - 3.13 (1 H, m), 2.69 - 2.96 (4 H, m), 1.94 - 2.19 (2 H, m), 1.45 - 1.86 (3 H, m). MS (LC/MS) R.T. = 0.76; $[M+H]^+$ = 304.30.

EXAMPLE 219

(R)-N-(5-(Cyclopentyloxy)pyrimidin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

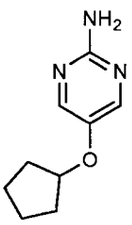


Step A: 2-Chloro-5-(cyclopentyloxy)pyrimidine



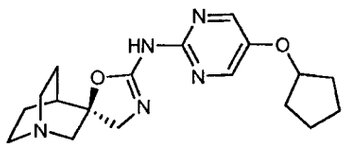
A mixture of 2-chloropyrimidin-5-ol (1 g, 7.66 mmol), chlorocyclopentane (2.39 mL, 22.98 mmol) and potassium carbonate (3.18 g, 22.98 mmol) in N,N-dimethylformamide were heated at 65° C for 16 h at ambient temperature. Water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate and concentrated i*n vacuo*. The residue was purified by column chromatography (0-25 % ethyl acetate/hexanes) to afford 2-chloro-5-(cyclopentyloxy)pyrimidine (831 mg, 4.18 mmol, 54.6 % yield) as a white solid. MS (LC/MS) R.T. = 2.32; $[M+H]^+$ = 199.23.

Step B: 5-(Cyclopentyloxy)pyrimidin-2-amine



5-(Cyclopentyloxy)pyrimidin-2-amine was prepared from 2-chloro-5-(cyclopentyloxy)pyrimidine by following the general procedures of **Example 218, Step C**. ^{1}H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 7.99 (2 H, s), 6.18 (2 H, s), 4.54 - 4.75 (1 H, m), 1.30 - 1.91 (8 H, m). MS (LC/MS) R.T. = 1.47; $[M+H]^+$ = 180.24.

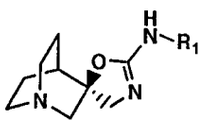
Step C: (R)-N-(5-(Cyclopentyloxy)pyrimidin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

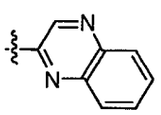


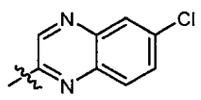
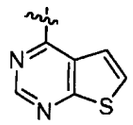
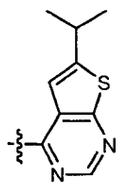
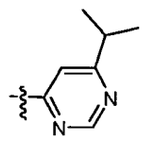
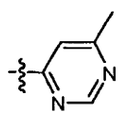
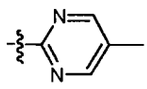
(R)-N-(5-(Cyclopentyloxy)pyrimidin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was prepared from 5-(cyclopentyloxy)pyrimidin-2-amine by following the general procedures of **Example 23, Steps A-B.** ^{1}H NMR (400 MHz, *MeOD-d$_4$*) δ ppm 8.24 (2 H, s), 4.76 - 4.86 (1 H, m), 3.98 (1 H, d, *J*=10.07 Hz), 3.69 (1 H, d, *J*=10.07 Hz), 3.33 (1 H, d), 3.20 (1 H, d), 2.77 - 3.08 (4 H, m), 2.04 - 2.26 (2 H, m), 1.49 - 2.03 (11 H, m). MS (LC/MS) R.T. = 1.56; $[M+H]^+$ = 344.32.

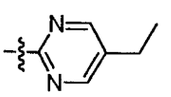
The compounds in Table 5 were synthesized according to the method of **Example 218** using the appropriate commercially available chlorides as in **Example 218, Step C.**

Table 4.



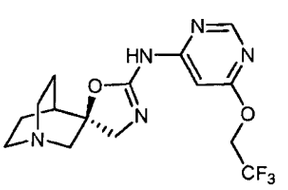
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^{1}H NMR
220		0.99	310.30	^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 9.82 (1 H, br. s.), 8.62 (1 H, s), 7.95 (1 H, dd, *J*=8.18, 1.13 Hz), 7.72 (1 H, dd, *J*=8.18, 1.13 Hz), 7.58 - 7.64 (1 H, m, *J*=7.62, 7.62, 7.05, 1.39 Hz), 7.51 (1 H, ddd, *J*=7.68, 7.05, 1.26 Hz), 4.05 (1 H, d, *J*=9.32 Hz), 3.70 (1 H, d, *J*=9.57 Hz), 3.39 (1 H, dd, *J*=14.86, 1.51 Hz), 2.72 - 3.06 (5 H, m), 2.12 - 2.26 (2 H, m), 1.69 - 1.80 (1 H, m), 1.45 - 1.64 (2 H, m). M.P. 212-5 °C.

Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^{1}H NMR
221		1.32	180.09	^{1}H NMR (400 MHz, *DMSO-d_6*) δ ppm 8.31 (1 H, s), 7.80 (1 H, d, *J*=2.52 Hz), 7.55 (1 H, dd, *J*=8.81, 2.52 Hz), 7.50 (1 H, d, *J*=9.06 Hz), 7.13 (2 H, s)
222		0.90	316.30	^{1}H NMR (400 MHz, *MeOD-d_4*) δ ppm 8.60 (s, 1 H), 7.60 (d, *J*=6.04 Hz, 1 H), 7.52 (s, 1 H), 4.04 - 4.17 (m, 1 H), 3.73 - 3.87 (m, 1 H), 3.23 - 3.26 (m, 1 H), 3.07 - 3.19 (m, 1 H), 2.88 - 3.01 (m, 2 H), 2.75 - 2.88 (m, 2 H), 2.08 - 2.27 (m, 2 H), 1.56 - 1.86 (m, 3 H)
223		2.28	358.20	^{1}H NMR (400 MHz, *MeOD-d_4*) δ ppm 8.52 (1 H, s), 7.30 (1 H, d, *J*=1.01 Hz), 4.03 - 4.09 (1 H, m), 3.76 (1 H, d, *J*=10.07 Hz), 3.16 - 3.27 (2 H, m), 3.06 - 3.14 (1 H, m), 2.68 - 3.01 (4 H, m), 2.01 - 2.23 (2 H, m), 1.54 - 1.82 (3 H, m), 1.37 (6 H, d, *J*=6.80 Hz)
224		0.86	302.24	^{1}H NMR (400 MHz, *MeOD-d_4*) δ ppm 8.63 (1 H, s), 6.73 (1 H, br. s.), 4.02 (1 H, d, *J*=10.32 Hz), 3.72 (1 H, d, *J*=10.32 Hz), 3.17 - 3.25 (1 H, m), 3.01 - 3.13 (1 H, m), 2.68 - 2.97 (5 H, m), 1.98 - 2.16 (2 H, m), 1.51 - 1.82 (3 H, m), 1.24 (6 H, d, *J*=7.05 Hz)
225		0.25	274.19	^{1}H NMR (400 MHz, *MeOD-d_4*) δ ppm 8.60 (1 H, s), 6.71 (1 H, br. s.), 4.02 (1 H, d, *J*=10.32 Hz), 3.71 (1 H, d, *J*=10.32 Hz), 3.17 - 3.24 (1 H, m), 3.04 - 3.13 (1 H, m), 2.65 - 3.02 (4 H, m), 2.37 (3 H, s), 1.99 - 2.20 (2 H, m), 1.32 - 1.88 (3 H, m)
226		0.37	274.26	^{1}H NMR (400 MHz, *MeOD-d_4*) δ ppm 8.38 (2 H, s), 3.97 (1 H, d, *J*=10.07 Hz), 3.66 (1 H, d, *J*=10.07 Hz), 3.16 - 3.25 (1 H, m), 3.02 - 3.13 (1 H, m), 2.92 (2 H, t, *J*=7.55 Hz), 2.73 - 2.86 (2 H, m), 2.21 (3 H, s), 2.03 - 2.16 (2 H, m), 1.45 - 1.86 (3 H, m)

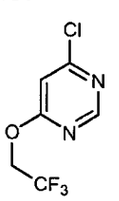
Example Number	R_1	LCMS RT (min)	LCMS Ion $[M+H]^+$	^1H NMR
227		0.96	288.31	^1H NMR (400 MHz, *MeOD-d*$_4$)δ ppm 8.41 (2 H, s), 3.98 (1 H, d, *J*=10.07 Hz), 3.67 (1 H, d, *J*=10.07 Hz), 3.17 - 3.25 (1 H, m), 3.02 - 3.13 (1 H, m), 2.92 (2 H, t, *J*=7.43 Hz), 2.72 - 2.87 (2 H, m), 2.57 (2 H, q, *J*=7.55 Hz), 2.01 - 2.23 (2 H, m), 1.48 - 1.84 (3 H, m), 1.22 (3 H, t, *J*=7.68 Hz)

EXAMPLE 228

(R)-N-(6-(2,2,2-Trifluoroethoxy)pyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

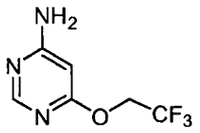


Step A: 4-Chloro-6-(2,2,2-trifluoroethoxy)pyrimidine



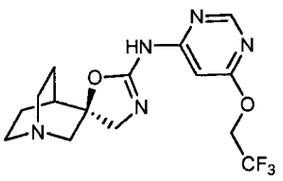
A solution of 2,2,2-trifluoroethanol (2.61 g, 26.10 mmol) in tetrahydrofuran (12 ml) was added dropwise to a suspension of sodium hydride (1.31 g, 32.60 mmol) in tetrahydrofuran (48 ml) at 0 °C. The mixture was stirred at 0° C for 30 min and a solution of 4,6-dichloropyrimidine (3.6 g, 24.16 mmol) in tetrahydrofuran (12 ml) was added at 0 °C. The reaction mixture was stirred at ambient temperature for 3 h and poured into sat. aqueous ammonium chloride and extracted with ethyl acetate. The ethyl acetate extract was washed with water, dried over magnesium sulfate and concentrated *in vacuo*. The orange residue was purified by column chromatography (10-40 % ethyl acetate/hexanes) to afford 4-chloro-6-(2,2,2-trifluoroethoxy)pyrimidine (2.0 g, 2.41 mmol, 38.9 % yield) as a pale yellow oil. MS (LC/MS) R.T. = 2.78; $[M+H]^+$ = 213.12.

Step B: 6-(2,2,2-Trifluoroethoxy)pyrimidin-4-amine



6-(2,2,2-trifluoroethoxy)pyrimidin-4-amine was prepared from 4-chloro-6-(2,2,2-trifluoroethoxy)pyrimidine by following the general procedure of **Example 218, Step C.** MS (LC/MS) R.T. = 1.16; $[M+H]^+$ = 194.07.

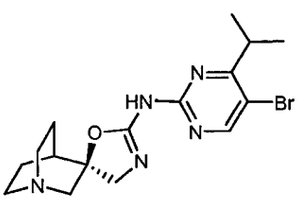
Step C: (R)-N-(6-(2,2,2-Trifluoroethoxy)pyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



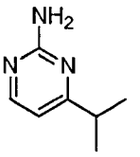
(R)-N-(6-(2,2,2-trifluoroethoxy)pyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was prepared from 6-(2,2,2-trifluoroethoxy)pyrimidin-4-amine by following the general procedures of **Example 23, Steps A-B.** ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 9.30 (1 H, br. s.), 8.39 (1 H, s), 6.38 (1 H, br. s.), 4.59 - 4.84 (2 H, m), 3.94 (1 H, d, *J*=9.32 Hz), 3.59 (1 H, d, *J*=9.57 Hz), 3.33 (1 H, d, *J*=16.62 Hz), 2.61 - 3.01 (5 H, m), 1.97 - 2.25 (2 H, m), 1.37 - 1.81 (3 H, m). MS (LC/MS) R.T. = 1.42; $[M+H]^+$ = 358.33.

EXAMPLE 229

(R)-N-(5-Bromo-4-isopropylpyrimidin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

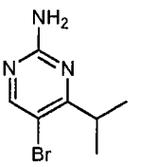


Step A: 4-Isopropylpyrimidin-2-amine



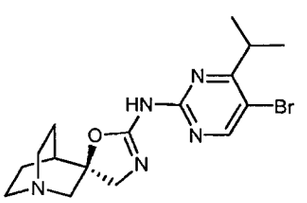
4-Isopropylpyrimidin-2-amine was prepared from 2-chloro-4-isopropylpyrimidine by following the general procedure for **Example 218, Step C.** ^{1}H NMR (400 MHz, *DMSO-d*$_6$) d ppm 8.10 (1 H, d, *J*=5.04 Hz), 6.45 (3 H, d, *J*=5.04 Hz), 2.59 - 2.80 (1 H, m), 1.15 (6 H, d, *J*=7.05 Hz). MS (LC/MS) R.T. = 0.76; $[M+H]^+$ = 138.12.

Step B: 5-Bromo-4-isopropylpyrimidin-2-amine



N-Bromosuccinimide (0.5 g, 2.8 mmol) was added to a solution of 4-isopropylpyrimidin-2-amine (0.39 g, 2.81 mmol) in chloroform. The resultant yellow solution was stirred at ambient temperature for 1 h and concentrated *in vacuo*. The residue was purified by column chromatography (3-10% 9:1 methanol:ammonium hydroxide in chloroform) to afford 5-bromo-4-isopropylpyrimidin-2-amine (0.69 g, 3.18 mmol, 113 %) as a pale yellow solid. ^{1}H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 8.21 (1 H, s), 6.75 (2 H, s), 3.10 - 3.23 (1 H, m), 1.14 (6 H, d, *J*=6.80 Hz). MS (LC/MS) R.T. = 2.58; $[M]^+$ = 216.09.

Step C: (R)-N-(5-Bromo-4-isopropylpyrimidin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

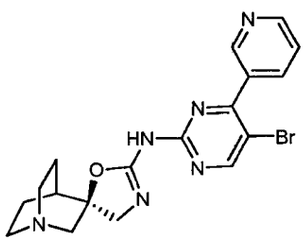


(R)-N-(5-Bromo-4-isopropylpyrimidin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was prepared from 5-bromo-4-isopropylpyrimidin-2-

amine by following the general procedures of **Example 23, Steps A-B**. ^{1}H NMR (400 MHz, *MeOD-d$_4$*) δ ppm 8.49 (1 H, s), 4.02 (1 H, d, *J*=10.07 Hz), 3.72 (1 H, d, *J*=10.07 Hz), 3.34 - 3.44 (1 H, m), 3.23 (1 H, s), 3.06 - 3.15 (1 H, m), 2.95 (2 H, t, *J*=7.55 Hz), 2.75 - 2.89 (2 H, m), 2.00 - 2.21 (2 H, m), 1.52 - 1.83 (3 H, m), 1.24 (6 H, d, *J*=6.80 Hz). MS (LC/MS) R.T. = 1.84; $[M+H]^+$ = 382.24.

EXAMPLE 230

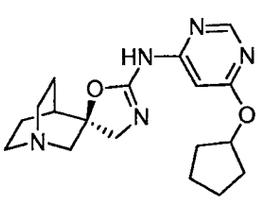
(R)-N-(5-Bromo-4-(pyridin-3-yl)pyrimidin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



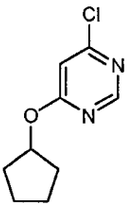
(R)-N-(5-Bromo-4-(pyridin-3-yl)pyrimidin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was prepared from 4-(pyridin-3-yl)pyrimidin-2-amine by following the general procedures of **Example 229, Steps B-C**. ^{1}H NMR (400 MHz, *MeOD-d$_4$*) δ ppm 8.92 (1 H, d, *J*=1.51 Hz), 8.73 (1 H, s), 8.64 (1 H, dd, *J*=4.91, 1.64 Hz), 8.23 (1 H, dt, *J*=8.06, 1.89 Hz), 7.56 (1 H, dd, *J*=7.93, 4.91 Hz), 4.00 (1 H, d, *J*=10.07 Hz), 3.69 (1 H, d, *J*=10.07 Hz), 3.22 (1 H, d), 3.07 (1 H, d), 2.60 - 2.99 (4 H, m), 2.00 - 2.21 (2 H, m), 1.50 - 1.83 (3 H, m). MS (LC/MS) R.T. = 0.76; $[M+H]^+$ = 416.30.

EXAMPLE 231

(R)-N-(6-(Cyclopentyloxy)pyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

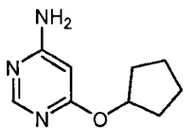


Step A: 4-Chloro-6-(cyclopentyloxy)pyrimidine



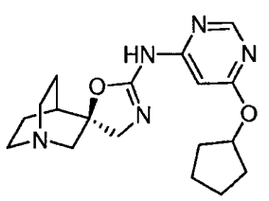
A solution of cyclopentanol (2.25 g, 26.1 mmol) in tetrahydrofuran (12 ml) was added dropwise to a suspension of sodium hydride (1.31 g, 32.6 mmol) in tetrahydrofuran (48 ml) at 0° C. The mixture was stirred at 0° C for 30 min and a solution of 4,6-dichloropyrimidine (3.6 g, 24.16 mmol) in tetrahydrofuran (12 ml) was added at 0° C. The reaction mixture was stirred at ambient temperature for 3 h and poured into sat. aqueous ammonium chloride and extracted with ethyl acetate. The organic layers were washed with water, dried over magnesium sulfate and concentrated *in vacuo*. The orange residue was purified by column chromatography (10-40 % ethyl acetate/hexanes). To afford 4-chloro-6-(cyclopentyloxy)pyrimidine as a pale yellow oil. This material was used directly for the next reaction.

Step B: 6-(Cyclopentyloxy)pyrimidin-4-amine



6-(Cyclopentyloxy)pyrimidin-4-amine was prepared from 4-chloro-6-(cyclopentyloxy)pyrimidine by following the general procedure of **Example 218, Step C.** MS (LC/MS) R.T. = 1.64; $[M+H]^+$ = 180.22.

Step C: (R)-N-(6-(Cyclopentyloxy)pyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

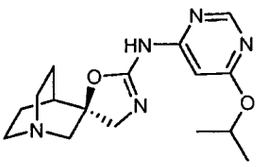


(R)-N-(6-(cyclopentyloxy)pyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was prepared from 6-(cyclopentyloxy)pyrimidin-4-

amine by following the general procedures of **Example 23, Steps A-B**. ^{1}H NMR (400 MHz, *MeOD-d4*) δ ppm 8.37 (1 H, s), 6.16 (1 H, br. s.), 5.27 (1 H, br. s.), 3.98 (1 H, d, *J*=10.32 Hz), 3.67 (1 H, d, *J*=10.32 Hz), 3.15 - 3.24 (1 H, m), 3.02 - 3.12 (1 H, m), 2.71 - 2.97 (4 H, m), 2.01 - 2.14 (2 H, m), 1.87 - 2.00 (3 H, m), 1.49 - 1.84 (8 H, m). MS (LC/MS) R.T. = 1.96; $[M+H]^+$ = 344.34.

EXAMPLE 232

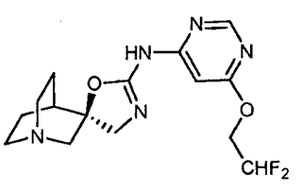
(R)-N-(6-Isopropoxypyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



(R)-N-(6-Isopropoxypyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was prepared from 4,6-dichloropyrimidine by following the general procedures of **Example 231, Steps A-C**. ^{1}H NMR (400 MHz, *MeOD-d4*) δ ppm 8.37 (1 H, s), 6.13 (1 H, br. s.), 5.09 - 5.30 (1 H, m), 3.98 (1 H, d, *J*=10.32 Hz), 3.67 (1 H, d, *J*=10.32 Hz), 3.13 - 3.24 (1 H, m), 3.01 - 3.09 (1 H, m), 2.68 - 2.98 (4 H, m), 1.98 - 2.17 (2 H, m), 1.49 - 1.83 (3 H, m), 1.30 (6 H, d, *J*=6.04 Hz). MS (LC/MS) R.T. = 1.36; $[M+H]^+$ = 318.24.

EXAMPLE 233

(R)-N-(6-(2,2-Difluoroethoxy)pyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

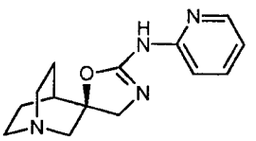


(R)-N-(6-(2,2-Difluoroethoxy)pyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was prepared from 4,6-dichloropyrimidine by following the general procedures of **Example 231, Steps A-C**. M.P. 83-8 °C. 1H NMR (400 MHz, *MeOD-d4*) δ ppm 8.42 (1 H, s), 5.93 - 6.37 (2 H, m), 4.52 (2 H, td, *J*=13.98, 3.78 Hz), 3.99 (1 H, d, *J*=10.32 Hz), 3.68 (1 H, d, *J*=10.32 Hz), 3.19 (1 H,

d), 3.07 (1 H, d), 2.67 - 2.97 (4 H, m), 1.99 - 2.19 (2 H, m), 1.51 - 1.82 (3 H, m). MS (LC/MS) R.T. = 0.99; $[M+H]^+$ = 340.26.

EXAMPLE 234

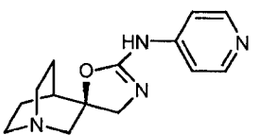
(R)-N-(Pyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



(R)-N-(Pyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was prepared from (R)-N-(6-bromopyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (from **Example 155**) according to the general procedure of **Example 19, Step C**. ^{1}H NMR (500 MHz, *MeOD-d$_4$*) δ ppm 8.26 (d, *J*=4.88 Hz, 1 H), 7.58 - 7.74 (m, 1 H), 6.85 - 7.02 (m, 2 H), 4.00 (d, *J*=10.07 Hz, 1 H), 3.70 (d, *J*=10.07 Hz, 1 H), 3.26 - 3.35 (m, 1 H), 3.14 - 3.21 (m, 1 H), 3.02 (d, *J*=8.24 Hz, 2 H), 2.84 - 2.97 (m, 2 H), 2.11 - 2.25 (m, 2 H), 1.58 - 1.92 (m, 3 H). MS (LC/MS) R.T. = 0.30; $[M+H]^+$ = 259.16.

EXAMPLE 235

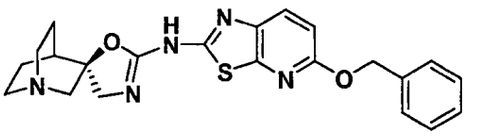
(R)-N-(Pyridin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



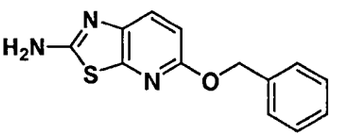
(R)-N-(Pyridin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was prepared from (R)-N-(2-bromopyridin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (from **Example 154)** according to the procedure of **Example 19, Step C.** ^{1}H NMR (500 MHz, *MeOD-d$_4$*) δ ppm 8.31 (d, *J*=6.41 Hz, 2 H), 7.39 (d, *J*=3.97 Hz, 2 H), 4.01 (d, *J*=12.21 Hz, 1 H), 3.70 (d, *J*=11.90 Hz, 1 H), 3.37 (s, 1 H), 3.29 (s, 1 H), 3.18 (d, *J*=1.83 Hz, 1 H), 3.15 (d, *J*=2.14 Hz, 1 H), 2.86 - 3.09 (m, 3 H), 2.02 - 2.20 (m, 1 H), 1.59 - 1.88 (m, 3 H). MS (LC/MS) R.T. = 0.22; $[M+H]^+$ = 259.16.

Example 236

(R)-N-(5-(Benzyloxy)thiazolo[5,4-b]pyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



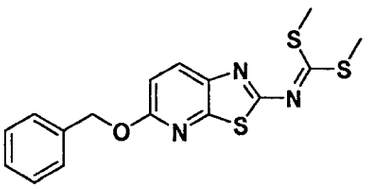
Step A: 5-(Benzyloxy)thiazolo[5,4-b]pyridin-2-amine



Potassium thiocyanate (12.42 g, 128 mmol) was suspended in acetic acid (45.0 mL) and cooled to 0 °C. 6-(Benzyloxy)pyridin-3-amine (3.2 g, 15.98 mmol), prepared according to WO2006/044707 was added. Bromine (2.55 mL, 49.5 mmol) in acetic acid (15 mL) was added dropwise over 30 minutes during which time the reaction mixture became very thick. It was allowed to warm to room temperature slowly and stirred overnight.

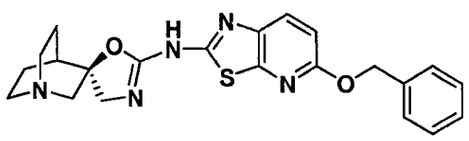
Water (20ml) was added and the reaction mixture was heated to 90 °C and filtered hot. The filtrate was saved and the filter cake returned to the reaction flask, to which was added an additional 40ml HOAc. The mixture was again heated to 90°C and filtered hot. The combined filtrates were cooled on ice bath and NH_4OH was added dropwise until pH >8. A yellow precipitate formed which was collected by filtration. The solids were dried *in vacuo* for 1h to provide 5-(benzyloxy)thiazolo[5,4-b]pyridin-2-amine (1.95 g, 7.58 mmol, 47.4 % yield), which was used without further purification. 1H NMR (400 MHz, $CDCl_3$) δ ppm 7.70 (d, *J*=8.78 Hz, 1 H) 7.48 (d, *J*=7.28 Hz, 2 H) 7.39 (t, *J*=7.28 Hz, 2 H) 7.30 - 7.36 (m, 1 H) 6.78 (d, *J*=8.78 Hz, 1 H) 5.39 (s, 2 H) 5.14 (br. s., 2 H).

Step B: Dimethyl 5-(benzyloxy)thiazolo[5,4-b]pyridin-2-ylcarbonimidodithioate



To a suspension of 5-(benzyloxy)thiazolo[5,4-b]pyridin-2-amine (800 mg, 3.11 mmol) in DMF (3.1 mL) was added 20.0M sodium hydroxide (0.3 mL, 6.22 mmol). The mixture was allowed to stir 10 min at room temperature at which time carbon disulfide was added (0.47 mL, 7.77 mmol) and the mixture was stirred for 10 minutes. An additional portion of 20.0M sodium hydroxide (0.3 mL, 6.22 mmol) was added and the mixture was again stirred for 10 minutes. Finally, iodomethane (0.47 mL, 7.46 mmol) was added dropwise. The mixture was stirred for 1 hour, at which time it was poured into water and extracted with EtOAc (3x). The combined organics were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude mixture was purified by silica gel chromatography (2-20% EtOAc/$CHCl_3$) to provide dimethyl 5-(benzyloxy)thiazolo[5,4-b]pyridin-2-ylcarbonimidodithioate (1.02g, 91% yield) as a yellow crystalline solid. 1H NMR (400 MHz, $CDCl_3$) δ ppm 8.02 (d, *J*=8.78 Hz, 1 H) 7.51 (d, *J*=7.28 Hz, 2 H) 7.38 - 7.45 (m, 2 H) 7.32 - 7.38 (m, 1 H) 6.89 (d, *J*=8.53 Hz, 1 H) 5.46 (s, 2 H) 2.65 (s, 6 H).

Step C: (R)-N-(5-(benzyloxy)thiazolo[5,4-b]pyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

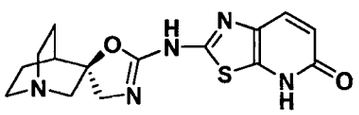


A mixture of dimethyl 5-(benzyloxy)thiazolo[5,4-b]pyridin-2-ylcarbonimidodithioate (500 mg, 1.38 mmol), (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (317 mg, 1.38 mmol) and cesium carbonate (1.0 g, 3.07 mmol) in DMF (7 mL) was heated to 100 °C for 2 hours. The reaction mixture was cooled to ambient temperature, poured into water and extracted with chloroform (4x). The

combined organics were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The mixture was purified by silica gel chromatography (2-20 % [9:1 methanol:ammonium hydroxide]-chloroform) to afford (R)-N-(5-(benzyloxy)thiazolo[5,4-b]pyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (390mg, 67% yield). 1H NMR (500 MHz, $CDCl_3$) δ ppm 9.18 (br. s., 1 H) 7.76 (d, *J*=8.85 Hz, 1 H) 7.50 (d, *J*=7.32 Hz, 2 H) 7.41 (t, *J*=7.32 Hz, 2 H) 7.32 - 7.37 (m, 1 H) 5.42 (s, 2 H) 4.02 (d, *J*=9.46 Hz, 1 H) 3.68 (d, *J*=9.46 Hz, 1 H) 3.37 - 3.44 (m, 1 H) 2.75 - 3.06 (m, 5 H) 2.13 - 2.25 (m, 2 H) 1.73 - 1.82 (m, 1 H) 1.49 - 1.70 (m, 3 H). MS (LC/MS) R.T. = 1.69; $[M+H]^+$ = 421.98.

Example 237

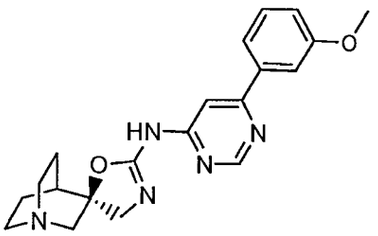
(R)-2-(4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octane]-2-ylamino)thiazolo[5,4-b]pyridin-5(4H)-one



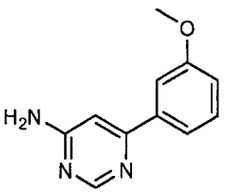
(R)-N-(5-(benzyloxy)thiazolo[5,4-b]pyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (390 mg, 0.925 mmol) was dissolved in TFA and allowed to react for 4 hours at ambient temperature, at which time LCMS and TLC showed the starting material to be mostly consumed. The TFA was removed *in vacuo* and the crude mixture was purified by preparative HPLC. The combined product fractions were concentrated *in vacuo* and triturated with ether to afford (R)-2-(4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octane]-2-ylamino)thiazolo[5,4-b]pyridin-5(4H)-one, TFA (164 mg, 0.368 mmol, 39.8 % yield). M.P. 245 (dec). 1H NMR (400 MHz, DMSO-d_6) δ ppm 9.99 (br. s., 1 H) 9.05 (br. s., 1 H) 7.81 (d, *J*=8.53 Hz, 1 H) 6.65 (d, *J*=8.78 Hz, 1 H) 3.96 (d, *J*=10.29 Hz, 1 H) 3.82 (d, *J*=10.54 Hz, 1 H) 3.63 - 3.78 (m, 2 H) 3.36 - 3.47 (m, 1 H) 3.16 - 3.34 (m, 3 H) 2.43 (br. s., 1 H) 2.16 (br. s., 1 H) 1.76 - 2.07 (m, 3 H). MS (LC/MS) R.T. = 0.50; $[M+H]^+$ = 332.15.

Example 238

(R)-N-(6-(3-Methoxyphenyl)pyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

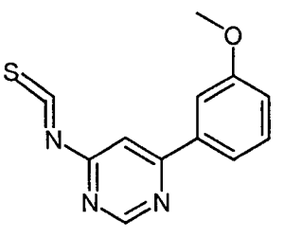


Step A: 6-(3-Methoxyphenyl)pyrimidin-4-amine



A mixture of 6-chloropyrimidin-4-amine (0.324 g, 2.5 mmol), 3-methoxyphenylboronic acid (0.475 g, 3.13 mmol), Na_2CO_3 (0.795 g, 7.50 mmol) and bis(triphenylphosphine)palladium(II) chloride (0.035 g, 0.050 mmol) was suspended in DME/EtOH/water(15:2:3 mL), heated in the microwave synthesizer at 125 °C for 20 min and concentrated. The residue was purified by silica gel chromatography (10-60 % ethyl acetate-hexanes) to afford 6-(3-methoxyphenyl)pyrimidin-4-amine (0.35 g, 1.74 mmol, 70 % yield) as an off-white solid. LCMS R.T. = 1.28; $[M+H]^+$ = 201.98.

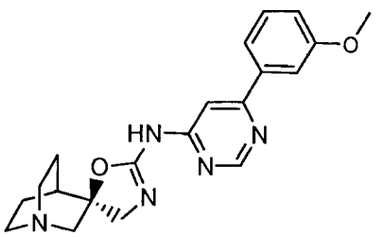
Step B: 4-Isothiocyanato-6-(3-methoxyphenyl)pyrimidine



To a solution of 1,1'-thiocarbonyldipyridin-2(1H)-one (0.970 g, 4.17 mmol) in dichloromethane at room temperature was added 6-(3-methoxyphenyl)pyrimidin-4-

amine (0.7 g, 3.48 mmol). The reaction was stirred at room temperature for 18 hours. The LC/MS showed the desired product peak as a major peak. The deep orange solution was concentrated and the remaining residue was filtered. The filtrate was purified by silica gel chromatography (0-10% ethyl acetate-hexanes) to afford 4-isothiocyanato-6-(3-methoxyphenyl)pyrimidine (0.39 g, 4.31 mmol, 46 % yield) as a yellow oil. LCMS R.T. = 2.91; $[M+H]^+ = 244.03$.

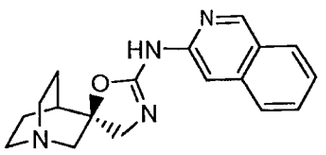
Step C: R)-N-(6-(3-Methoxyphenyl)pyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



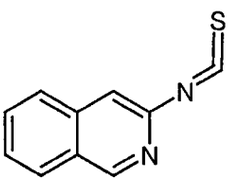
To (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (0.363 g, 1.583 mmol) in N,N-dimethylformamide (20 mL) was added Cs_2CO_3 (1.289 g, 3.96 mmol) and 4-isothiocyanato-6-(3-methoxyphenyl)pyrimidine. The suspension was stirred at room temperature for 30 minutes. N,N'-diisopropylcarbodiimide (0.740 mL, 4.75 mmol) was then added and the mixture was continued to stir at room temperature for 18 hours. The mixture was concentrated and purified by silica gel chromatography (5-25 % 9:1 methanol:ammonium hydroxide-ethyl acetate) to afford (R)-N-(6-methoxypyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.294 g, 0.788 mmol, 50 % yield) as a a pale yellow solid. M.P 80-5 °C. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.77 (1 H, s), 7.47 - 7.58 (2 H, m), 7.39 (1 H, t), 7.20 (1 H, br. s.), 7.04 (1 H, dd), 4.05 (1 H, d), 3.85 (3 H, s), 3.74 (1 H, d), 3.23 (1 H, d), 3.10 (1 H, d), 2.71 - 3.00 (4 H, m), 2.03 - 2.22 (2 H, m), 1.53 - 1.85 (3 H, m). MS (LC/MS) R.T. = 1.58; $[M+H]^+ = 366.15$.

Example 239

(R)-N-(Isoquinolin-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

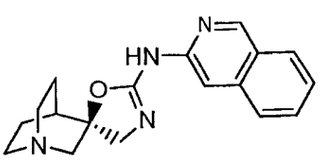


Step A: 3-Isothiocyanatoisoquinoline



To a solution of 1,1'-thiocarbonyldipyridin-2(1H)-one (0.805 g, 3.47 mmol) in dichloromethane at room temperature was added isoquinolin-3-amine (0.5 g, 3.47 mmol). The reaction was stirred at room temperature for 18 hours. The LC/MS showed the desired product peak a major peak. The deep orange solution was concentrated and filtered. The filtrate was purified by silica gel chromatography (0-40% ethyl acetate-hexanes) to afford 4-isothiocyanato-6-(3-methoxyphenyl)pyrimidine (0.55 g, 2.96 mmol, 85 % yield) a white solid. LCMS R.T. = 2.47; $[M+H]^+$ = 187.23.

Step B: (R)-N-(Isoquinolin-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

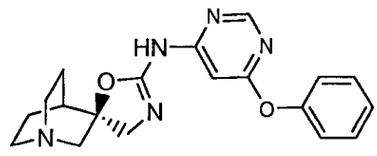


To (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (0.2 g, 0.873 mmol) in N,N-dimethylformamide (20 mL) was added Cs_2CO_3 (0.711 g, 2.182 mmol) and 3-isothiocyanatoisoquinoline (0.163 g, 0.873 mmol). The suspension was stirred at room temperature for 30 minutes. N,N'-Diisopropylcarbodiimide (0.408 mL, 2.62 mmol) was then added and the mixture was stirred at room temperature for 18 hours. The mixture was concentrated and purified by silica gel chromatography (5-25 % [9:1 methanol:ammonium hydroxide]-ethyl acetate) to afford (R)-N-(isoquinolin-3-

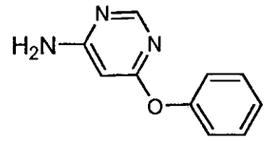
yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.16 g, 0.508 mmol, 58 % yield) as an off-white solid. M.P. 196-200 °C. ^{1}H NMR (400 MHz, *MeOD*) δ ppm 9.00 (1 H, s), 7.92 (1 H, d), 7.71 (1 H, d), 7.59 (1 H, t), 7.20 - 7.45 (2 H, m), 3.96 (1 H, d), 3.65 (1 H, d), 3.22 (1 H, d), 3.08 (1 H, d), 2.66 - 3.00 (4 H, m), 2.05 - 2.23 (2 H, m), 1.50 - 1.86 (3 H, m). R.T. = 1.37; $[M+H]^+$ = 309.31.

Example 240

(R)-N-(6-Phenoxypyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

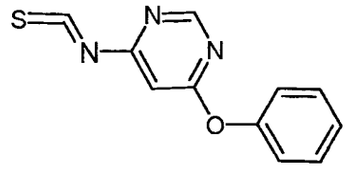


Step A: 6-Phenoxypyrimidin-4-amine



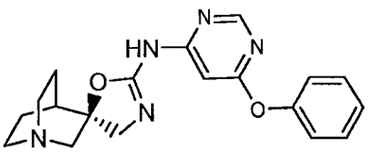
6-Chloropyrimidin-4-amine (3.00 g, 23.14 mmol) was added to a solution of sodium (0.197 g, 8.57 mmol) in phenol (11.29 g, 120 mmol) at 55 °C. The mixture was heated at 140 °C for 2 h, then held at room temperature for 20 h. The reaction mixture was poured into 32% aqueous NaOH on ice/water keeping the mixture temperature below 20 °C. The mixture was extracted with chloroform and the organic extract dried over calcium chloride and concentrated. The residue was purified by silica gel chromatography (2-20 % ethyl acetate in hexanes) to afford 6-phenoxypyrimidin-4-amine (0.6 g, 3.21 mmol, 75 % yield) as a white solid. LCMS R.T. = 1.37; $[M+H]^+$ = 197.95.

Step B: 4-Isothiocyanato-6-phenoxypyrimidine



A mixture of 6-phenoxypyrimidin-4-amine (0.288 g, 1.538 mmol) and 1,1'-thiocarbonyldipyridin-2(1H)-one (0.357 g, 1.538 mmol) in DCM was stirred at rt for 18 h. The pale orange mixture was purified by silica gel chromatography (5-35 % ethyl acetate-hexanes) to afford 4-isothiocyanato-6-phenoxypyrimidine (0.55 g, 2.96 mmol, 85 % yield) a yellow oil. LCMS R.T. = 2.78; $[M+H]^+$ = 229.94.

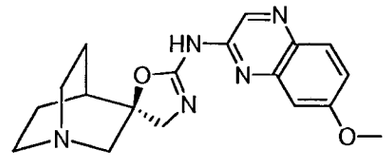
Step C: (R)-N-(6-Phenoxypyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



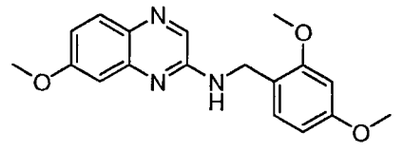
To (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (0.170 g, 0.742 mmol) in N,N-dimethylformamide (20 mL) was added Cs_2CO_3 (0.604 g, 1.854 mmol) and 4-isothiocyanato-6-phenoxypyrimidine (0.17 g, 0.742 mmol). The suspension was stirred at room temperature for 30 minutes. N,N'-diisopropylcarbodiimide (0.347 mL, 2.225 mmol) was then added and the mixture was continued to stir at room temperature for 18 hours. The mixture was concentrated and purified by silica gel chromatography (5-25 % 9:1 methanol:ammonium hydroxide-ethyl acetate) to afford (R)-N-(6-phenoxypyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'- bicyclo[2.2.2]octan]-2-amine (0.21 g, 0.72 mmol, 48.2% yield) as a pale yellow solid. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 8.43 (1 H, s), 7.47 (2 H, t), 7.30 (1 H, t), 7.16 (2 H, d), 6.21 (1 H, br. s.), 4.03 (1 H, d), 3.72 (1 H, d), 3.22 (1 H, d), 3.11 (1 H, d), 2.73 - 2.99 (4 H, m), 2.00 - 2.18 (2 H, m), 1.54 - 1.88 (3 H, m). LCMS R.T. = 1.46; $[M+H]^+$ = 352.19.

EXAMPLE 241

(R)-N-(7-methoxyquinoxalin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



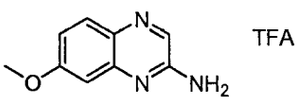
Step A: N-(2,4-Dimethoxybenzyl)-7-methoxyquinoxalin-2-amine



2-Chloro-7-methoxyquinoxaline (0.51 g, 2.62 mmol), prepared according to *J. Chem. Soc. Perk Trans. 1*, **2001**, 978-984, and (2,4-dimethoxyphenyl)methanamine (1.181 mL, 7.86 mmol) were microwaved in DMSO (2.5 mL) for 30 min at 150 °C. This was diluted into 150 mL EtOAc and extracted three times with 100 mL brine. The crude product was purified by flash chromatography on a 90 g silica gel cartridge with 20 to 80% EtOAc in hexane, 50 min, at 40 mL/min to afford N-(2,4-dimethoxybenzyl)-7-methoxyquinoxalin-2-amine (795 mg, 2.443 mmol, 93 % yield).

1H NMR (400 MHz, $CDCl_3$) δ ppm 8.00 (1 H, s), 7.70 (1 H, d, *J*=8.81 Hz), 7.29 (1 H, d, *J*=8.31 Hz), 7.05 (1 H, d, *J*=2.77 Hz), 6.97 (1 H, dd, *J*=9.06, 2.77 Hz), 6.47 (1 H, d, *J*=2.27 Hz), 6.43 (1 H, dd, *J*=8.18, 2.39 Hz), 5.22 (1 H, t, *J*=5.29 Hz), 4.63 (2 H, d, *J*=5.54 Hz), 3.91 (3 H, s), 3.83 (3 H, s), 3.78 (3 H, s)
LCMS: RT = 1.91 min, MH+ = 326.15.

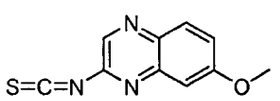
Step B : 7-Methoxyquinoxalin-2-amine 2,2,2-trifluoroacetate



N-(2,4-Dimethoxybenzyl)-7-methoxyquinoxalin-2-amine (0.79 g, 2.428 mmol) was stirred in TFA (10 mL, 130 mmol)/CH_2Cl_2 (10 mL) at room temperature for 30 min. Solvents were removed on the rotary evaporator. Saturated aqueous $NaHCO_3$ (200 mL) was added to the red residue, which precipitated a yellow solid. The mixture was extracted extensively with DCM. The organic layer was concentrated and dried under vacuum to yield 7-methoxyquinoxalin-2-amine 2,2,2-trifluoroacetate (0.70 g, 2.4 mmol, 99 % yield).

1H NMR (400 MHz, *DMSO-d_6*) δ ppm 8.10 (1 H, s), 7.63 (1 H, d, *J*=9.07 Hz), 6.95 (1 H, dd, *J*=9.06, 2.77 Hz), 6.89 (1 H, d, *J*=2.77 Hz), 6.85 (2 H, br. s.), 3.84 (3 H, s)
LCMS: RT = 1.04 min, MH+ = 176.14.

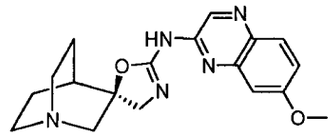
Step C: 2-Isothiocyanato-7-methoxyquinoxaline



A mixture of 7-methoxyquinoxalin-2-amine 2,2,2-trifluoroacetate (578 mg, 2 mmol), triethylamine (335 µL, 2.400 mmol), and 1,1'-thiocarbonyldipyridin-2(1H)-one (557 mg, 2.400 mmol) was stirred in 5 mL DCM for 24 h. The reaction was directly eluted on a 120 g silica gel cartridge with 0 to 25% EtOAc in hexane, 25 min, at 35 mL/min to afford 2-isothiocyanato-7-methoxyquinoxaline (84 mg, 0.387 mmol, 19 % yield).

LCMS: RT = 2.49 min, MH+ = 218.06.

Step D: (R)-N-(7-Methoxyquinoxalin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



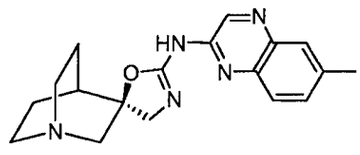
(R)-N-(7-Methoxyquinoxalin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was synthesized by the method of Example 23, Step B. Flash chromatography on a 120 g silica gel cartridge with 1-4% [9:1 MeOH/NH4OH] in CHCl3, 50 min, afforded 24 mg (17 % yield).

1H NMR (400 MHz, $CDCl_3$) δ ppm 9.73 (1 H, br. s.), 8.45 (1 H, s), 7.80 (1 H, d, J=9.07 Hz), 7.12 (1 H, dd, J=9.06, 2.77 Hz), 7.03 (1 H, d, J=2.52 Hz), 4.02 (1 H, d, J=9.32 Hz), 3.90 (3 H, s), 3.67 (1 H, d, J=9.32 Hz), 3.36 (1 H, dd, J=14.86, 1.51 Hz), 2.69 - 3.06 (5 H, m), 2.10 - 2.26 (2 H, m), 1.66 - 1.80 (1 H, m), 1.43 - 1.63 (2 H, m)

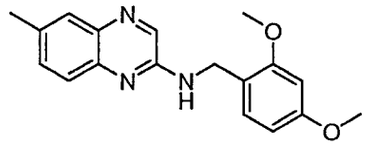
LCMS: RT = 0.835 min, MH- = 338.2, MH+ = 340.1.

EXAMPLE 242

(R)-N-(6-Methylquinoxalin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



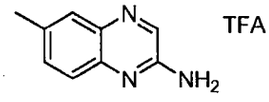
Step A: N-(2,4-Dimethoxybenzyl)-6-methylquinoxalin-2-amine



2-Chloro-6-methylquinoxaline (0.51 g, 2.86 mmol), prepared according to *J. Chem. Soc.* **1948** ,1310-1313, and (2,4-dimethoxyphenyl)methanamine (1.29 mL, 8.57 mmol) were microwaved in DMSO (2.5 mL) for 30 min at 150 °C. This was diluted into 150 mL EtOAc and extracted three times with 100 mL brine. The crude product was purified by flash chromatography on a 90 g silica gel cartridge with 20 to 60% EtOAc in hexane, 50 min, at 40 mL/min to afford N-(2,4-dimethoxybenzyl)-6-methylquinoxalin-2-amine (848 mg, 2.74 mmol, 96 % yield).

1H NMR (400 MHz, *CDCl*$_3$) δ ppm 8.12 (1 H, s), 7.60 (1 H, s), 7.59 (1 H, d, *J*=5.79 Hz), 7.38 (1 H, dd, *J*=8.56, 1.76 Hz), 7.30 (1 H, d, *J*=8.31 Hz), 6.46 (1 H, d, *J*=2.27 Hz), 6.42 (1 H, dd, *J*=8.18, 2.39 Hz), 5.20 (1 H, t, *J*=5.41 Hz), 4.62 (2 H, d, *J*=5.54 Hz), 3.83 (3 H, s), 3.77 (3 H, s), 2.46 (3 H, s)
LCMS: RT = 1.93 min, MH+ = 310.20.

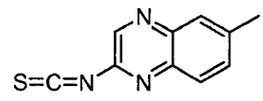
Step B: 6-Methylquinoxalin-2-amine 2,2,2-trifluoroacetate



N-(2,4-Dimethoxybenzyl)-6-methylquinoxalin-2-amine (0.84 g, 2.72 mmol) was stirred in TFA (10 mL, 130 mmol)/CH_2Cl_2 (10 mL) at room temperature for 30 min. Solvents were removed on the rotary evaporator. Saturated aqueous Na_2CO_3 (200 mL) was added to the red residue, which then precipitated a tan solid. The mixture was extracted extensively with DCM. The organic layer was dried over sodium sulfate, concentrated, and dried under vacuum to afford 6-methylquinoxalin-2-amine 2,2,2-trifluoroacetate (640 mg, 2.343 mmol, 86 % yield).

1H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 8.24 (1 H, s), 7.55 (1 H, s), 7.34 - 7.45 (2 H, m), 6.82 (2 H, s), 2.41 (3 H, s)
LCMS: RT = 1.07 min, MH+ = 160.12.

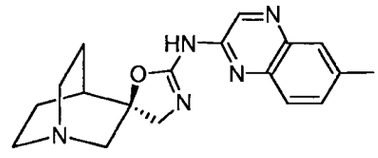
Step C : 2-Isothiocyanato-6-methylquinoxaline



A mixture of 6-methylquinoxalin-2-amine 2,2,2-trifluoroacetate (546 mg, 2 mmol), triethylamine (243 mg, 2.400 mmol), and 1,1'-thiocarbonyldipyridin-2(1H)-one (557 mg, 2.40 mmol) was stirred in 5 mL DCM for 4 h. The reaction was directly eluted on a 120 g silica gel cartridge with 0 to 25% EtOAc in hexane, 25 min, at 35 mL/min to afford 2-isothiocyanato-6-methylquinoxaline (153 mg, 0.760 mmol, 38 % yield).

LCMS: RT = 2.59 min, MH+ = 202.04

Step D : (R)-N-(6-Methylquinoxalin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



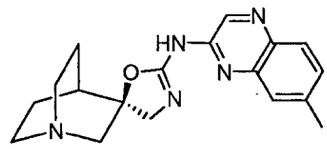
(R)-N-(6-Methylquinoxalin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was synthesized by the method of Example 23, Step B. Flash chromatography on a 120 g silica gel cartridge with 1 to 4% [9:1 MeOH/NH_4OH] in $CHCl_3$, 50 min, afforded 46 mg (19 % yield).

1H NMR (400 MHz, *$CDCl_3$*) δ ppm 9.75 (1 H, br. s.), 8.57 (1 H, s), 7.71 (1 H, s), 7.60 (1 H, d, J=8.56 Hz), 7.42 (1 H, dd, J=8.44, 1.89 Hz), 4.01 (1 H, d, J=9.57 Hz), 3.68 (1 H, d, J=9.32 Hz), 3.38 (1 H, dd, J=14.86, 1.01 Hz), 2.73 - 3.08 (5 H, m), 2.50 (3 H, s), 2.16 - 2.26 (1 H, m), 2.14 (1 H, br. s.), 1.67 - 1.79 (1 H, m), 1.45 - 1.65 (2 H, m).

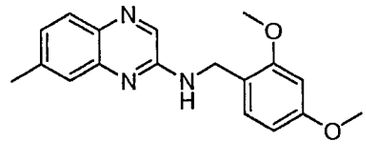
LCMS: RT = 0.838 min, MH- = 322.2, MH+ = 324.2.

EXAMPLE 243

(R)-N-(7-Methylquinoxalin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



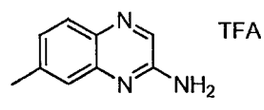
Step A: N-(2,4-Dimethoxybenzyl)-7-methylquinoxalin-2-amine



2-Chloro-7-methylquinoxaline (0.51 g, 2.86 mmol),), prepared according to *J. Chem. Soc.* **1948** 1310-1313, and (2,4-dimethoxyphenyl)methanamine (1.29 mL, 8.57 mmol) were microwaved in DMSO (2.5 mL) for 30 min at 150 °C. This was diluted into 150 mL EtOAc and extracted three times with 100 mL brine. The crude product was purified by flash chromatography on a 90 g silica gel cartridge with 20 to 80% EtOAc in hexane, 50 min, at 40 mL/min to afford N-(2,4-dimethoxybenzyl)-7-methylquinoxalin-2-amine (860 mg, 2.78 mmol, 97 % yield).

1H NMR (400 MHz, $CDCl_3$) δ ppm 8.08 (1 H, s), 7.70 (1 H, d, *J*=8.31 Hz), 7.49 (1 H, s), 7.30 (1 H, d, *J*=8.06 Hz), 7.17 (1 H, dd, *J*=8.31, 2.01 Hz), 6.47 (1 H, d, *J*=2.52 Hz), 6.42 (1 H, dd, *J*=8.31, 2.52 Hz), 5.23 (1 H, t, *J*=5.16 Hz), 4.63 (2 H, d, *J*=5.79 Hz), 3.83 (3 H, s), 3.78 (3 H, s), 2.48 (3 H, s).
LCMS: RT = 1.93 min, MH+ = 310.20.

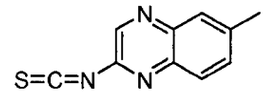
Step B: 7-Methylquinoxalin-2-amine 2,2,2-trifluoroacetate



N-(2,4-Dimethoxybenzyl)-7-methylquinoxalin-2-amine (0.85 g, 2.75 mmol) was stirred in TFA (10 mL, 130 mmol)/CH2Cl2 (10 mL) at room temperature for 30 min. Solvents were removed on the rotary evaporator. Saturated aqueous $NaHCO_3$ (200 mL) was added to the red residue, which then precipitated a pink solid. The mixture was extracted extensively with DCM. The organic layer was dried over sodium sulfate, concentrated, and dried under vacuum to afford 7-methylquinoxalin-2-amine 2,2,2-trifluoroacetate (640 mg, 2.34 mmol, 85 % yield).

1H NMR (400 MHz, *DMSO-d_6*) δ ppm 8.20 (1 H, s), 7.64 (1 H, d, *J*=8.31 Hz), 7.28 (1 H, s), 7.15 (1 H, dd, *J*=8.31, 1.76 Hz), 6.89 (2 H, s), 2.42 (3 H, s).
LCMS: RT = 1.07 min, MH+ = 160.12.

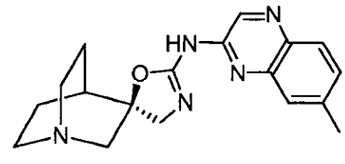
Step C : 2-Isothiocyanato-6-methylquinoxaline



A mixture of 7-methylquinoxalin-2-amine 2,2,2-trifluoroacetate (546 mg, 2 mmol) 78263-058-01, triethylamine (243 mg, 2.40 mmol), and 1,1'-thiocarbonyldipyridin-2(1H)-one (557 mg, 2.40 mmol) was stirred in 5 mL DCM for 2 h. The reaction was directly eluted on a 120 g silica gel cartridge with 0 to 25% EtOAc in hexane, 25 min, at 35 mL/min to afford 2-isothiocyanato-7-methylquinoxaline (185 mg, 0.919 mmol, 46 % yield).

LCMS: RT = 2.58 min, MH+ = 202.04

Step D : (R)-N-(7-Methylquinoxalin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

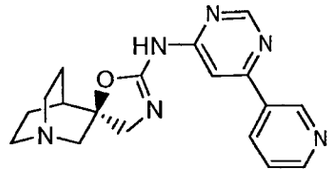


(R)-N-(7-Methylquinoxalin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was synthesized by the method of Example 23, Step B. Flash chromatography on a 120 g silica gel cartridge with 1 to 3% [9:1 MeOH/NH4OH] in CHCl3, 50 min, afforded 22 mg (7 % yield).

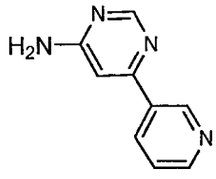
1H NMR (400 MHz, *CDCl3*) δ ppm 9.80 (1 H, br. s.), 8.53 (1 H, s), 7.81 (1 H, d, *J*=8.31 Hz), 7.50 (1 H, s), 7.31 (1 H, dd, *J*=8.56, 1.76 Hz), 4.01 (1 H, d, *J*=9.57 Hz), 3.66 (1 H, d, *J*=9.32 Hz), 3.36 (1 H, d, *J*=14.86 Hz), 2.70 - 3.04 (5 H, m), 2.50 (3 H, s), 2.15 - 2.24 (1 H, m), 2.13 (1 H, br. s.), 1.66 - 1.79 (1 H, m), 1.44 - 1.63 (2 H, m)
LCMS: RT = 8.67 min, MH- = 322.6, MH+ = 324.1.

Example 244

(R)-N-(6-(Pyridin-3-yl)pyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

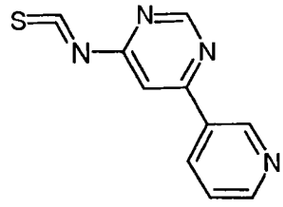


Step A: 6-(Pyridin-3-yl)pyrimidin-4-amine



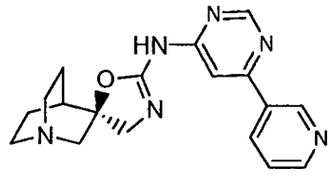
A mixture of 6-chloropyrimidin-4-amine (0.324 g, 2.5 mmol), pyridin-3-ylboronic acid (0.384 g, 3.13 mmol), Na_2CO_3 (0.795 g, 7.50 mmol) and bis(triphenylphosphine)palladium(II) chloride (0.035 g, 0.050 mmol) was suspended in a mixture of DME/EtOH/water. The mixture was heated in the microwave synthesizer at 125 °C for 20 min and concentrated. The residue was purified by silica gel chromatography (10-60 % ethyl acetate in hexanes, then 5-25 % 9:1 methanol:ammonium hydroxide-ethyl acetate) to afford 6-(pyridin-3-yl)pyrimidin-4-amine (0.17 g, 0.987 mmol, 40 % yield) as an off-white solid. LCMS R.T. = 0.31; $[M+H]^+$ = 173.11.

Step B: 4-Isothiocyanato-6-(pyridin-3-yl)pyrimidine



To a solution of 1,1'-thiocarbonyldipyridin-2(1H)-one (0.682 g, 2.94 mmol) in dichloromethane/N,N-dimethylformamide at room temperature was added 6-(pyridin-3-yl)pyrimidin-4-amine (0.337 g, 1.957 mmol). The mixture was heated at 60 °C for 18 hours. LC/MS showed the desired product peak as the major peak. The deep orange mixture was purified by silica gel chromatography (1-40 % ethyl acetate-hexanes) to afford 4-isothiocyanato-6-methoxypyrimidine (0.12 g, 0.56 mmol, 28.6 % yield) as an orange oil.

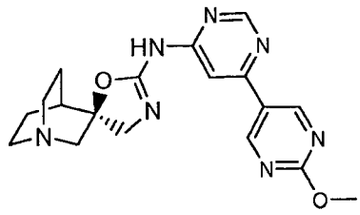
Step C: (R)-N-(6-(Pyridin-3-yl)pyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



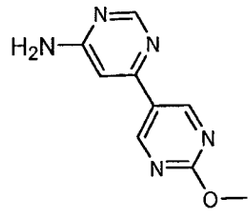
To (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (0.13 g, 0.560 mmol) in N,N-dimethylformamide (20 mL) was added Cs_2CO_3 (0.46 g, 1.4 mmol) and 4-isothiocyanato-6-(pyridin-3-yl)pyrimidine (0.12 g, 0.56 mmol). The suspension was stirred at room temperature for 30 minutes. N,N'-Diisopropylcarbodiimide (0.26 mL, 1.7 mmol) was then added and the mixture was stirred at room temperature for 18 hours. The mixture was concentrated and purified by silica gel chromatography (0-10 % [9:1 methanol:ammonium hydroxide]-ethyl acetate) to afford (S)-N-(5-chloropyrazin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.182 g, 0.613 mmol, 35 % yield) as an off-white solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 9.13 - 9.21 (1 H, m), 8.82 (1 H, d), 8.63 (1 H, dd), 8.44 (1 H, dt), 7.56 (1 H, dd), 7.31 (1 H, s), 4.06 (1 H, d), 3.76 (1 H, d), 3.20 - 3.28 (1 H, m), 3.08 - 3.16 (1 H, m), 2.72 - 3.01 (4 H, m), 2.00 - 2.24 (2 H, m), 1.52 - 1.83 (3 H, m). LCMS R.T. = 0.72; $[M+H]^+$ = 337.2.

Example 245

(R)-N-(2'-Methoxy-4,5'-bipyrimidin-6-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

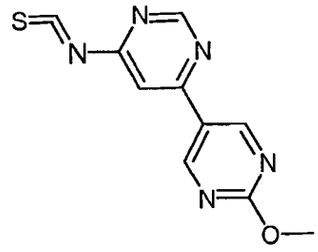


Step A: 2'-Methoxy-4,5'-bipyrimidin-6-amine



6-Chloropyrimidin-4-amine (0.35 g, 2.70 mmol), 2-methoxypyrimidin-5-ylboronic acid (0.520 g, 3.38 mmol), Na_2CO_3 (0.859 g, 8.11 mmol) and bis(triphenylphosphine)palladium(II) chloride (0.038 g, 0.054 mmol) were suspended in a mixture of DME/EtOH/water. (15:2:3 mL). The mixture was heated in the microwave synthesizer at 125 °C for 20 min and concentrated. The residue was purified by silica gel chromatography (0-5 % 9:1 methanol:ammonium hydroxide-ethyl acetate) to afford 6-(pyridin-3-yl)pyrimidin-4-amine (0.28 g, 1.378 mmol, 51 % yield) as an off-white solid. LCMS R.T. = 0.53; $[M+H]^+ = 204.11$.

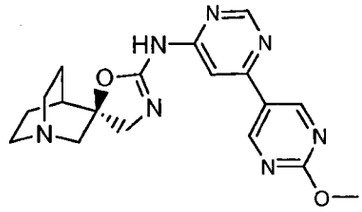
Step B: 6-Isothiocyanato-2'-methoxy-4,5'-bipyrimidine



To a solution of 1,1'-thiocarbonyldipyridin-2(1H)-one (0.832 g, 3.58 mmol) in dichloromethane/N,N-dimethylformamide at room temperature was added 2'-methoxy-4,5'-bipyrimidin-6-amine (0.56 g, 2.76 mmol). The orange mixture was heated at 60 °C for 18 hours. The LC/MS showed the desired product peak as the

major peak. The deep orange mixture was purified by silica gel chromatography (0-40 % ethyl acetate-hexanes) to afford 4-isothiocyanato-6-methoxypyrimidine (0.1 g, 0.408 mmol, 15 % yield) as an orange solid. LCMS R.T. = 2.29; $[M+H]^+$ = 246.03.

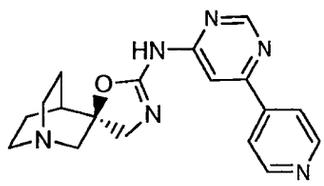
Step C: (R)-N-(2'-Methoxy-4,5'-bipyrimidin-6-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



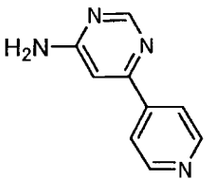
To (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (0.093 g, 0.41 mmol) in N,N-dimethylformamide (20 mL) was added Cs_2CO_3 (0.33 g, 1 mmol)) and 6-isothiocyanato-2'-methoxy-4,5'-bipyrimidine (0.1 g, 0.41 mmol). The suspension was stirred at room temperature for 30 minutes. N,N'-Diisopropylcarbodiimide (0.19 mL, 1.2 mmol) was then added and the mixture was stirred at room temperature for 18 hours. The mixture was concentrated and purified by silica gel chromatography (5-25 % [9:1 methanol:ammonium hydroxide]-ethyl acetate) to afford (R)-N-(2'-methoxy-4,5'-bipyrimidin-6-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine(0.072 g, 0.188 mmol, 46 % yield) as an off-white solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 9.19 (2 H, s), 8.80 (1 H, d), 7.24 (1 H, br. s.), 4.00 - 4.09 (4 H, m), 3.76 (1 H, d), 3.23 (1 H, s), 3.08 - 3.15 (1 H, m), 2.72 - 3.04 (4 H, m), 1.97 - 2.22 (2 H, m), 1.38 - 1.85 (3 H, m). R.T. = 1.22; $[M+H]^+$ = 368.22.

Example 246

(R)-N-(6-(Pyridin-4-yl)pyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

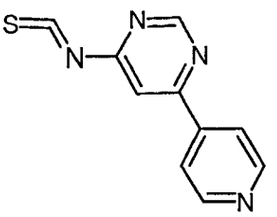


Step A: 6-(Pyridin-4-yl)pyrimidin-4-amine



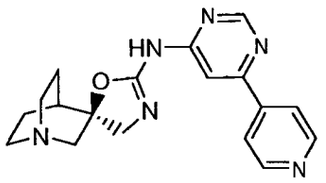
6-Chloropyrimidin-4-amine (0.324 g, 2.5 mmol), pyridin-4-ylboronic acid (0.384 g, 3.13 mmol), Na_2CO_3 (0.795 g, 7.50 mmol) and bis(triphenylphosphine)palladium(II) chloride (0.035 g, 0.050 mmol) were suspended in a mixture of DME/EtOH/water(15:2:3 mL). The mixture was heated in the microwave synthesizer at 125 °C for 20 min and concentrated. The residue was purified by silica gel chromatography (5-25 % [9:1 methanol:ammonium hydroxide]-ethyl acetate) to afford 6-(pyridin-3-yl)pyrimidin-4-amine (0.15 g, 0.871 mmol, 35 % yield) as an off-white solid. LCMS R.T. = 0.30; $[M+H]^+$ = 173.11.

Step B: 4-Isothiocyanato-6-(pyridin-4-yl)pyrimidine



To a solution of 1,1'-thiocarbonyldipyridin-2(1H)-one (0.601 g, 2.59 mmol) in dichloromethane/N,N-dimethylformamide at room temperature was added 6-(pyridin-4-yl)pyrimidin-4-amine (0.297 g, 1.725 mmol). The orange mixture was heated at 60 °C for 18 hours. LC/MS showed the desired product peak as the major peak. The deep orange mixture was purified by silica gel chromatography (0-40% ethyl acetate-hexanes) to afford 4-isothiocyanato-6-(pyridin-4-yl)pyrimidine (0.055 g, 0.257 mmol, 15 % yield) as an orange solid. LCMS R.T. = 1.46; $[M+H]^+$ = 215.09.

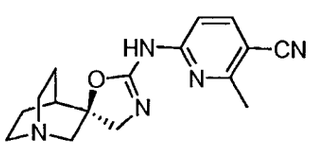
Step C: (R)-N-(6-(Pyridin-4-yl)pyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



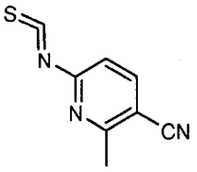
To (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (0.059 g, 0.257 mmol) in N,N-dimethylformamide (15 mL) was added Cs_2CO_3 (0.209 g, 0.642 mmol) and 4-isothiocyanato-6-(pyridin-4-yl)pyrimidine (0.055 g, 0.257 mmol). The suspension was stirred at room temperature for 30 minutes. N,N'-diisopropylcarbodiimide (0.12 mL, 0.77 mmol) was then added and the mixture was continued to stir at room temperature for 18 hours. The mixture was concentrated and purified by silica gel chromatography (0-10 % [9:1 methanol:ammonium hydroxide]-ethyl acetate) to afford (R)-N-(6-(pyridin-4-yl)pyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.014 g, 0.04 mmol, 16 % yield) as a yellow film. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.85 (1 H, d), 8.67 (2 H, dd), 8.04 (2 H, dd), 7.34 (1 H, br. s.), 4.06 (1 H, d), 3.76 (1 H, d), 3.23 (1 H, d), 3.10 (1 H, d), 2.70 - 2.99 (4 H, m), 2.01 - 2.22 (2 H, m), 1.53 - 1.86 (3 H, m). LCMS R.T. = 0.42; $[M+H]^+$ = 337.14.

EXAMPLE 247

(R)-6-(4H-1'-Azaspiro[oxazole-5,3'-bicyclo[2.2.2]octane]-2-ylamino)-2-methylnicotinonitrile

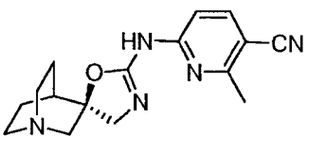


Step A: 6-Isothiocyanato-2-methylnicotinonitrile



To 6-amino-2-methylnicotinonitrile (0.41 g, 3.08 mmol) in dichloromethane (20 mL) was added 1,1'-thiocarbonyldipyridin-2(1H)-one (0.75 g, 3.23 mmol). The reaction was stirred at 40 °C for 3 hours. The reaction was cooled to room temperature. The crude was purified by chromatography (Biotage: 25-100% ethyl acetate/hexane) to yield 6-isothiocyanato-2-methylnicotinonitrile (0.52 g, 2.97 mmol, 96 % yield). 1H NMR (500 MHz, *DMSO-D6*) δ ppm 8.36 (d, *J*=8.24 Hz, 1 H), 7.39 (d, *J*=8.24 Hz, 1 H), 2.65 (s, 3 H). MS (LC/MS) R.T. = 2.09; $[M+H]^+$ = 176.0.

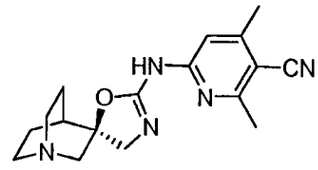
Step B: (R)-6-(4H-1'-Azaspiro[oxazole-5,3'-bicyclo[2.2.2]octane]-2-ylamino)-2-methylnicotinonitrile



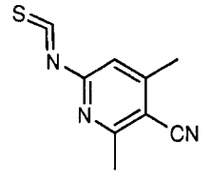
To 6-isothiocyanato-2-methylnicotinonitrile (0.25 g, 1.43 mmol) in N, N-dimethylformamide (20 mL) was added triethylamine (0.5 mL, 3.666 mmol) and 3-(aminomethyl)quinuclidin-3-ol dihydrochloride (0.33 g, 1.46 mmol) at room temperature. The reaction was stirred at 70 °C for 2 hours. The reaction was cooled to room temperature and concentrated *in vacuo*. The crude urea was purified by chromatography (Biotage: 85% $CHCl_3$, 14% MeOH, 1% NH_4OH). The product was then treated with N, N-dimethylformamide (20 mL) and N,N'-diisopropylcarbodiimide (0.67 mL, 4.28 mmol). The reaction was heated to 70°C for 2 hours. The reaction was cooled to room temperature and concentrated *in vacuo* to yield the crude product. The crude product was purified by chromatography (Biotage: 85% $CHCl_3$, 14% MeOH, 1% NH_4OH) to yield (R)-6-(4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octane]-2-ylamino)-2-methylnicotinonitrile (0.09 g, 0.3 mmol, 21 % yield) as a white powder. 1H NMR (500 MHz, *DMSO-D6*) δ ppm 9.11 (s, 1 H), 7.87 (d, *J*=7.93 Hz, 2 H), 6.69 (s, 1 H), 3.89 (d, *J*=10.38 Hz, 2 H), 3.63 (d, *J*=10.38 Hz, 3 H), 3.00 (s, 5 H), 2.72 - 2.80 (m, 4 H), 2.64 - 2.69 (m, 5 H), 2.60 (s, 7 H), 2.00 (d, *J*=2.14 Hz, 3 H), 1.91 (s, 1 H), 1.87 (s, 2 H), 1.58 (s, 5 H), 1.42 - 1.50 (m, 2 H). MS (LC/MS) R.T. = 0.48; $[M+H]^+$ = 298.13.

EXAMPLE 248

(R)-6-(4H-1'-Azaspiro[oxazole-5,3'-bicyclo[2.2.2]octane]-2-ylamino)-2,4-dimethylnicotinonitrile

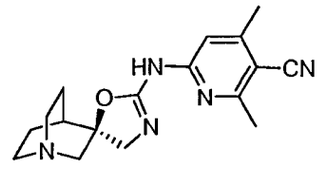


Step A: 6-Isothiocyanato-2,4-dimethylnicotinonitrile



To 6-amino-2,4-dimethylnicotinonitrile (0.14 g, 0.95 mmol) in dichloromethane (20 mL) was added 1,1'-thiocarbonyldipyridin-2(1H)-one (0.23 g, 0.1 mmol). The reaction was stirred at 40 °C for 3 hours. The reaction was cooled to room temperature. The crude was purified by chromatography (Biotage: 25-100% ethyl acetate/hexane) to yield 6-isothiocyanato-2,4-dimethylnicotinonitrile (0.15 g, 0.79 mmol, 83 % yield). 1H NMR (500 MHz, *DMSO-D6*) δ ppm 7.37 (s, 1 H), 2.63 (s, 3 H). MS (LC/MS) R.T. = 2.40; $[M+H]^+$ = 190.

Step B: (R)-6-(4H-1'-Azaspiro[oxazole-5,3'-bicyclo[2.2.2]octane]-2-ylamino)-2,4-dimethylnicotinonitrile

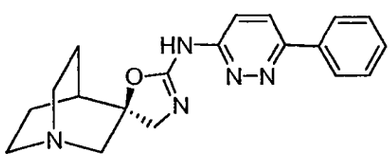


To 6-isothiocyanato-2,4-dimethylnicotinonitrile (0.09 g, 0.48 mmol) in N, N-dimethylformamide (20 mL) was added triethylamine (0.17 mL, 1.19 mmol) and 3-(aminomethyl)quinuclidin-3-ol dihydrochloride (0.11 g, 0.49 mmol) at room temperature. The reaction was stirred at 70 °C for 2 hours. The reaction was cooled to room temperature and concentrated *in vacuo*. The crude urea was purified by chromatography (Biotage: 85% $CHCl_3$, 14% MeOH, 1% NH_4OH). The product was

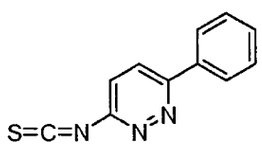
then treated with N, N-dimethylformamide (20 mL) and N,N'-diisopropylcarbodiimide (0.22 mL, 1.43 mmol). The reaction was heated to 70 °C for 2 hours. The reaction was cooled to room temperature and concentrated *in vacuo* to yield the crude product. The crude product was purified by chromatography (Biotage: 85% $CHCl_3$, 14% MeOH, 1% NH_4OH) to yield (R)-6-(4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octane]-2-ylamino)-2,4-dimethylnicotinonitrile (0.10 g, 0.32 mmol, 66 % yield) as a white powder. 1H NMR (500 MHz, *DMSO-D6*) δ ppm 9.08 (s, 1 H), 6.60 (s, 1 H), 3.88 (d, *J*=10.38 Hz, 1 H), 3.61 (d, *J*=10.38 Hz, 1 H), 2.98 (s, 2 H), 2.70 - 2.79 (m, 2 H), 2.63 - 2.69 (m, 2 H), 2.55 - 2.60 (m, 4 H), 2.31 - 2.39 (m, 4 H), 1.99 (s, 1 H), 1.89 (s, 1 H), 1.54 - 1.62 (m, 2 H), 1.41 - 1.49 (m, 1 H). MS (LC/MS) R.T. = 0.78; $[M+H]^+$ = 312.1.

EXAMPLE 249

(R)-N-(6-Phenylpyridazin-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



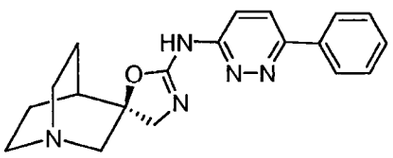
Step A: 3-Isothiocyanato-6-phenylpyridazine



3-Isothiocyanato-6-phenylpyridazine was synthesized by the method of Example 23, Step B. Flash chromatography on a 120 g silica gel cartridge with 0 to 25% EtOAc in hexane, 25 min, at 35 mL/min afforded 420 mg (49 % yield).

LCMS: RT = 2.17 min, MH+ = 214.06.

Step B : (R)-N-(6-Phenylpyridazin-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

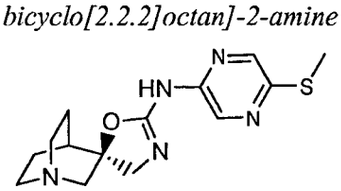


(R)-N-(6-Phenylpyridazin-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was synthesized by the method of Example 23, Step B. Flash chromatography on a 160 g silica gel cartridge with 1-4 % [9:1 MeOH/NH_4OH] in $CHCl_3$, 50 min, at 40 mL/min afforded 67 mg (R)-N-(6-phenylpyridazin-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (17 % yield).

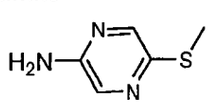
1H NMR (400 MHz, *$CDCl_3$*) δ ppm 9.61 (1 H, br. s.), 7.95 - 7.99 (2 H, m), 7.74 (1 H, d, *J*=9.32 Hz), 7.39 - 7.52 (3 H, m), 7.22 (1 H, partial d), 3.97 (1 H, d, *J*=9.32 Hz), 3.64 (1 H, d, *J*=9.32 Hz), 3.37 (1 H, dd, *J*=14.73, 1.38 Hz), 2.69 - 3.06 (5 H, m), 2.16 - 2.26 (1 H, m), 2.14 (1 H, br. s.), 1.66 - 1.79 (1 H, m), 1.45 - 1.60 (2 H, m)
1H NMR (400 MHz, *MeOD*) δ ppm 7.87 - 8.02 (3 H, m), 7.44 - 7.55 (3 H, m), 7.13 - 7.29 (1 H, m), 4.05 (1 H, d, *J*=9.82 Hz), 3.74 (1 H, d, *J*=10.07 Hz), 3.17 (2 H, dd, *J*=49.35, 14.60 Hz), 2.73 - 3.04 (4 H, m), 2.16 (2 H, br. s.), 1.55 - 1.85 (3 H, m)
LCMS: RT = 0.82 min, MH- = 334.2, MH+ = 336.2.

EXAMPLE 250

(R)-N-(5-(Methylthio)pyrazin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

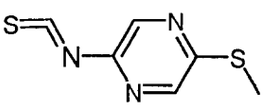


Step A: 5-(Methylthio)pyrazin-2-amine



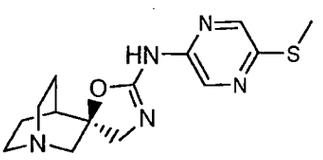
To a solution of 5-bromopyrazin-2-amine (2 g, 11.49 mmol) in N,N-dimethylformamide (20 ml) was added sodium thiomethoxide (1.611 g, 22.99 mmol). The mixture was stirred and heated at 100 °C under nitrogen for 18 h and concentrated. The residue was treated with water and the mixture was extracted with dichloromethane. The combined organics were dried with sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (0-10 % 9:1methanol:ammonium hydroxide-ethyl acetate) to afford 6-(pyridin-3-yl)pyrimidin-4-amine (0.15 g, 0.871 mmol, 35 % yield) as a yellow solid. LCMS R.T. = 0.91; $[M+H]^+$ = 141.89.

Step B: 2-Isothiocyanato-5-(methylthio)pyrazine



To a solution of 1,1'-thiocarbonyldipyridin-2(1H)-one (1.069 g, 4.60 mmol) in dichloromethane at room temperature was added 5-(methylthio)pyrazin-2-amine (0.50 g, 3.54 mmol). The reaction was stirred at room temperature for 18 hours. LC/MS showed the desired product peak as the major peak. The deep orange mixture was purified by silica gel chromatography (0-40 % ethyl acetate-hexanes) to afford 2-isothiocyanato-5-(methylthio)pyrazine (0.545 g, 0.257 mmol, 84 % yield) as an orange oil. LCMS R.T. = 2.65; $[M+H]^+$ = 184.02.

Step C: (R)-N-(5-(Methylthio)pyrazin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

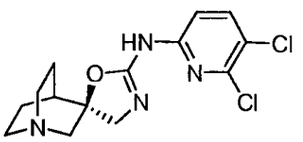


To (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (0.375 g, 1.637 mmol) in N,N-dimethylformamide (15 mL) was added Cs_2CO_3 (1.333 g, 4.09 mmol) and 2-isothiocyanato-5-(methylthio)pyrazine (0.3 g, 1.637 mmol),. The suspension was stirred at room temperature for 30 minutes. N,N'-diisopropylcarbodiimide (0.765 mL, 4.9 mmol) was then added and the mixture was continued to stir at room

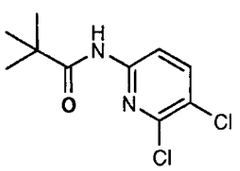
temperature for 18 hours. The mixture was concentrated and purified by silica gel chromatography (5-25 % 9:1 methanol:ammonium hydroxide-ethyl acetate) to afford (R)-N-(5-(methylthio)pyrazin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.014 g, 0.04 mmol, 16 % yield) as a yellow solid. M.P. 155-60 °C. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.13 (1 H, d), 8.06 (1 H, s), 3.96 (1 H, d), 3.66 (1 H, d), 3.20 (1 H, d), 3.08 (1 H, d), 2.87 - 2.96 (2 H, m), 2.72 - 2.82 (2 H, m), 2.52 (3 H, s), 2.00 - 2.19 (2 H, m), 1.51 - 1.81 (3 H, m). LCMS R.T. = 1.01; $[M+H]^+$ = 306.12.

EXAMPLE 251

(R)-N-(5,6-Dichloropyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



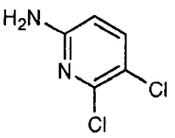
Step A: N-(5,6-Dichloropyridin-2-yl)pivalamide



To a solution of N-(6-chloropyridin-2-yl)pivalamide, synthesized as in *J. Org. Chem* **2005**, *70*, 1771, (1.02 g, 4.80 mmol) in chloroform (25 mL) was added 1-chloropyrrolidine-2,5-dione (0.62 g, 4.67 mmol) and the mixture was refluxed in an oil bath for 3 hrs. It was allowed to cool to room temperature overnight. The reaction mixture was evaporated *in vacuo* and re-dissolved in DMF (15 mL). Another 480 mg 1-chloropyrrolidine-2,5-dione was added and the resulting solution was heated overnight in an oil bath at 95-100^O, then cooled again to room temperature. The solvent was removed *in vacuo* and the residue was partitioned between water and ethyl acetate. The aqueous phase was washed twice more with ethyl acetate and the combined organic phases were washed with brine, dried over magnesium sulfate, and evaporated *in vacuo*. TLC (10% ethyl acetate/hexane) showed a robust spot at Rf 0.6 with smaller spots at Rf 0.4 and 0.2. The material was subjected to the Biotage in 5-10% ethyl acetate/hexane, collecting the Rf 0.6 fraction

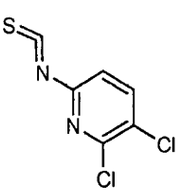
to give 790 mg (66%) white solid, N-(5,6-dichloropyridin-2-yl)pivalamide. 1H NMR (500 MHz, $CDCl_3$) δ ppm 8.17 (s, 1 H), 7.96 (s, 1 H), 7.72 (s, 1 H), 1.31 (s, 10 H). MS (LC/MS) R.T. = 1.85; $[M+H]^+$ = 248.8.

Step B: 5,6-Dichloropyridin-2-amine



A mixture of N-(5,6-dichloropyridin-2-yl)pivalamide (790 mg, 3.20 mmol), hydrochloric acid, 37% (1.25 mL), water (1.25 mL), and EtOH (3 mL) was heated for 4 hrs in an oil bath at 85-90 °C. LCMS showed nearly complete conversion to product. The reaction was cooled to room temperature and the reaction mixture was evaporated down to a small volume, then transferred to a separatory funnel where it was partitioned between aqueous sodium carbonate and ethyl acetate. The layers were separated, the aqueous phase was washed again with ethyl acetate, and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and evaporated to give a white solid. The material was subjected to a Biotage column in 20% ethyl acetate/hexane, collecting the main component. 5,6-Dichloropyridin-2-amine (0.49 g, 2.98 mmol, 93%) was obtained as a white solid. 1H NMR (500 MHz, $CDCl_3$) δ ppm 7.44 (d, *J*=8.55 Hz, 1 H), 6.36 (d, *J*=8.24 Hz, 1 H), 4.58 (s, 2 H). MS (LC/MS) R.T. = 1.28; $[M+H]^+$ = 164.8.

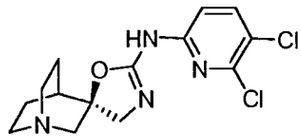
Step C: 5,6-Dichloro-2-isothiocyanatopyridine



To 5,6-dichloropyridin-2-amine (0.47 g, 2.88 mmol) in dichloromethane (25 mL) was added 1,1'-thiocarbonyldipyridin-2(1H)-one (0.68 g, 2.94 mmol). The reaction was stirred at 40 °C for 3 hours, then cooled to room temperature. The crude material was purified by chromatography (Biotage: 25-100% ethyl acetate/hexane) 2,3-dichloro-6-isothiocyanatopyridine (0.48 g, 2.34 mmol, 81 % yield) as a white

powder. 1H NMR (500 MHz, *DMSO-D6*) δ ppm 8.26 (d, *J*=8.55 Hz, 1 H), 7.47 (d, *J*=8.24 Hz, 1 H). MS (LC/MS) R.T. = 2.83; $[M+H]^+$ = 204.8.

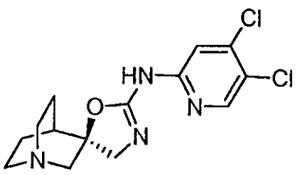
Step D: (R)-N-(5,6-Dichloropyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



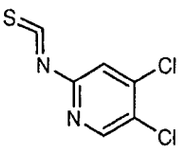
To 2,3-dichloro-6-isothiocyanatopyridine (0.47 g, 2.29 mmol) in N,N-dimethylformamide (20 mL) was added triethylamine (0.8 mL, 5.7 mmol) and 3-(aminomethyl)quinuclidin-3-ol dihydrochloride (0.54 g, 2.34 mmol) at room temperature. The reaction was stirred at 70 °C for 2 hours, cooled to room temperature and concentrated *in vacuo*. The crude urea was purified by chromatography (Biotage: 85% $CHCl_3$, 14% MeOH, 1% NH_4OH). The product was then treated with N,N-dimethylformamide (20 mL) and N,N'-diisopropylcarbodiimide (1.07 mL, 6.88 mmol). The reaction was heated to 70°C for 2 hours. The reaction was cooled to room temperature and concentrated *in vacuo*. The crude product was purified by chromatography (Biotage: 85% $CHCl_3$, 14% MeOH, 1% NH_4OH) to yield (R)-N-(5,6-dichloropyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.36 g, 1.08 mmol, 47 % yield) as a white powder. 1H NMR (500 MHz, *DMSO-D6*) δ ppm 8.31 (d, *J*=1.22 Hz, 1 H), 7.84 (s, 1 H), 6.80 (s, 1 H), 3.85 (d, *J*=10.07 Hz, 1 H), 3.57 (d, *J*=10.38 Hz, 2 H), 2.98 (s, 3 H), 2.69 - 2.78 (m, 3 H), 2.65 (t, *J*=7.78 Hz, 3 H), 2.00 (s, 2 H), 1.86 (s, 2 H), 1.58 (dd, *J*=7.48, 2.90 Hz, 2 H), 1.56 (s, 1 H), 1.41 - 1.49 (m, 2 H). MS (LC/MS) R.T. = 0.81; $[M+H]^+$ = 327.1.

EXAMPLE 252

(R)-N-(4,5-Dichloropyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

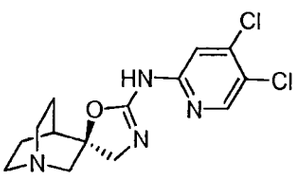


Step A: 4,5-Dichloro-2-isothiocyanatopyridine



To 4,5-dichloropyridin-2-amine (0.25 g, 1.53 mmol) in dichloromethane (25 mL) was added 1,1'-thiocarbonyldipyridin-2(1H)-one (0.36 g, 1.56 mmol). The reaction was stirred at 40°C for 3 hours, then cooled to room temperature. The crude material was purified by chromatography (Biotage: 25-100% ethyl acetate/hexane) to yield 4,5-dichloro-2-isothiocyanatopyridine (0.26 g, 1.27 mmol, 83 % yield) as a yellow powder. The product was carried directly to the next step.

Step B: (R)-N-(4,5-Dichloropyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

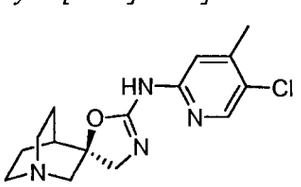


To 4,5-dichloro-2-isothiocyanatopyridine (0.25 g, 1.22 mmol) in N,N-dimethylformamide (20 mL) was added triethylamine (0.43 mL, 3.05 mmol) and (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (0.29 g, 1.24 mmol) at room temperature. The reaction was stirred at 70 °C for 2 hours. The reaction was cooled to room temperature and concentrated *in vacuo*. The crude urea was purified by chromatography (Biotage: 85% $CHCl_3$, 14% MeOH, 1% NH_4OH). The product was

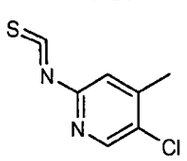
then treated with N,N-dimethylformamide (20 mL) and N,N'-diisopropylcarbodiimide (0.57 mL, 3.66 mmol). The reaction was heated to 70 °C for 2 hours. The reaction was cooled to room temperature and concentrated to yield the crude product. The crude product was purified by chromatography (Biotage: 85% $CHCl_3$, 14% MeOH, 1% NH_4OH) to yield (R)-N-(4,5-dichloropyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.09 g, 0.27 mmol, 22 % yield) as a white powder. 1H NMR (500 MHz, *DMSO-D6*) δ ppm 8.81 (s, 1 H), 8.32 (d, *J*=6.10 Hz, 1 H), 7.03 (s, 1 H), 3.83 (d, *J*=9.46 Hz, 1 H), 3.57 (d, *J*=9.77 Hz, 1 H), 2.98 (s, 2 H), 2.71 - 2.79 (m, 2 H), 2.65 (t, *J*=7.78 Hz, 2 H), 1.99 (s, 1 H), 1.86 (s, 1 H), 1.53 - 1.61 (m, 2 H), 1.41 - 1.49 (m, 1 H). MS (LC/MS) R.T. = 0.78; $[M+H]^+$ = 327.0.

EXAMPLE 253

(R)-N-(5-Chloro-4-methylpyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

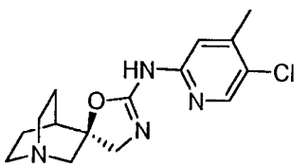


Step A: 5-Chloro-2-isothiocyanato-4-methylpyridine



To 5-chloro-4-methylpyridin-2-amine (0.41 g, 2.88 mmol) in dichloromethane (25 mL) was added 1,1'-thiocarbonyldipyridin-2(1H)-one (0.70 g, 3.0 mmol). The reaction was stirred at 40 °C for 3 hours. The reaction was cooled to room temperature. The crude mixture was purified by chromatography (Biotage: 25-100% ethyl acetate/hexane) to yield 5-chloro-2-isothiocyanato-4-methylpyridine (0.45 g, 2.44 mmol, 85 % yield). 1H NMR (500 MHz, *DMSO-D6*) δ ppm 8.45 (s, 1 H), 7.47 (s, 1 H), 2.37 (s, 3 H). LC/MS RT=2.79; $[M+H]^+$ = 184.9.

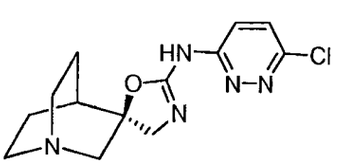
Step B: (R)-N-(5-Chloro-4-methylpyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



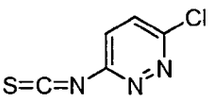
To 5-chloro-2-isothiocyanato-4-methylpyridine (0.37 g, 2.0 mmol) in N,N-dimethylformamide (20 mL) was added triethylamine (0.7 mL, 5.0 mmol) and (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (from Step B of Example 17) (0.47 g, 2.0 mmol) at room temperature. The reaction was stirred at 70 °C for 2 hours. The reaction was cooled to room temperature and concentrated *in vacuo*. The crude urea was purified by chromatography (Biotage: 85% $CHCl_3$, 14% MeOH, 1% NH_4OH). The product was then treated with N,N-dimethylformamide (20 mL) and N,N'-diisopropylcarbodiimide (0.94 mL, 6.0 mmol). The reaction was heated to 70°C for 2 hours. The reaction was cooled to room temperature and concentrated to yield the crude product. The crude product was purified by chromatography (Biotage: 85% $CHCl_3$, 14% MeOH, 1% NH_4OH) to yield (R)-N-(5-chloro-4-methylpyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.19 g, 0.61 mmol, 30.3 % yield) as a white powder. 1H NMR (500 MHz, *DMSO-D6*) δ ppm 8.79 (s, 1 H), 8.08 - 8.15 (m, 2 H), 6.78 (s, 1 H), 3.82 (d, *J*=8.55 Hz, 2 H), 3.55 (d, *J*=10.38 Hz, 2 H), 2.93 - 3.02 (m, 5 H), 2.71 - 2.80 (m, 5 H), 2.66 (t, *J*=7.63 Hz, 4 H), 2.23 - 2.29 (m, 7 H), 1.94 - 2.02 (m, 2 H), 1.92 (s, 1 H), 1.86 (s, 2 H), 1.53 - 1.62 (m, 5 H), 1.41 - 1.49 (m, *J*=12.55, 9.88, 7.02, 2.29 Hz, 2 H). MS (LC/MS) R.T. = 0.72; $[M+H]^+$ = 307.1.

EXAMPLE 254

(R)-N-(6-Chloropyridazin-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



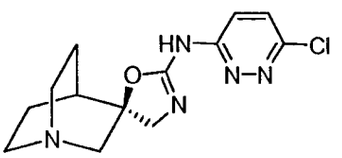
Step A: 3-Chloro-6-isothiocyanatopyridazine



3-Chloro-6-isothiocyanatopyridazine was synthesized by the method of Example 218, Step D. Flash chromatography on a 120 g silica gel cartridge with 0 to 25% EtOAc in hexane, 25 min, at 35 mL/min afforded 213 mg (31 % yield).

LCMS: RT = 1.25 min, MH+ = 172.00.

Step B : (R)-N-(6-Chloropyridazin-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



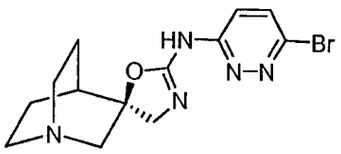
(R)-N-(6-Chloropyridazin-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was synthesized by the method of Example 218, Step E. Flash chromatography on a 160 g silica gel cartridge with 1-3 % [9:1 MeOH/NH4OH] in CHCl3, 50 min, at 40 mL/min afforded 29 mg (8 % yield).

1H NMR (400 MHz, *$CDCl_3$*) δ ppm 9.27 (1 H, br. s.), 7.28 (1 H, d, *J*=9.07 Hz), 7.10 (1 H, d, *J*=9.07 Hz), 3.95 (1 H, d, *J*=9.57 Hz), 3.62 (1 H, d, *J*=9.57 Hz), 3.34 (1 H, dd, *J*=14.98, 1.64 Hz), 2.67 - 3.04 (5 H, m), 2.14 - 2.21 (1 H, m), 2.12 (1 H, br. s.), 1.65 - 1.79 (1 H, m), 1.45 - 1.61 (2 H, m).

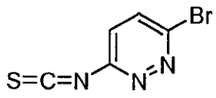
LCMS: RT = 0.62 min, MH- = 292.1, MH+ = 294.1.

EXAMPLE 255

(R)-N-(6-Bromopyridazin-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



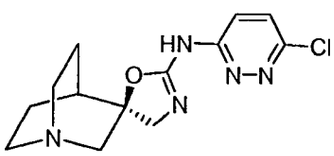
Step A: 3-Bromo-6-isothiocyanatopyridazine



3-Bromo-6-isothiocyanatopyridazine was synthesized by the method of Example 218, Step D. Flash chromatography on a 120 g silica gel cartridge with 0 to 25% EtOAc in hexane, 25 min, at 35 mL/min afforded 364 mg (42 % yield).

LCMS: RT = 1.34 min, MH+ = 215.92.

Step B : (R)-N-(6-Bromopyridazin-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



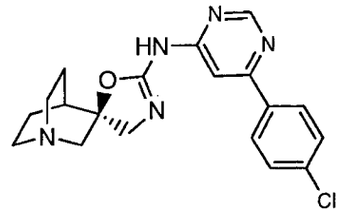
(R)-N-(6-Bromopyridazin-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was synthesized by the method of **Example 218**, Step E. Flash chromatography on a 160 g silica gel cartridge with 1-3 % [9:1 MeOH/NH4OH] in CHCl3, 50 min, at 40 mL/min afforded 211 mg (37 % yield).

1H NMR (400 MHz, $CDCl_3$) δ ppm 9.23 (1 H, br. s.), 7.37 (1 H, d, *J*=9.07 Hz), 6.97 (1 H, d, *J*=9.07 Hz), 3.92 (1 H, d, *J*=9.57 Hz), 3.59 (1 H, d, *J*=9.82 Hz), 3.29 (1 H, dd, *J*=14.98, 1.64 Hz), 2.63 - 2.99 (5 H, m), 2.04 - 2.19 (2 H, m), 1.59 - 1.74 (1 H, m), 1.39 - 1.58 (2 H, m)

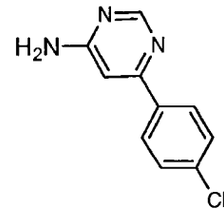
LCMS: RT= 0.64 min., MH- 336.1, MH+ 338.0.

EXAMPLE 256

(R)-N-(6-(4-Chlorophenyl)pyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

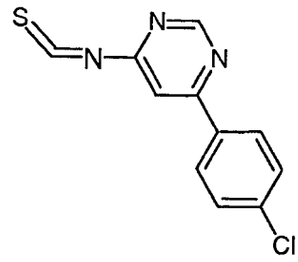


Step A: 6-(Pyridin-4-yl)pyrimidin-4-amine



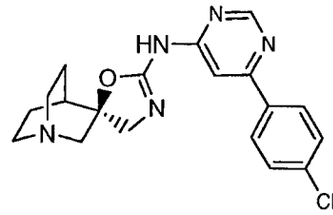
A mixture of 6-chloropyrimidin-4-amine (0.324 g, 2.5 mmol), 4-chlorophenylboronic acid (0.489 g, 3.13 mmol), Na_2CO_3 (0.795 g, 7.50 mmol) and bis(triphenylphosphine)palladium(II) chloride (0.035 g, 0.050 mmol) was suspended in a mixture of DME/EtOH/water (15:2:3 mL). The mixture was heated in the microwave synthesizer at 125 °C for 20 min and concentrated. The residue was purified by silica gel chromatography (2-15 % 9:1 methanol:ammonium hydroxide-ethyl acetate) to afford:6-(pyridin-3-yl)pyrimidin-4-amine (0.3 g, 0.871 mmol, 58.4 % yield) as an off-white solid. LCMS R.T. = 1.42; $[M+2H]^+$ = 207.91.

Step B: 4-(4-Chlorophenyl)-6-isothiocyanatopyrimidine



To a bright orange solution of 1,1'-thiocarbonyldipyridin-2(1H)-one(0.666 g, 2.87 mmol) dichloromethane/ N,N-dimethylformamide at room temperature was added 6-(4-chlorophenyl)pyrimidin-4-amine (0.59 g, 2.87 mmol). The orange mixture was heated at 60 °C for 18 hours. The LC/MS showed the desired product peak as a major peak. The deep orange mixture was purified by silica gel chromatography (0-40 % ethyl acetate-hexanes) to afford 4-(4-chlorophenyl)-6-isothiocyanatopyrimidine (0.322 g, 1.300 mmol, 45 % yield) as an orange oil. LCMS R.T. = 2.82; $[M]^+$ = 248.03.

Step C: (R)-N-(6-(4-Chlorophenyl)pyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

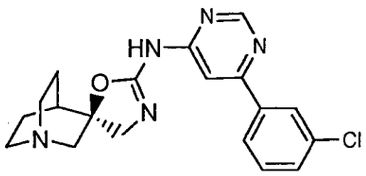


To (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (0.298 g, 1.300 mmol) in N,N-dimethylformamide (15 mL) was added Cs_2CO_3 (1.059 g, 3.25 mmol) and 4-(4-chlorophenyl)-6-isothiocyanatopyrimidine (0.322 g, 1.300 mmol). The suspension was stirred at room temperature for 30 minutes. N,N'-Diisopropylcarbodiimide (0.608 mL, 3.90 mmol) was then added and the mixture was stirred at room temperature for 18 hours. The mixture was concentrated and purified by silica gel chromatography (5-25 % 9:1 methanol:ammonium hydroxide-ethyl acetate) to afford (R)-N-(6-(pyridin-4-yl)pyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.104 g, 0.276 mmol, 21 % yield) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 9.54 (1 H, br. s.), 8.83 (1 H, d), 7.89 - 8.04 (2 H, m), 7.41 - 7.54 (2 H, m), 7.33 (1 H, br. s.), 4.02 (1 H, d),

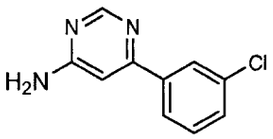
3.71 (1 H, d), 3.42 (1 H, d), 2.73 - 3.15 (5 H, m), 2.10 - 2.31 (2 H, m), 1.46 - 1.89 (3 H, m). LCMS R.T. = 1.92; $[M]^+$ = 370.35.

EXAMPLE 257

(R)-N-(6-(3-Chlorophenyl)pyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

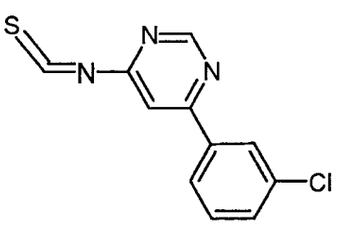


Step A: 6-(3-Chlorophenyl)pyrimidin-4-amine



A mixture of 6-chloropyrimidin-4-amine (0.324 g, 2.5 mmol), 3-chlorophenylboronic acid (0.489 g, 3.13 mmol), Na_2CO_3 (0.795 g, 7.50 mmol) and bis(triphenylphosphine)palladium(II) chloride (0.035 g, 0.050 mmol) was suspended in a mixture of DME/EtOH/wate(15:2:3 mL). The mixture was heated in the microwave synthesizer at 125 °C for 20 min and concentrated. The residue was purified by silica gel chromatography (30-70 % ethyl acetate in hexanes) to afford: 6-(3-chlorophenyl)pyrimidin-4-amine (0.47g, 2.286 mmol, 91 % yield) as a yellow solid. LCMS R.T. = 1.45; $[M+2H]^+$ = 208.05.

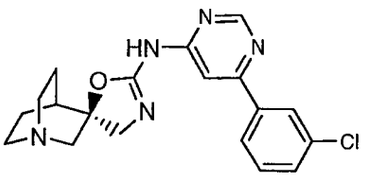
Step B: 4-(3-Chlorophenyl)-6-isothiocyanatopyrimidine



To a bright orange solution of 1,1'-thiocarbonyldipyridin-2(1H)-one(0.486 g, 2.091 mmol) in dichloromethane/ N,N-dimethylformamide at room temperature was added 6-(3-chlorophenyl)pyrimidin-4-amine (0.43 g, 2.091 mmol). The orange mixture was heated at 60 °C for 18 hours. The LC/MS showed the desired product

peak as a major peak. The deep orange mixture was purified by silica gel chromatography (0-40 % ethyl acetate-hexanes)to afford 4-(3-chlorophenyl)-6-isothiocyanatopyrimidine (0.12 g, 0.484 mmol, 23 % yield) as an orange oil. LCMS R.T. = 2.15; $[M]^+ = 248.31$.

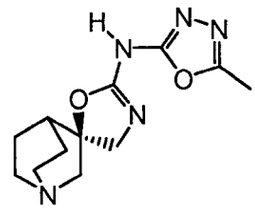
Step C: (R)-N-(6-(3-Chlorophenyl)pyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



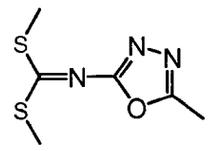
To (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (0.111 g, 0.484 mmol) in N,N-dimethylformamide (15 mL) was added Cs_2CO_3 (0.395 g, 1.211 mmol) and 4-(3-chlorophenyl)-6-isothiocyanatopyrimidine (0.12 g, 0.484 mmol). The suspension was stirred at room temperature for 30 minutes. N,N'-diisopropylcarbodiimide (0.226 mL, 1.453 mmol) was then added and the mixture was continued to stir at room temperature for 18 hours. The mixture was concentrated and purified by silica gel chromatography (5-25 %, then, 2-10 % 9:1 methanol:ammonium hydroxide-ethyl acetate) to afford (R)-N-(6-(3-chlorophenyl)pyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.086 g, 0.221 mmol, 46 % yield) as a yellow solid. ^1H NMR (400 MHz, MeOD) δ ppm 8.82 (1 H, d), 8.05 (1 H, d), 7.93 (1 H, ddd), 7.43 - 7.52 (2 H, m), 7.35 (1 H, br. s.), 4.13 (1 H, d), 3.93 (1 H, d), 3.63 - 3.81 (2 H, m), 3.42 - 3.53 (1 H, m), 3.30 - 3.40 (3 H, m), 2.46 (1 H, d), 2.26 - 2.40 (1 H, m), 1.88 - 2.16 (3 H, m). LCMS R.T. = 1.90; $[M]^+ = 370.28$.

EXAMPLE 258

(R)-N-(5-Methyl-1,3,4-oxadiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

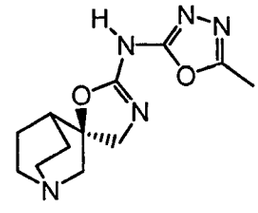


Step A: Dimethyl 5-methyl-1,3,4-oxadiazol-2-ylcarbonimidodithioate



To a solution of 5-methyl-1, 3, 4-oxadiazol-2-amine (1.92g, 20 mmol) in DMF (10ml) was added NaOH (20M, 2ml), CS_2 (3ml), NaOH (20M, 2ml) and iodomethane (3ml) slowly over 10 minutes. The mixture was stirred at room temperature for 1 h and poured into 20 ml water. The precipitated solid was filtered, washed with water, and dried to obtain the desired product, dimethyl 5-methyl-1,3,4-oxadiazol-2-ylcarbonimidodithioate as a white solid (1.45g, 35.7%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.63 (s, 6H), 2.50 (s, 3H). LCMS R.T. 1.66 min; [M+H] = 203.91.

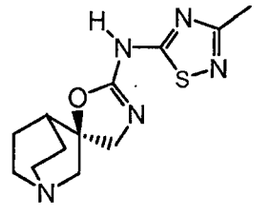
Step B: (R)-N-(5-Methyl-1,3,4-oxadiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



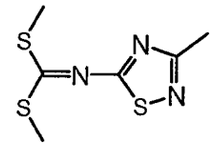
A mixture of dimethyl 5-methyl-1,3,4-oxadiazol-2-ylcarbonimidodithioate (260 mg, 1.28 mmol), (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (200 mg, 1.28 mmol) and cesium carbonate (876 mg, 2.69 mmol) in DMF (5ml) was stirred overnight at room temperature. The mixture was concentrated and purified on a Biotage silica gel column (100% ethyl acetate, then 10-35 % 9:1 methanol:ammonium hydroxide-chloroform) to obtain the desired product, (R)-N-(5-methyl-1,3,4-oxadiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (192mg, 54.1%). ^{1}H NMR (500 MHz, MeOD) δ ppm 4.05 (d, 1H), 3.74 (d, 1H), 3.25 (d, 1H), 3.15 (d, 1H), 2.94 (m, 2H), 2.85 (m, 2H), 2.43 (s, 3H), 2.19(m, 1H), 2.10 (m, 1H), 1.6-1.8 (m, 3H). MS (LCMS) [M+H] = 264.05. R.T. 0.16 min.

EXAMPLE 259

(R)-N-(3-Methyl-1,2,4-thiadiazol-5-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

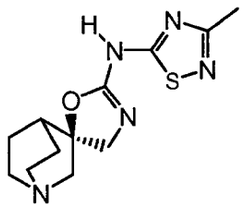


Step A: Dimethyl 3-methyl-1,2,4-thiadiazol-5-ylcarbonimidodithioate



To a solution of 3-methyl-1, 2, 4-thiadiazol-5-amine (2.3g, 20 mmol) in DMF (10ml) was added NaOH (20M, 2ml), CS_2 (3ml), NaOH (20M, 2ml) and iodomethane (3ml) slowly over 10 minutes. The mixture was stirred at room temperature for 1 h and poured into 20 ml water. The precipitated solid was filtered and washed with water, and dried to obtain impure dimethyl 3-methyl-1,2,4-thiadiazol-5-ylcarbonimidodithioate , a yellow solid (2.3 g, 52.5%). ^{1}H NMR (500 MHz, CDCl3) δ ppm 2.67 (s), 2.62 (s). MS [M+H] = 219.85.

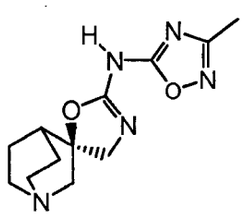
Step B: (R)-N-(3-Methyl-1,2,4-thiadiazol-5-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



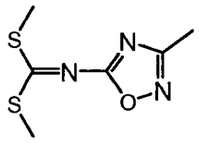
A mixture of dimethyl 3-methyl-1,2,4-thiadiazol-5-ylcarbonimidodithioate (281 mg, 1.28 mmol), (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (200 mg, 1.28 mmol) and cesium carbonate (876 mg, 2.69 mmol) in DMF (5 ml) was stirred overnight at room temperature. The mixture was concentrated and purified on a Biotage silica gel column (100% ethyl acetate, then 10-35 % 9:1 methanol:ammonium hydroxide-chloroform) to obtain the desired product, (R)-N-(3-methyl-1,2,4-thiadiazol-5-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (147.8 mg, 40.5%). ^{1}H NMR (500 MHz, MeOD) δ ppm 4.01-3.99 (d, 1H), 3.72-3.70 (d, 1H), 3.27 (d, 1H), 3.16 (d, 1H), 3.01-2.9 (m, 2H), 2.86-2.83 (m, 2H), 2.43 (s, 3H), 2.21-2.0(m, 2H), 1.81-1.75(m, 1H), 1.75-1.70 (m, 2H). MS (LCMS) [M+H] = 279.99; R.T. = 0.2 min.

EXAMPLE 260

(R)-N-(3-Methyl-1,2,4-oxadiazol-5-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

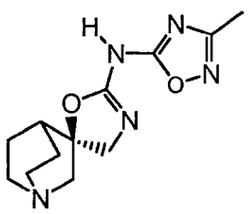


Step A: Dimethyl 3-methyl-1,2,4-oxadiazol-5-ylcarbonimidodithioate



To a solution of 3-methyl-1, 2, 4-oxadiazol-5-amine (490 mg, 4.94mmol) in DMF (5ml) was added NaOH (20M, 0.5ml), CS_2 (1ml), NaOH (20M, 0.5ml) and iodomethane (1ml) slowly over 10 minutes. The mixture was stirred at room temperature for 1 hour. The mixture became very thick, and 20 ml water was added. The solid was filtered off, washed with water, and dried to obtain impure dimethyl 3-methyl-1,2,4-oxadiazol-5-ylcarbonimidodithioate, a yellow solid (770 mg, 77%). MS (LCMS) [M+H] = 203.91; R.T. = 1.84 min. The product was used directly in the next step.

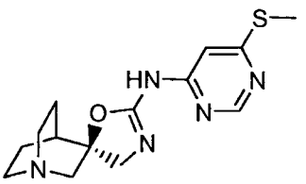
Step B: (R)-N-(3-Methyl-1,2,4-oxadiazol-5-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



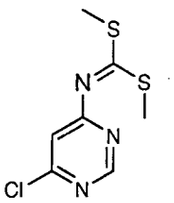
A mixture of dimethyl 3-methyl-1,2,4-oxadiazol-5-ylcarbonimidodithioate (280 mg, 1.37 mmol), (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (215 mg, 1.37 mmol) and cesium carbonate (942 mg, 2.89 mmol) in DMF (5ml) was stirred overnight at room temperature. The mixture was concentrated and purified on a Biotage silica gel column (100% ethyl acetate, then 10-35 % 9:1 methanol:ammonium hydroxide-chloroform) to obtain the desired product, (R)-N-(3-methyl-1,2,4-oxadiazol-5-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (198 mg, 51.9%). ^{1}H NMR (500 MHz, MeOD) δ ppm 4.1-4.0 (d, 1H), 3.8-3.7 (d, 1H), 3.4-3.2 (d, 1H), 3.2-3.1 (d, 1H), 3.0-2.9 (m, 2H), 2.9-2.8 (m, 2H), 2.27 (s, 3H), 2.2 (m, 1H), 2.2-2.0 (m, 1H), 1.9-1.6 (m, 3H). MS (LCMS) [M+H] = 264.05; R.T. = 0.26 min.

EXAMPLE 261

(R)-N-(6-(Methylthio)pyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

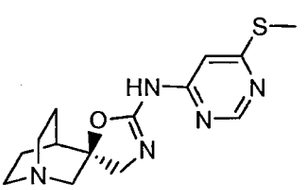


Step A: Dimethyl 6-chloropyrimidin-4-ylcarbonimidodithioate



To a solution of 6-chloropyrimidin-4-amine (1.295 g, 10 mmol) in N,N-dimethylformamide (12 mL) was added dropwise NaOH (1 mL, 20.00 mmol, 20 M), CS2 (1.5 mL, 24.88 mmol), NaOH (1 mL, 20.00 mmol, 20 M) and iodomethane (1.5 mL, 23.99 mmol) at 15 min intervals. Stirring was continued for 1.5 h and the mixture was poured into water. The orange solid was separated washed with water, dried and recrystallised from methanol to afford dimethyl 6-chloropyrimidin-4-ylcarbonimidodithioate (0.966 g, 4.13 mmol, 41.3 % yield) as a yellow solid. LCMS R.T. = 2.39; $[M+H]^+$ = 234.08.

Step B: (R)-N-(6-(Methylthio)pyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

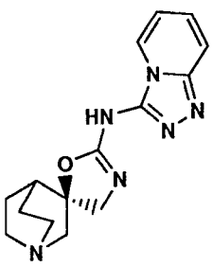


To (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (0.9 g, 3.93 mmol) in N,N-dimethylformamide (20 mL) was added Cs_2CO_3 (2.69 g, 8.25 mmol) and dimethyl 6-chloropyrimidin-4-ylcarbonimidodithioate (0.964 g, 4.12 mmol). The suspension was stirred at room temperature for 18 hours, then heated at 100 C for 3

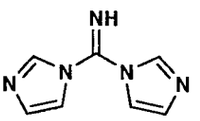
hours. The mixture was concentrated and purified by silica gel chromatography (5-15 % 9:1 methanol:ammonium hydroxide-ethyl acetate) to afford (R)-N-(6-(methylthio)pyrimidin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.21 g, 0.72 mmol, 48.2% yield) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.43 (1 H, br. s.), 8.55 (1 H, d), 6.78 (1 H, br. s.), 3.98 (1 H, d), 3.64 (1 H, d), 3.37 (1 H, dd), 2.72 - 3.06 (5 H, m), 2.51 (3 H, s), 2.08 - 2.24 (2 H, m), 1.69 - 1.81 (1 H, m), 1.41 - 1.64 (2 H, m). LCMS R.T. = 0.93; $[M+H]^+$ = 306.29.

EXAMPLE 262

(R)-N-([1,2,4]Triazol[4,3-a]pyridine-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

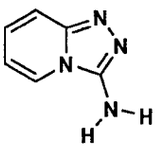


Step A: Di(1H-imidazol-1-yl)methanimine



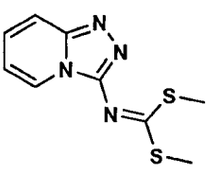
To a solution of 1H-imidazole (42g, 617mmol) in dichloromethane (1L) was added cyanogen bromide (22.5, 212 mmol) and the mixture was heated to reflux for 30 minutes, allowed to cool to room temperature and the white solid was filtered off. The filtrate was concentrated to 100ml and stored in the refrigerator for 3 days. The precipitated solid was filtered off to obtain 8g di(1H-imidazol-1-yl)methanimine (49.6mmol, 8%). ^{1}H NMR (500 MHz, DMSO) δ ppm 8.09 (s, 1H), 7.55 (s, 1H), 7.13 (s, 1H).

Step B: [1, 2, 4]Triazolo[4,3-a]pyridine-3-amine



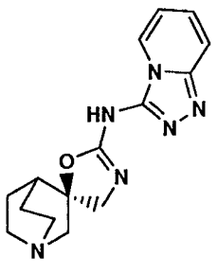
To a solution of 2-hydrazinylpyridine (5.2g, 47.6 mmol) in THF (70ml) was added di(1H-imidazol-1-yl)methanimine (7.8g, 48.4mmol). The mixture was heated to reflux overnight. The crude mixture was evaporated and purified on a Biotage silica gel column (0-25%, methanol-methylene chloride) collecting the purple-colored spot, [1, 2, 4]triazolo[4,3-a]pyridine-3-amine (4.7g, 35mmol, 73.5%). ^{1}H NMR (500 MHz, DMSO) δ ppm 8.05-8.0 (m, 1H), 7.44-7.40 (m, 1H), 7.08-7.0 (m, 1H), 6.74-6.70 (m, 1H), 6.35 (s, 2H). MS (LCMS) [M+H] = 134.98; R.T. = 0.1 min.

Step C: Dimethyl [1, 2, 4]triazol[4,3-a]pyridine-3-ylcarbonimidodithioate



To a solution of [1, 2, 4]triazolo[4,3-a]pyridine-3-amine (300 mg, 2.24mmol) in DMF (5ml) was added NaOH (20M, 0.25ml), CS_2 (0.5ml), NaOH (20M, 0.25ml) and iodomethane (0.5ml) slowly over 10 minutes. The mixture was stirred at room temperature for 1 h and 10ml water was added to the reaction mixture. The precipitated solid was filtered off, washed with water (100ml), and dried to obtain 230 mg dimethyl [1, 2, 4]triazol[4,3-a]pyridine-3-ylcarbonimidodithioate (0.96 mmol, 43.1%), a white solid. ^{1}H NMR (500 MHz, CDCl3) δ ppm 8.17 (d, 1H), 7.7 (d, 1H), 7.24-7.22 (t, 1H), 6.84-6.80 (t, 1H), 2.71-2.68 (d, 6H). MS (LCMS) [M+H] = 238.94; R.T. = 1.26 min.

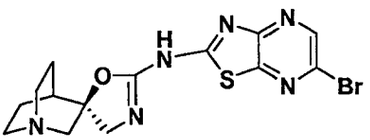
Step D: (R)-N-([1,2,4]Triazol[4,3-a]pyridine-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



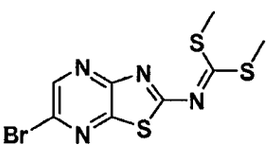
A mixture of dimethyl [1, 2, 4]triazol[4,3-a]pyridine-3-ylcarbonimidothioate (120 mg, 0.50 mmol), (S)-3-(aminomcthyl)quinuclidin-3-ol dihydrochloridc (120 mg, 0.76 mmol) and cesium carbonate (492 mg, 1.5 mmol) in DMF (5ml) was heated at 70 °C for 6 hours. The mixture was concentrated and purified on a Biotage silica gel column (100% ethyl acetate, then 10-35 % 9:1 methanol:ammonium hydroxide-chloroform) to obtain the desired product, (R)-N-([1,2,4]triazol[4,3-a]pyridine-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (97.2 mg, 61.5%). ^{1}H NMR (500 MHz, CDCl3) δ ppm 8.2-8.1 (d, 1H), 7.6-7.5 (d, 1H), 7.2-7.1 (t, 1H), 6.7-6.6 (t, 1H), 4.1-4.0 (d, 1H), 3.7-3.6 (d, 1H), 3.5-3.4 (m, 1H), 3.1-2.7 (m, 5H), 2.4-2.2 (m, 2H), 1.8-1.7 (m, 1H), 1.7-1.5(m, 2H). MS (LCMS) [M+H] = 299.3; R.T. = 1.22 min.

EXAMPLE 263

(R)-N-(6-bromothiazolo[5,4-b]pyrazin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

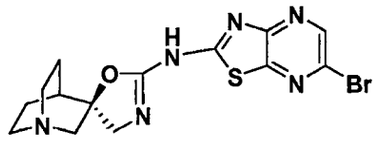


Step A: Dimethyl 6-bromothiazolo[5,4-b]pyrazin-2-ylcarbonimidodithioate



To a suspension of 6-bromothiazolo[5,4-b]pyrazin-2-amine (700 mg, 3.03 mmol) in DMF (3 mL) was added 16.0M sodium hydroxide (400 µL, 6.40 mmol). The mixture was allowed to stir 10 min at room temperature at which time carbon disulfide was added (450 µL, 7.57 mmol) and the resulting reddish brown mixture was stirred for 10 minutes. An additional portion of 16.0M sodium hydroxide (400 µL, 6.40 mmol) was added and the mixture was again stirred for 10 minutes. Finally, iodomethane (450 µL, 7.27 mmol) was added dropwise. The mixture was stirred for 5 minutes, at which time a voluminous yellow precipitate had formed. The mixture was poured into water and the solids were collected by filtration to afford dimethyl 6-bromothiazolo[5,4-b]pyrazin-2-ylcarbonimidodithioate (680 mg, 67% yield) as a yellow solid of sufficient purity to use without further purification. 1H NMR (400 MHz, $CDCl_3$) δ ppm 8.63 (s, 1 H) 2.68 (s, 6 H).

Step B: (R)-N-(6-bromothiazolo[5,4-b]pyrazin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

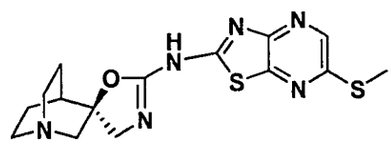


A mixture of dimethyl 6-bromothiazolo[5,4-b]pyrazin-2-ylcarbonimidodithioate (300 mg, 0.895 mmol), (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (210 mg, 0.895 mmol) and cesium carbonate (600 mg, 1.79 mmol) in acetonitrile (25 mL) was heated on a 100 °C oil bath for 2 hours in an open flask, with nitrogen bubbling through the solution the entire time to help in the removal of methanethiol. After 2 hours, TLC showed the reaction to be complete, so the mixture was cooled to ambient temperature, diluted with water and concentrated *in vacuo*. The mixture was extracted with chloroform (4x). The combined organics were washed with brine, dried over sodium sulfate, filtered , concentrated *in vacuo*, and the crude residue was purified by silica gel chromatography (2-40 % 9:1 methanol:ammonium hydroxide-chloroform). The product fractions were combined

and concentrated *in vacuo* to afford (R)-N-(6-bromothiazolo[5,4-b]pyrazin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (200 mg, 57% yield). 1H NMR (400 MHz, $CDCl_3$) δ ppm 9.39 (br. s., 1 H) 8.48 (s, 1 H) 4.05 (d, *J*=9.79 Hz, 1 H) 3.72 (d, *J*=9.79 Hz, 1 H) 3.42 (dd, *J*=15.06, 1.76 Hz, 1 H) 2.73 - 3.08 (m, 5 H) 2.10 - 2.22 (m, 2 H) 1.73 - 1.84 (m, *J*=14.09, 9.94, 4.17, 4.17 Hz, 1 H) 1.52 - 1.65 (m, 2 H). MS (LC/MS) R.T. = 1.29; $[M+H]^+$ = 394.99.

EXAMPLE 264

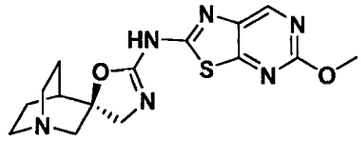
(R)-N-(6-(methylthio)thiazolo[5,4-b]pyrazin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



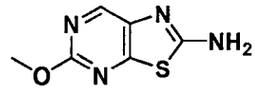
A mixture of dimethyl 6-bromothiazolo[5,4-b]pyrazin-2-ylcarbonimidodithioate from **Step A of Example 263** (100 mg, 0.298 mmol), (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (68 mg, 0.298 mmol) and cesium carbonate (100 mg, 0.60 mmol) in DMF (1.5 mL) was placed in a 1 dram vial and heated on a 100 °C oil bath for 1 hour, at which time, sodium thiomethoxide (100 mg, 1.43 mmol) was added and the mixture was heated overnight. The mixture was cooled to ambient temperature and poured into water (20 mL) and the resulting solids were collected by filtration and then purified by silica gel chromatography (2-40 % 9:1 methanol:ammonium hydroxide-chloroform). The product fractions were combined and concentrated *in vacuo* to afford (R)-N-(6-(methylthio)thiazolo[5,4-b]pyrazin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (52 mg, 46% yield). 1H NMR (500 MHz, $CDCl_3$) δ ppm 9.39 (br. s., 1 H) 8.31 (s, 1 H) 4.03 (d, *J*=9.77 Hz, 1 H) 3.70 (d, *J*=9.77 Hz, 1 H) 3.41 (dd, *J*=14.95, 1.83 Hz, 1 H) 2.73 - 3.10 (m, 5 H) 2.63 (s, 3 H) 2.10 - 2.25 (m, 2 H) 1.47 - 1.86 (m, 3 H). MS (LC/MS) R.T. = 1.04; $[M+H]^+$ = 363.04.

EXAMPLE 265

(R)-N-(5-Methoxythiazolo[5,4-d]pyrimidin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

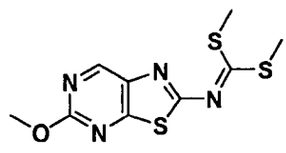


Step A: 5-Methoxythiazolo[5,4-d]pyrimidin-2-amine



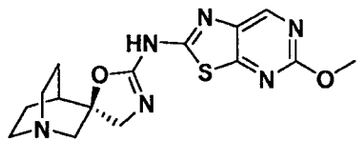
Ethyl 5-chlorothiazolo[5,4-d]pyrimidin-2-ylcarbamate (250 mg, 0.966 mmol) was suspended in MeOH (10 mL) and a 25% (w/w) solution of sodium methoxide in methanol was added (10 mL, 46.3 mmol). The resulting solution was refluxed overnight, cooled to ambient temperature, poured into an equal volume of water and extracted with chloroform (4x). A signifincant amount of compound was still present in the aqueous phase, so this was concentrated to residue, and then dissolved in a small amount of 1N HCl (not enough to make the resulting solution acidic) and extracted again with EtOAc (5x). The combined organics were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. 5-Methoxythiazolo[5,4-d]pyrimidin-2-amine (144mg, 0.790 mmol, 82 % yield) was thus obtained as a white solid. 1H NMR (400 MHz, DMSO-d_6) δ ppm 8.43 (s, 1 H) 7.81 (s, 2 H) 3.90 (s, 3 H). MS (LC/MS) R.T. = 0.73; $[M+H]^+$ = 183.03.

Step B: Dimethyl 5-methoxythiazolo[5,4-d]pyrimidin-2-ylcarbonimidodithioate



To a suspension of 5-methoxythiazolo[5,4-d]pyrimidin-2-amine (911 mg, 5.00 mmol) in DMF (5 mL) was added 20.0M sodium hydroxide (500 μL, 10.00 mmol). The mixture was allowed to stir 10 min at room temperature at which time carbon disulfide was added (750 μL, 12.50 mmol) and the resulting reddish brown mixture was stirred for 10 minutes. An additional portion of 20.0M sodium hydroxide (500 μL, 10.00 mmol) was added and the mixture was again stirred for 10 minutes. Finally, iodomethane (750 μL, 12.00mmol) was added dropwise. The mixture was stirred for 5 minutes, at which time a voluminous yellow precipitate had formed. The mixture was poured into water and the solids were collected by filtration to afford a yellow solid that was further purified by silica gel chromatography (2-20% EtOAc/$CHCl_3$) to provide dimethyl 5-methoxythiazolo[5,4-d]pyrimidin-2-ylcarbonimidodithioate (380 mg, 27% yield).
1H NMR (400 MHz, $CDCl_3$) δ ppm 8.90 (s, 1 H) 4.09 (s, 3 H) 2.66 (s, 6 H).

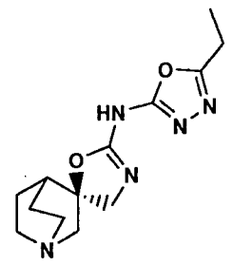
Step C: (R)-N-(5-methoxythiazolo[5,4-d]pyrimidin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



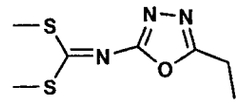
A mixture of dimethyl 5-methoxythiazolo[5,4-d]pyrimidin-2-ylcarbonimidodithioate (100 mg, 0.349 mmol), (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (80mg, 0.349 mmol) and cesium carbonate (228mg, 0.698 mmol) in DMF (1.7 mL) was heated to 100 °C for 2 hours. The reaction mixture was cooled to ambient temperature, poured into water and the solids were collected by filtration to afford (R)-N-(5-methoxythiazolo[5,4-d]pyrimidin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (78 mg, 64% yield). 1H NMR (500 MHz, $CDCl_3$) δ ppm 9.12 (br. s., 1 H) 8.63 (s, 1 H) 3.95 - 4.18 (m, 4 H) 3.71 (d, *J*=9.77 Hz, 1 H) 3.41 (d, *J*=15.26 Hz, 1 H) 2.74 - 3.10 (m, 5 H) 2.11 - 2.27 (m, 2 H) 1.71 - 1.86 (m, 1 H) 1.50 - 1.70 (m, 2 H). MS (LC/MS) R.T. = 1.66; $[M+H]^+$ = 347.0.

EXAMPLE 266

(R)-N-(5-Ethyl-1,3,4-oxadiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

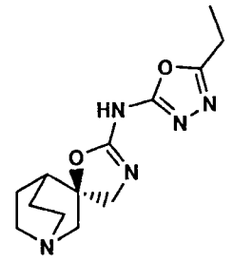


Step A: Dimethyl 5-ethyl-1,3,4-oxadiazol-2-ylcarbonimidodithioate



To a solution of 5-ethyl-1, 3, 4-oxadiazol-2-amine (2.26g, 20 mmol) in DMF (10ml) was added NaOH (20M, 2ml), CS_2 (3ml), NaOH (20M, 2ml) and iodomethane (3ml) slowly over 10 minutes. The mixture was stirred at room temperature for 2 h and poured into 30 ml water. The precipitated yellow solid was filtered off, washed with water, and dried to obtain the desired product, dimethyl 5-ethyl-1,3,4-oxadiazol-2-ylcarbonimidodithioate, a white solid (2.6 g, 59.8%). ^{1}H NMR (500 MHz, CDCl3) δ ppm 2.86-2.83 (q, 2H), 2.63 (s, 6H), 1.3901.35 (t, 3H). MS (LCMS) [M+H] = 217.95; R.T. = 1.93 min.

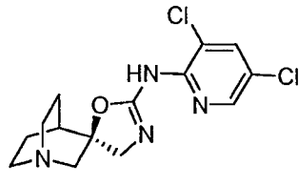
Step B: (R)-N-(5-Ethyl-1,3,4-oxadiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



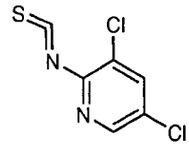
A mixture of dimethyl 5-ethyl-1,3,4-oxadiazol-2-ylcarbonimidodithioate (327 mg, 1.5 mmol), (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (235 mg, 1.5 mmol) and cesium carbonate (1000 mg, 3.16 mmol) in DMF (10ml) was stirred overnight at room temperature. The mixture was concentrated and purified on a Biotage silica gel column (100% ethyl acetate, then 10-35 % 9:1 methanol:ammonium hydroxide-chloroform) to obtain the desired product, (R)-N-(5-ethyl-1,3,4-oxadiazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (290mg, 66%). ^{1}H NMR (500 MHz, MeOD) δ ppm 4.05 (d, 1H), 3.74 (d, 1H), 3.3-3.2 (d, 1H), 3.2-3.1(d, 1H), 3.0-2.9(m, 2H), 2.9-2.8 (m, 5H), 2.2 (s, 1H), 2.15-2.0 (m, 1H), 1.9-1.6 (m, 3H), 1.4-1.3 (t, 3H). (m, 2H). MS (LCMS) [M+H] = 278.09; R.T. = 0.48 min.

EXAMPLE 267

(R)-N-(3,5-Dichloropyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

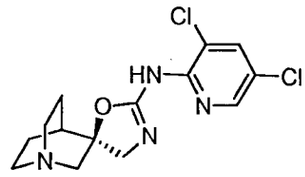


Step A: 3,5-Dichloro-2-isothiocyanatopyridine



To 3,5-dichloropyridin-2-amine (0.36 g, 2.209 mmol) in dichloromethane (25 mL) was added 1,1'-thiocarbonyldipyridin-2(1H)-one (0.523 g, 2.253 mmol). The reaction was stirred at 40 °C for 3 hours. The reaction was cooled to room temperature and the crude was purified by chromatography (Biotage: 25-100% ethyl acetate/hexane) to yield to yield 3,5-dichloro-2-isothiocyanatopyridine (0.4 g, 1.951 mmol, 88 % yield). 1H NMR (500 MHz, *DMSO-D6*) δ ppm 8.50 (t, *J*=2.59 Hz, 1 H), 8.45 (t, *J*=2.59 Hz, 1 H). MS (LC/MS) R.T. = 2.07; $[M+H]^+$ = 204.8.

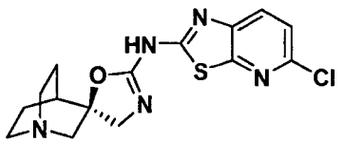
Step B: (R)-N-(3,5-Dichloropyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



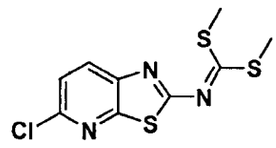
To 3,5-dichloro-2-isothiocyanatopyridine (0.11 g, 0.55 mmol) in N,N-dimethylformamide (10 mL) was added Et_3N (0.17 mL, 1.21 mmol) and (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (0.13 g, 0.56 mmol) at room temperature. The reaction was stirred at 70 °C for 2 hours. The reaction was cooled to room temperature and concentrated *in vacuo*. The crude urea was purified by chromatography (Biotage: 85% $CHCl_3$, 14% MeOH, 1% NH_4OH). The product was then treated with N,N-dimethylformamide (10 mL) and N, N'-diisopropylcarbodiimide (0.26 mL, 1.65 mmol). The reaction was heated to 70°C for 2 hours. The reaction was cooled to room temperature and concentrated *in vacuo* to yield the crude product. The crude product was purified by chromatography (Biotage: 85% $CHCl_3$, 14% MeOH, 1% NH_4OH) to yield (R)-N-(3, 5-dichloropyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.08 g, 0.24 mmol, 44 % yield) as a white powder. 1H NMR (500 MHz, *DMSO-D6*) δ ppm 8.91 (s, 1 H), 8.11 - 8.17 (m, 1 H), 7.97 (d, *J*=2.44 Hz, 1 H), 3.84 (d, *J*=9.77 Hz, 1 H), 3.59 (d, *J*=9.77 Hz, 1 H), 2.95 - 3.04 (m, 2 H), 2.72 - 2.81 (m, 2 H), 2.66 (t, *J*=7.63 Hz, 2 H), 2.01 (s, 1 H), 1.89 (s, 1 H), 1.54 - 1.62 (m, 2 H), 1.42 - 1.50 (m, 1 H). MS (LC/MS) R.T. = 0.78; $[M+]^+$ = 326.1.

EXAMPLE 268

(R)-N-(5-chlorothiazolo[5,4-b]pyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3' bicyclo[2.2.2]octan]-2-amine

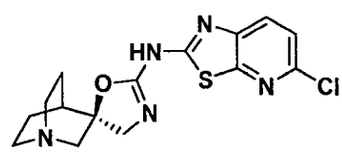


Step A: Dimethyl 5-chlorothiazolo[5,4-b]pyridin-2-ylcarbonimidodithioate



To a suspension of 5-chlorothiazolo[5,4-b]pyridin-2-amine (930 mg, 5.00 mmol) in DMF (5 mL) was added 20.0M sodium hydroxide (500 μL, 10.00 mmol). The mixture was allowed to stir 10 min at room temperature at which time carbon disulfide was added (750 μL, 12.50 mmol) and the mixture was stirred for 10 minutes. An additional portion of 20.0M sodium hydroxide (500 μL, 10.0 mmol) was added and the mixture was again stirred for 10 minutes. Finally, iodomethane (750 μL, 12.00 mmol) was added dropwise. An exotherm was noticed during this addition. The mixture was stirred for 15 minutes, at which time a voluminous precipitate had formed. The mixture was poured into water and the solids were collected by filtration. Most of the collected solids were pale yellow and crystalline. A few small clumps of a slightly darker gummy orange solid were also present, and these were manually removed and discarded. The remainder was the title compound, dimethyl 5-chlorothiazolo[5,4-b]pyridin-2-ylcarbonimidodithioate (1.00g, 69% yield). 1H NMR (400 MHz, $CDCl_3$) δ ppm 8.04 (d, *J*=8.53 Hz, 1 H) 7.38 (d, *J*=8.53 Hz, 1 H) 2.66 (s, 6 H).

Step B: (R)-N-(5-chlorothiazolo[5,4-b]pyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3' bicyclo[2.2.2]octan]-2-amine

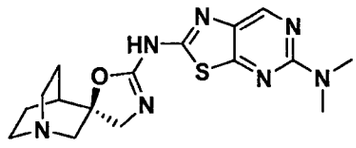


A mixture of dimethyl 5-chlorothiazolo[5,4-b]pyridin-2-ylcarbonimidodithioate (100 mg, 0.35 mmol), (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (79mg, 0.35mmol) and cesium carbonate (225mg, 0.69mmol) in DMF (1.7 mL) was heated to 100 °C for 2 hours. The reaction mixture was cooled to ambient temperature, poured into water and the solids collected by filtration. The

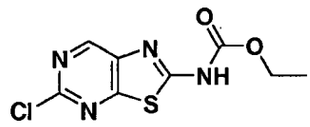
crude solids were purified by silica gel chromatography (2-40 % 9:1 methanol:ammonium hydroxide-chloroform) to afford (R)-N-(5-chlorothiazolo[5,4-b]pyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3' bicyclo[2.2.2]octan]-2-amine (62mg, 51% yield). 1H NMR (400 MHz, DMSO-d_6) δ ppm 9.13 (br. s., 1 H) 7.93 (d, J=8.53 Hz, 1 H) 7.45 (d, J=8.28 Hz, 1 H) 3.92 (d, J=10.29 Hz, 1 H) 3.67 (d, J=10.29 Hz, 1 H) 3.00 - 3.14 (m, 2 H) 2.77 - 2.93 (m, 2 H) 2.69 (t, J=7.65 Hz, 2 H) 2.12 (br. s., 1 H) 1.95 (br. s., 1 H) 1.43 - 1.72 (m, 3 H). MS (LC/MS) R.T. = 1.10; $[M+H]^+$ = 350.10.

EXAMPLE 269

(R)-N^5,N^5-dimethyl-N^2-(4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octane]-2-yl)thiazolo[5,4-d]pyrimidine-2,5-diamine

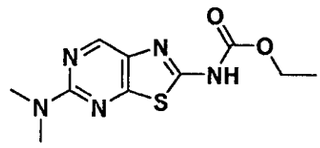


Step A: Ethyl 5-chlorothiazolo[5,4-d]pyrimidin-2-ylcarbamate



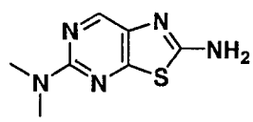
Ethoxycarbonyl isothiocyanate (4.32 mL, 36.6mmol) and 2,4-dichloro-pyrimidin-5-ylamine (3.00 g, 18.29 mmol) were mixed neat and sonicated for 5 minutes to help dissolve. The mixture was stirred at ambient temperature for 10 minutes, at which time the entire mixture had solidified. Methanol (100 mL) was added and the mixture was refluxed for 30 minutes, cooled to ambient temperature and the solids were collected by filtration to afford ethyl 5-chlorothiazolo[5,4-d]pyrimidin-2-ylcarbamate (3.8g, 80% yield). 1H NMR (400 MHz, DMSO-d_6) δ ppm 12.64 (s, 1 H) 9.05 (s, 1 H) 4.31 (q, J=7.19 Hz, 2 H) 1.32 (t, J=7.15 Hz, 3 H).

Step B: Ethyl 5-(dimethylamino)thiazolo[5,4-d]pyrimidin-2-ylcarbamate



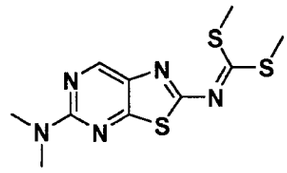
Ethyl 5-chlorothiazolo[5,4-d]pyrimidin-2-ylcarbamate (300 mg, 1.16 mmol) was suspended in a 2.0 M solution of dimethylamine in methanol (5.0 mL, 10.00 mmol) in a pressure vessel, which was sealed and heated overnight on a 75 °C oil bath. The mixture was cooled to ambient temperature, the solvent was evaporated and the residue was partitioned between aqueous bicarbonate and chloroform and extracted 3 times. The combined organics were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford ethyl 5-(dimethylamino)thiazolo[5,4-d]pyrimidin-2-ylcarbamate (236 mg, 99% yield). 1H NMR (400 MHz, DMSO-d_6) δ ppm 11.97 (s, 1 H) 8.67 (s, 1 H) 4.26 (q, *J*=7.03 Hz, 2 H) 3.17 (s, 6 H) 1.16 - 1.40 (m, 3 H). MS (LC/MS) R.T. = 1.88; $[M+H]^+$ = 268.09.

Step C: Ethyl N^5,N^5-dimethylthiazolo[5,4-d]pyrimidine-2,5-diamine



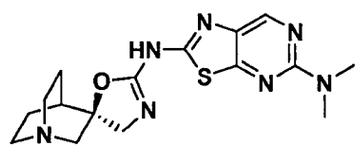
Ethyl 5-(dimethylamino)thiazolo[5,4-d]pyrimidin-2-ylcarbamate (236mg, 0.88 mmol) was suspended in a 25% (w/w) solution of sodium methoxide in methanol (5 mL, 23.0 mmol) and the mixture was heated to reflux overnight. The reaction mixture was evaporated to dryness and the residue was partitioned between water and chloroform and extracted 3 times. The combined organics were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford ethyl N^5,N^5-dimethylthiazolo[5,4-d]pyrimidine-2,5-diamine (170 mg, 99% yield) as a white solid. 1H NMR (400 MHz, DMSO-d_6) δ ppm 8.27 (s, 1 H) 7.44 (s, 2 H) 3.10 (s, 6 H).

Step D: Dimethyl 5-(dimethylamino)thiazolo[5,4-d]pyrimidin-2-ylcarbonimidodithioate



To a suspension of ethyl N^5,N^5-dimethylthiazolo[5,4-d]pyrimidine-2,5-diamine (160 mg, 0.819 mmol) in DMF (1 mL) was added 20.0 M sodium hydroxide (100 μL, 2.00 mmol). The mixture was allowed to stir 10 min at room temperature at which time carbon disulfide was added (120 μL, 2 mmol) and the resulting reddish brown mixture was stirred for 10 minutes. An additional portion of 20.0 M sodium hydroxide (100 μL, 2.0 mmol) was added and the mixture was again stirred for 10 minutes. Finally, iodomethane (120 μL, 1.9 mmol) was added dropwise. The mixture was stirred for 5 minutes, at which time a voluminous yellow precipitate had formed. The mixture was poured into water and the solids were collected by filtration to afford dimethyl 5-(dimethylamino)thiazolo[5,4-d]pyrimidin-2-ylcarbonimidodithioate (194 mg, 79% yield). 1H NMR (400 MHz, $CDCl_3$) δ ppm 8.75 (s, 1 H) 3.26 (s, 6 H) 2.64 (s, 6 H).

Step E: (R)-N^5,N^5-dimethyl-N^2-(4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octane]-2-yl)thiazolo[5,4-d]pyrimidine-2,5-diamine

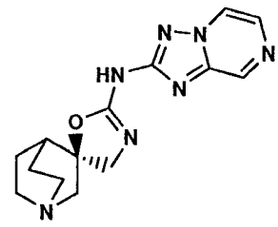


A mixture of dimethyl 5-(dimethylamino)thiazolo[5,4-d]pyrimidin-2-ylcarbonimidodithioate (90 mg, 0.301 mmol), (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (83mg, 0.361 mmol) and cesium carbonate (196 mg, 0.60 mmol) in DMF (1.0 mL) was heated to 100 °C for 1.5 hours. The reaction mixture was cooled to ambient temperature, poured into water and extracted with chloroform (4x). The

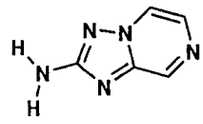
combined organics were washed with brine, dried over sodium sulfate, filtered , concentrated *in vacuo* , and the crude residue was purified by silica gel chromatography (2-40 % 9:1 methanol:ammonium hydroxide-chloroform) to afford (R)-N^5,N^5-dimethyl-N^2-(4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octane]-2-yl)thiazolo[5,4-d]pyrimidine-2,5-diamine (81 mg, 71% yield) as a tan solid. 1H NMR (400 MHz, $CDCl_3$) δ ppm 9.07 (br. s., 1 H) 8.50 (s, 1 H) 4.01 (d, *J*=9.54 Hz, 1 H) 3.67 (d, *J*=9.54 Hz, 1 H) 3.39 (dd, *J*=14.93, 1.63 Hz, 1 H) 3.23 (s, 6 H) 2.71 - 3.10 (m, 5 H) 2.10 - 2.24 (m, 2 H) 1.68 - 1.84 (m, 1 H) 1.46 - 1.68 (m, 2 H). MS (LC/MS) R.T. = 0.87; $[M+H]^+$ = 360.23.

EXAMPLE 270

(R)-N-([1,2,4]Triazol[1,5-a]pyrazin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



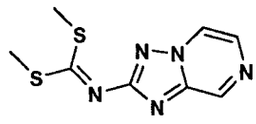
Step A: [1, 2, 4]Triazolo[1,5-a]pyrazin-2-amine



To a solution of pyrazin-2-amine (25 g, 260 mmol) in dioxane (300 ml) at room temperature was added ethoxycarbonyl-isothiocyanate (37. 9g, 289 mmol) slowly. The mixture was stirred for 18 hours and the solvent was evaporated under vacuum. The residual solid was dissolved in a mixture of methanol (150 ml) and ethanol (150 ml). To this solution was added TEA (109 ml, 780 mmol) and hydroxylamine hydrochloride (72.5g, 1040 mmol). The mixture was stirred at room temperature for 2 hours and was heated to reflux for 4 hours. The crude mixture was cooled to room temperature and the solvent was evaporated. The residual solid was

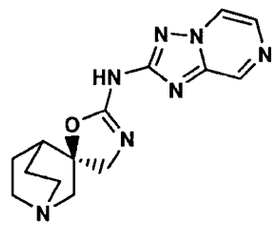
purified by column chromatography (0-20% methanol/CH_2Cl_2) to obtain a white solid (60g). The solid was taken into EtOAc and water. The aqueous layer was extracted with EtOAc twice. The combined organic layer was washed with brine and dried over sodium sulfate to obtain [1, 2, 4]triazolo[1,5-a]pyrazin-2-amine as a white solid (12g, 88mmol, 33%). MS (LCMS) [M+H] = 135.96; R.T. = 0.21 min.

Step B: Dimethyl [1, 2, 4]triazol[1,5-a]pyrazin-2-ylcarbonimidodithioate



To a solution of [1, 2, 4]triazolo[1,5-a]pyrazin-2-amine (676 mg, 5 mmol) in DMF (10 ml) was added NaOH (20 M, 0.5 ml), CS_2 (1 ml), NaOH (20 M, 0.5 ml) and iodomethane (1 ml) slowly over 10 minutes. The mixture was stirred at room temperature for 1 h and 10 ml water was added to the reaction mixture, which became cloudy. The mixture was extracted with EtOAc (100ml x 3). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and evaporated. The residue was purified on a Biotage silica gel column (ethyl acetate-hexane 10-30%) to obtain dimethyl [1, 2, 4]triazol[1,5-a]pyrazin-2-ylcarbonimidodithioate as a yellow solid (720mg, 3mmol, 60%). ^{1}H NMR (500 MHz, CDCl3) δ ppm 9.2 (2, 1H), 8.5 (d, 1H), 8.2 (d, 1H), 2.67 (s, 6H). MS (LCMS) [M+H] = 239.92. [M+Na] = 261.89; R.T. = 1.55 min.

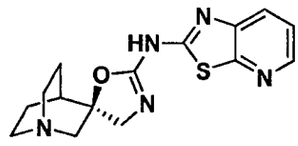
Step C: (R)-N-([1,2,4]Triazol[1,5-a]pyrazin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



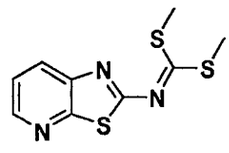
A mixture of dimethyl [1, 2, 4]triazol[1,5-a]pyrazin-2-ylcarbonimidodithioate (120 mg, 0.50 mmol), (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (120 mg, 0.76 mmol) and cesium carbonate (492 mg, 1.5 mmol) in DMF (5 ml) was heated at 70 °C for 6 hours. The mixture was concentrated and purified on a Biotage silica gel column (100% ethyl acetate, then 10-35 % 9:1 methanol:ammonium hydroxide-chloroform) to obtain the desired product, (R)-N-([1,2,4]triazol[1,5-a]pyrazin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (85mg, 26.7%) as a white solid. ^{1}H NMR (500 MHz, MeOD) δ ppm 9.0 (m, 1H), 8.71-8.70 (m, 1H), 8.15-8.10 (m, 1H), 4.15-4.0 (d, 1H), 3.85-3.8 (d, 1H), 3.6-3.5 (d, 1H), 3.4-3.3 (d, 1H), 3.3-3.0 (m, 4H), 2.4-2.2 (m, 2H), 2.0-1.8 (m, 3H).
MS (LCMS) [M+H] = 300.06; R.T. = 0.2 min.

Example 271

(R)-N-(Thiazolo[5,4-b]pyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



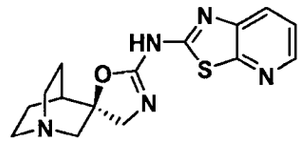
Step A: Dimethyl thiazolo[5,4-b]pyridin-2-ylcarbonimidodithioate



To a suspension of thiazolo[5,4-b]pyridin-2-amine (300 mg, 1.98 mmol) in DMF (2 mL) was added 20.0M sodium hydroxide (200 μL, 4.0 mmol). The mixture was allowed to stir 10 min at room temperature at which time carbon disulfide was added (300 μL, 4.96 mmol) and the resulting reddish brown mixture was stirred for 10 minutes. An additional portion of 20.0M sodium hydroxide (200 μL, 4.0 mmol) was added and the mixture was again stirred for 10 minutes. Finally, iodomethane (300 μL, 4.76 mmol) was added dropwise. The mixture was stirred for 5 minutes, at

which time a voluminous yellow precipitate had formed. The mixture was poured into water and the solids were collected by filtration to afford dimethyl thiazolo[5,4-b]pyridin-2-ylcarbonimidodithioate (190 mg, 38% yield) as a yellow solid of sufficient purity to use without further purification. 1H NMR (500 MHz, *CDCl3*) δ ppm 8.47 (d, *J*=4.58 Hz, 1 H) 8.11 (dd, *J*=8.24, 1.53 Hz, 1 H) 7.37 (dd, *J*=8.24, 4.88 Hz, 1 H) 2.66 (s, 6 H).

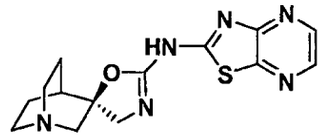
Step B: (R)-N-(Thiazolo[5,4-b]pyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



A mixture of dimethyl thiazolo[5,4-b]pyridin-2-ylcarbonimidodithioate (90 mg, 0.35 mmol), (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (97mg, 0.42 mmol) and cesium carbonate (230 mg, 0.71 mmol) in DMF (1 mL) was heated to 100 °C for 2 hours. The reaction mixture was cooled to ambient temperature, poured into water and extracted with chloroform (4x). The combined organics were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The mixture was purified by silica gel chromatography (2-40 % 9:1 methanol:ammonium hydroxide-chloroform). The product fractions were combined and concentrated *in vacuo* to afford (R)-N-(thiazolo[5,4-b]pyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (84mg, 76% yield). 1H NMR (400 MHz, *CDCl3*) δ ppm 9.30 (br. s., 1 H) 8.37 (dd, *J*=4.77, 1.51 Hz, 1 H) 7.82 (dd, *J*=8.03, 1.51 Hz, 1 H) 7.28 (dd, *J*=8.03, 4.77 Hz, 1 H) 4.05 (d, *J*=9.54 Hz, 1 H) 3.70 (d, *J*=9.54 Hz, 1 H) 3.42 (dd, *J*=15.06, 1.76 Hz, 1 H) 2.75 - 3.07 (m, 5 H) 2.14 - 2.26 (m, 2 H) 1.71 - 1.84 (m, *J*=13.99, 9.79, 4.17, 4.17 Hz, 1 H) 1.48 - 1.68 (m, 2 H). MS (LC/MS) R.T. = 0.64; $[M+H]^+$ = 316.15.

Example 272

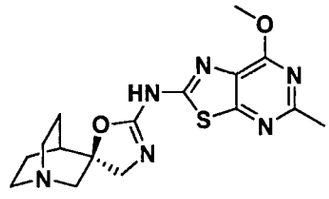
(R)-N-(Thiazolo[5,4-b]pyrazin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



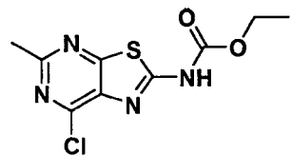
(R)-N-(6-Bromothiazolo[5,4-b]pyrazin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (44 mg, 0.111 mmol) was suspended in MeOH (50 mL) and 3N HCl was added until all solids had dissolved (~10ml). The reaction flask was flushed with nitrogen and then 10% palladium on carbon (35 mg) was added, and the flask was fitted with a hydrogen balloon. The mixture was allowed to react overnight, at which time TLC showed consumption of the starting material. The flask was flushed with nitrogen, filtered through celite and washed with methanol. The combined filtrates were concentrated by ~90% to remove most of the methanol, and the solution was made basic by the addition of a saturated solution of sodium bicarbonate. The basic aqueous phase was extracted with chloroform (4x). The combined organics were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The mixture was purified by silica gel chromatography (2-40 % [9:1 methanol:ammonium hydroxide]-chloroform). The product fractions were combined and concentrated *in vacuo* to afford (R)-N-(thiazolo[5,4-b]pyrazin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (24 mg, 0.075 mmol, 67.5 % yield). 1H NMR (400 MHz, $CDCl_3$) δ ppm 9.50 (br. s., 1 H) 8.41 (d, *J*=2.76 Hz, 1 H) 8.27 (d, *J*=2.76 Hz, 1 H) 4.06 (d, *J*=9.79 Hz, 1 H) 3.72 (d, *J*=9.79 Hz, 1 H) 3.43 (dd, *J*=15.06, 1.76 Hz, 1 H) 2.74 - 3.09 (m, 5 H) 2.12 - 2.25 (m, 2 H) 1.71 - 1.86 (m, 1 H) 1.49 - 1.67 (m, 2 H). MS (LC/MS) R.T. = 0.75; $[M+H]^+$ = 317.13.

Example 273

(R)-N-(7-Methoxy-5-methylthiazolo[5,4-d]pyrimidin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

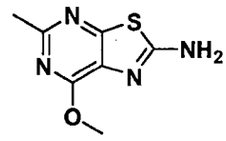


Step A: Ethyl 7-chloro-5-methylthiazolo[5,4-d]pyrimidin-2-ylcarbamate



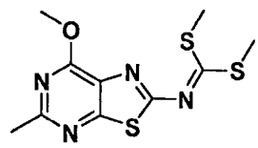
To a mixture of 4,6-dichloro-2-methylpyrimidin-5-amine (1 g, 5.62 mmol) and O-ethyl carbonisothiocyanatidate (0.66 mL, 5.62 mmol) was added toluene (2 mL) to wet the solids completely. The mixture was placed on 100 °C oil bath for 1.5 hours, at which time, the mixture had seized to give a solid mass. The solids were cooled to ambient temperature and triturated with ether, then the resulting solids were collected by filtration to give ethyl 7-chloro-5-methylthiazolo[5,4-d]pyrimidin-2-ylcarbamate (1.08 g, 3.96 mmol, 70.5 % yield). 1H NMR (400 MHz, DMSO-d_6) δ ppm 12.70 (br. s., 1 H) 4.30 (q, *J*=7.19 Hz, 2 H) 2.69 (s, 3 H) 1.30 (t, *J*=7.15 Hz, 3 H).

Step B: 7-Methoxy-5-methylthiazolo[5,4-d]pyrimidin-2-amine



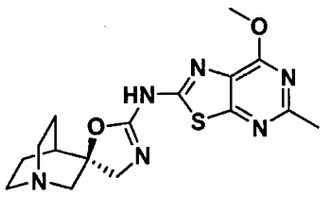
Ethyl 7-chloro-5-methylthiazolo[5,4-d]pyrimidin-2-ylcarbamate (300 mg, 1.100 mmol) was suspended in a 25% w/w solution of sodium methoxide in methanol (5 mL, 23.14 mmol) and the mixture was refluxed overnight. The mixture was cooled to ambient temperature, diluted with water and extracted with chloroform (4x). The combined organics were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 7-methoxy-5-methylthiazolo[5,4-d]pyrimidin-2-amine (120mg, 0.612 mmol, 55.6 % yield). 1H NMR (400 MHz, DMSO-d_6) δ ppm 7.71 (s, 2 H) 3.98 (s, 3 H) 2.52 (s, 3 H).

Step C: Dimethyl 7-methoxy-5-methylthiazolo[5,4-d]pyrimidin-2-ylcarbonimidodithioate



To a suspension of 7-methoxy-5-methylthiazolo[5,4-d]pyrimidin-2-amine (100 mg, 0.51 mmol) in DMF (0.5 mL) was added 16.0M sodium hydroxide (75 µL, 1.2 mmol). The mixture was allowed to stir 10 min at room temperature at which time carbon disulfide was added (80 µL, 1.27 mmol) and the resulting reddish brown mixture was stirred for 10 minutes. An additional portion of 16.0M sodium hydroxide (75 µL, 1.2 mmol) was added and the mixture was again stirred for 10 minutes. Finally, iodomethane (80 µL, 1.29 mmol) was added dropwise. The mixture was stirred for 5 minutes, at which time a voluminous yellow precipitate had formed. The mixture was poured into water and the solids were collected by filtration to afford a crude yellow solid that was further purified by silica gel chromatography (2-20 % ethyl acetate-chloroform). The product fractions were combined and concentrated *in vacuo* to afford dimethyl 7-methoxy-5-methylthiazolo[5,4-d]pyrimidin-2-ylcarbonimidodithioate (90 mg, 59% yield) as a yellow solid. 1H NMR (400 MHz, $CDCl_3$) δ ppm 4.17 (s, 3 H) 2.71 (s, 3 H) 2.64 (s, 6 H).

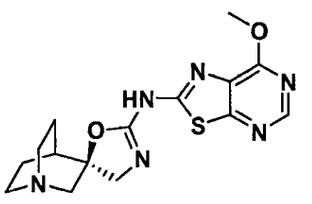
Step D: (R)-N-(7-Methoxy-5-methylthiazolo[5,4-d]pyrimidin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



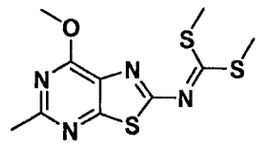
A mixture of dimethyl 7-methoxy-5-methylthiazolo[5,4-d]pyrimidin-2-ylcarbonimidodithioate (56 mg, 0.19 mmol), (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (51mg, 0.22 mmol) and cesium carbonate (175 mg, 0.54 mmol) in DMF (0.5 mL) was heated to 100 °C for 2 hours. The reaction mixture was cooled to ambient temperature, poured into water and extracted with chloroform (4x). The combined organics were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The mixture was purified by silica gel chromatography (2-40 % [9:1 methanol:ammonium hydroxide]-chloroform). The product fractions were combined and concentrated *in vacuo* to afford (R)-N-(7-methoxy-5-methylthiazolo[5,4-d]pyrimidin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (34 mg, 50% yield). 1H NMR (400 MHz, $CDCl_3$) δ ppm 9.10 (br. s., 1 H) 4.14 (s, 3 H) 4.03 (d, *J*=9.54 Hz, 1 H) 3.68 (d, *J*=9.54 Hz, 1 H) 3.39 (dd, *J*=14.93, 1.63 Hz, 1 H) 2.74 - 3.07 (m, 5 H) 2.68 (s, 3 H) 2.04 - 2.28 (m, 2 H) 1.70 - 1.86 (m, 1 H) 1.44 - 1.67 (m, 2 H). MS (LC/MS) R.T. = 1.10; $[M+H]^+$ = 361.32.

Example 274

(R)-N-(7-Methoxythiazolo[5,4-d]pyrimidin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

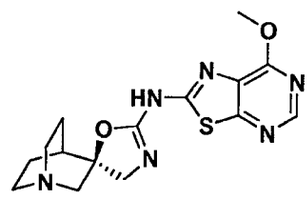


Step A: Dimethyl 7-methoxy-5-methylthiazolo[5,4-d]pyrimidin-2-ylcarbonimidodithioate



To a suspension of 7-methoxythiazolo[5,4-d]pyrimidin-2-amine (300 mg, 1.67 mmol) in DMF (1.5 mL) was added 16.0M sodium hydroxide (210 μL, 3.4 mmol). The mixture was allowed to stir 10 min at room temperature at which time carbon disulfide was added (250 μL, 4.15 mmol) and the resulting reddish brown mixture was stirred for 10 minutes. An additional portion of 16.0M sodium hydroxide (210 μL, 3.4 mmol) was added and the mixture was again stirred for 10 minutes. Finally, iodomethane (250 μL, 4.00 mmol) was added dropwise. The mixture was stirred for 10 minutes, at which time a voluminous yellow precipitate had formed. The mixture was poured into water and the solids were collected by filtration to afford dimethyl 7-methoxy-5-methylthiazolo[5,4-d]pyrimidin-2-ylcarbonimidodithioate (324 mg, 69% yield) as a yellow solid. 1H NMR (400 MHz, $CDCl_3$) δ ppm 8.60 (s, 1 H) 4.20 (s, 3 H) 2.65 (s, 6 H).

Step B: (R)-N-(7-Methoxythiazolo[5,4-d]pyrimidin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

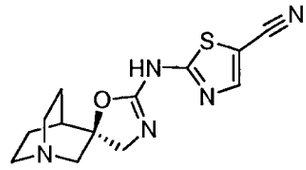


A mixture of dimethyl 7-methoxythiazolo[5,4-d]pyrimidin-2-ylcarbonimidodithioate (150 mg, 0.52 mmol), (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (132mg, 0.58 mmol) and cesium carbonate (427 mg, 1.31 mmol) in DMF (3mL) was heated to 100 °C for 2 hours. The reaction mixture was cooled to ambient temperature, poured into water and extracted with chloroform (4x). The

combined organics were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The mixture was purified by silica gel chromatography (2-40 % [9:1 methanol:ammonium hydroxide]-chloroform). The product fractions were combined and concentrated *in vacuo* to afford (R)-N-(7-methoxythiazolo[5,4-d]pyrimidin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (95 mg, 51% yield). 1H NMR (400 MHz, *CDCl3*) δ ppm 9.12 (br. s., 1 H) 8.52 (s, 1 H) 4.16 (s, 3 H) 4.05 (d, *J*=9.54 Hz, 1 H) 3.70 (d, *J*=9.54 Hz, 1 H) 3.40 (dd, *J*=14.93, 1.88 Hz, 1 H) 2.70 - 3.07 (m, 5 H) 2.08 - 2.27 (m, 2 H) 1.68 - 1.85 (m, 1 H) 1.48 - 1.66 (m, 2 H). MS (LC/MS) R.T. = 0.90; $[M+H]^+$ = 347.34.

EXAMPLE 275

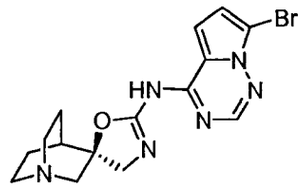
(R)-2-(4H-1'-Azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-ylamino)thiazole-5-carbonitrile



(R)-2-(4H-1'-Azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-ylamino)thiazole-5-carbonitrile was synthesized by the method of Example 274, starting from 2-amino-5-cyanothiazole. 1H NMR (500 MHz, *DMSO-D6*) δ ppm 9.05 (s, 1 H), 8.13 (s, 1 H), 3.86 (d, *J*=10.38 Hz, 1 H), 3.61 (d, *J*=10.38 Hz, 1 H), 3.01 - 3.10 (m, 2 H), 2.83 (t, *J*=7.63 Hz, 2 H), 2.62 - 2.71 (m, 2 H), 2.09 (s, 1 H), 1.90 - 1.97 (m, 2 H), 1.54 - 1.62 (m, 3 H). MS (LC/MS) R.T. = 0.52; $[M+H]^+$ = 290.0.

EXAMPLE 276

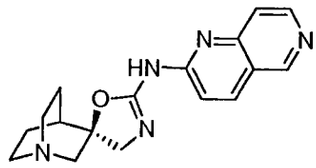
(R)-N-(7-Bromopyrrolo[1,2-f][1,2,4]triazin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



(R)-N-(7-bromopyrrolo[1,2-f][1,2,4]triazin-4-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was synthesized by the method of Example 274 starting from 7-bromopyrrolo[1,2-f][1,2,4]triazin-4-amine. 1H NMR (400 MHz, *MeOD*) δ ppm 8.13 (1 H, s), 7.04 (1 H, d, *J*=4.53 Hz), 6.77 (1 H, d, *J*=4.53 Hz), 4.09 (1 H, d, *J*=10.32 Hz), 3.79 (1 H, d, *J*=10.58 Hz), 3.24 (1 H, d), 3.12 (1 H, d), 2.70 - 3.00 (4 H, m), 2.06 - 2.25 (2 H, m), 1.52 - 1.86 (3 H, m) MS (LC/MS) R.T. = 1.62; $[M+H]^+$ = 377.2.

EXAMPLE 277

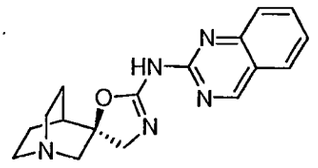
(R)-N-(1,6-Naphthyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



(R)-N-(1,6-Naphthyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was synthesized by the method of Example 274 starting from 1,6-naphthyridin-2-amine. 1H NMR (400 MHz, *MeOD*) δ ppm 8.99 (1 H, s), 8.48 (1 H, d, *J*=6.04 Hz), 8.20 (1 H, d, *J*=8.56 Hz), 7.77 (1 H, d, *J*=6.04 Hz), 7.12 (1 H, d, *J*=8.81 Hz), 4.12 (1 H, d, *J*=10.32 Hz), 3.82 (1 H, d, *J*=10.32 Hz), 3.36 (1 H, d), 3.21 (1 H, d), 2.79 - 3.09 (4 H, m), 2.08 - 2.30 (2 H, m), 1.56 - 1.95 (3 H, m). (LC/MS) R.T. = 0.38; $[M+H]^+$ = 310.3.

EXAMPLE 278

(R)-N-(Quinazolin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

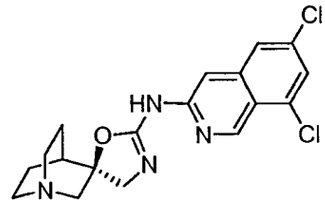


(R)-N-(Quinazolin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan] -2-amine was synthesized by the method of Example 274 starting from 2-

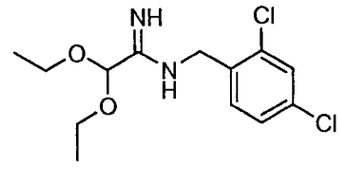
aminoquinazoline. ^{1}H NMR (400 MHz, *MeOD*) δ ppm 9.27 (1 H, s), 7.72 - 7.99 (3 H, m), 7.47 (1 H, dd, *J*=7.55, 3.78 Hz), 4.07 (1 H, d, *J*=10.07 Hz), 3.76 (1 H, d, *J*=10.07 Hz), 3.26 (1 H, br. s.), 3.13 (1 H, d), 2.70 - 3.03 (4 H, m), 2.17 (2 H, br. s.), 1.50 - 1.88 (3 H, m). (LC/MS) R.T. = 1.11; $[M+H]^+$ = 310.3.

EXAMPLE 279

(R)-N-(6,8-Dichloroisoquinolin-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

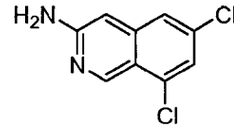


Step A: N-(2,4-Dichlorobenzyl)-2,2-diethoxyacetimidamide



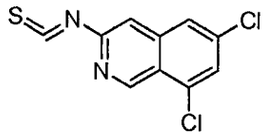
(2,4-Dichlorophenyl)methanamine (2 g, 11.4 mmol) was added to a solution of methyl 2,2-diethoxyacetimidate (2.04 g, 12.6 mmol) in methanol (10 ml). The mixture was heated at 70°C for 1 h. The mixture was purified by chromatography (Biotage: 100% ethyl acetate). The desired fractions were concentrated to yield N-(2,4-dichlorobenzyl)-2,2-diethoxyacetimidamide (2.8 g, 9.2 mmol, 72.7 % yield) as a colorless viscous oil. 1H NMR (500 MHz, *DMSO-D6*) δ ppm 7.27 - 7.70 (m, 3 H), 4.77 (s, 1 H), 4.14 - 4.35 (m, 2 H), 3.45 - 3.68 (m, 4 H), 1.09 - 1.29 (m, 6 H). LC/MS RT=2.03; $[M+H]^+$ = 304.9.

Step B: 6,8-Dichloroisoquinolin-3-amine



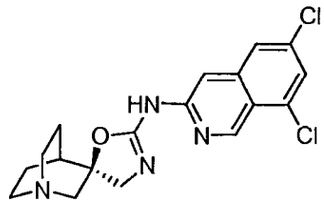
To sulfuric acid (4 mL, 75 mmol) was added N-(2,4-dichlorobenzyl)-2,2-diethoxyacetimidamide (2 g, 6.6 mmol) at room temperature. The reaction was heated to 40°C for 18 hours. TLC and LC/MS indicated the presence of product. The reaction was cooled to room temperature and quenched with aq. NaOH (~15 M) until the reaction mixture was ~pH 7. The crude product was extracted with ethyl acetate (2 x 50 mL) and the organics were dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the product. The crude product was purified by chromatography (Biotage: 10-80% ethyl acetate/ hexanes) to yield 5,7-dichloroisoquinolin-1-amine (0.32 g, 1.50 mmol, 22.9 % yield) as a dark yellow powder. 1H NMR (400 MHz, *DMSO-D6*) δ ppm 8.99 (s, 1 H), 7.64 - 7.73 (m, 1 H), 7.30 (d, *J*=2.01 Hz, 1 H), 6.61 (s, 1 H), 6.43 (s, 2 H). MS (LC/MS) R.T. = 1.40; $[M+H]^+$ = 213.1.

Step C: 6,8-Dichloro-3-isothiocyanatoisoquinoline



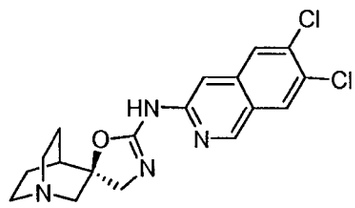
To 6,8-dichloroisoquinolin-3-amine (0.27 g, 1.28 mmol) in dichloromethane (20 mL) was added 1,1'-thiocarbonyldipyridin-2(1H)-one (0.30 g, 1.29 mmol) and the reaction mixture was stirred at 40°C for 4 hours. The reaction was cooled to room temperature and chromatographed (Biotage: 10-100% ethyl acetate/hexanes) to yield 6,8-dichloro-3-isothiocyanatoisoquinoline (0.2 g, 0.78 mmol, 61.9 % yield) as a powder. 1H NMR (500 MHz, *DMSO-D6*) δ ppm 9.42 (s, 1 H), 8.16 (d, *J*=1.83 Hz, 1 H), 8.02 (d, *J*=2.14 Hz, 1 H), 7.92 (s, 1 H). MS (LC/MS) R.T. = 3.63; $[M+H]^+$ = 255.0.

Step D: (R)-N-(6,8-Dichloroisoquinolin-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

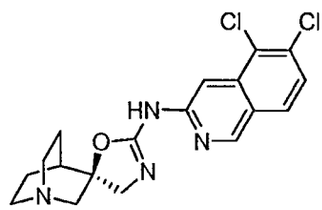


To 6,8-dichloro-3-isothiocyanatoisoquinoline (0.17 g, 0.67 mmol) in DMF (10 mL) was added cesium carbonate (0.543 g, 1.67 mmol) and (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (0.15 g, 0.67 mmol) at room temperature. The reaction was stirred at 70°C for 2 hours. The reaction was cooled to room temperature and concentrated *in vacuo*. The product was treated with N,N'-diisopropylcarbodiimide (0.31 mL, 2.0 mmol). The reaction was heated to 90°C for 4 hours. The reaction was cooled to room temperature and concentrated to yield the crude product. The crude product was purified by chromatography (Biotage: 85% $CHCl_3$, 14% MeOH, 1% NH_4OH). The product was taken up in a small amount of ethyl acetate, which resulted in the formation of a precipate. It was filtered off, washed with a small amount of ethyl acetate, and dried in a vacuum oven to yield (R)-N-(6,8-dichloroisoquinolin-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.094 g, 0.24 mmol, 36.6 % yield) as a white powder. 1H NMR (400 MHz, *DMSO-D_6*) δ ppm 9.23 (s, 1 H), 8.71 - 8.83 (m, 1 H), 7.90 - 8.00 (m, 1 H), 7.57 - 7.67 (m, 1 H), 7.13 - 7.24 (m, 1 H), 3.79 - 3.90 (m, 1 H), 3.53 - 3.64 (m, 1 H), 2.93 - 3.04 (m, 2 H), 2.72 - 2.82 (m, 2 H), 2.61 - 2.70 (m, 2 H), 1.99 (s, 1 H), 1.90 (s, 1 H), 1.59 (d, *J*=4.78 Hz, 2 H), 1.40 - 1.50 (m, 1 H). MS (LC/MS) R.T. = 1.68; $[M+H]^+$ = 377.1.

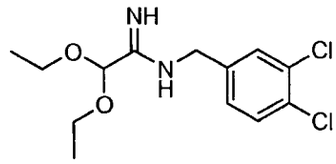
EXAMPLE 280



(R)-N-(6,7-Dichloroisoquinolin-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



Step A: N-(3,4-Dichlorobenzyl)-2,2-diethoxyacetimidamide



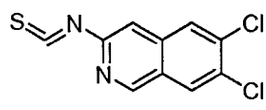
(3,4-Dichlorophenyl)methanamine (2 g, 11.4 mmol) was added to a solution of methyl 2,2-diethoxyacetimidate (2.04 g, 12.6 mmol) in methanol (10 ml). The mixture was heated at 70°C for 1 h. The mixture was purified by chromatography (Biotage: 100% ethyl acetate). The desired fractions were concentrated to yield N-(3,4-dichlorobenzyl)-2,2-diethoxyacetimidamide (2.8 g, 9.2 mmol, 72.7 % yield) as a colorless viscous oil. 1H NMR (500 MHz, $CDCl_3$) δ ppm 7.45 (m, 1 H), 7.40 (m, 1 H), 7.19 (dd, *J*=8.09, 1.98 Hz, 1 H), 4.94 (s, 1 H), 4.43 (s, 2 H), 3.47 - 3.77 (m, 4 H), 1.41 - 1.79 (m, 6 H). LC/MS RT=2.15; $[M+H]^+ = 305.1$.

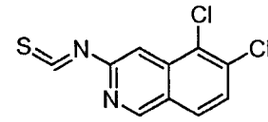
Step B: 6,7-Dichloroisoquinolin-3-amine and 5,6-dichloroisoquinolin-3-amine



To sulfuric acid (4 mL, 75 mmol) was added N-(3,4-dichlorobenzyl)-2,2-diethoxyacetimidamide (2 g, 6.6 mmol) at room temperature. The reaction was heated to 40°C for 49 hours. TLC and LC/MS indicated the presence of product. The reaction was cooled to room temperature and quenched with aq. NaOH (~15 M) until the reaction mixture was ~pH 7. The crude product was extracted with ethyl acetate (2 x 50 mL) and the organics were dried with $MgSO_4$, filtered, and concentrated in *vacuo* to yield the product. The crude product was purified by chromatography (Biotage: 100% ethyl acetate to [90/10% ethyl acetate/MeOH]) to yield approximately a 1:1 mixture of regioisomers 6,7-dichloroisoquinolin-1-amine and 5,6-dichloroisoquinolin-3-amine (1.2 g, 5.64 mmol, 86.0 % yield) as a dark yellow powder. The regioisomers were carried on without separation. 1H NMR : 1H NMR (500 MHz, *DMSO-D6*) δ ppm 8.90 (s, 1 H), 8.83 (s, 1 H), 8.12 (s, 1 H), 7.89 (s, 1 H), 7.84 (d, *J*=8.54 Hz, 1 H), 7.28 (d, *J*=8.85 Hz, 1 H), 6.83 (s, 1 H), 6.58 (s, 1 H), 6.48 (s, 2 H), 6.25 (s, 2 H). MS (LC/MS) R.T. = 1.59; $[M+H]^+$ = 213.0.

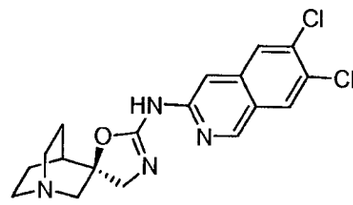
Step C: 6,7-Dichloro-3-isothiocyanatoisoquinoline and 5,6-dichloro-3-isothiocyanatoisoquinoline





To 6,7-dichloroisoquinolin-3-amine and 5,6-dichloroisoquinolin-3-amine (0.410 g, 1.924 mmol) in dichloromethane (20 mL) was added 1,1'-thiocarbonyldipyridin-2(1H)-one (0.469 g, 2.021 mmol) and the reaction mixture was stirred at 40°C for 4 hours. The reaction was cooled to room temperature and chromatographed (Biotage: 10-100% ethyl acetate/hexanes) to yield the separated regioisomers, 6,7-dichloro-3-isothiocyanatoisoquinoline (0.2 g, 0.784 mmol, 40.7 % yield) and 5,6-dichloro-3-isothiocyanatoisoquinoline (0.23 g, 0.902 mmol, 46.8 % yield) as yellow solids. 5,6-dichloro-3-isothiocyanatoisoquinoline: 1H NMR (500 MHz, *CDCl3*) δ ppm 9.10 (s, 1 H), 7.87 (d, *J*=8.85 Hz, 1 H), 7.82 (s, 1 H), 7.66 (d, *J*=8.55 Hz, 1 H). MS (LC/MS) R.T. = 3.63; $[M+H]^+$ = 255.0. 6,7-dichloro-3-isothiocyanatoisoquinoline: 1H NMR (500 MHz, *CDCl3*) δ ppm 9.04 (s, 1 H), 8.11 (s, 1 H), 7.94 (s, 1 H), 7.37 (s, 1 H). MS (LC/MS) R.T. = 3.42; $[M+H]^+$ = 255.0.

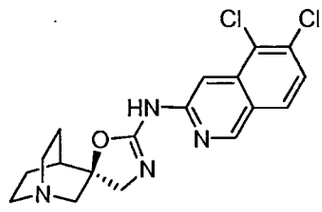
Step C: (R)-N-(6,7-Dichloroisoquinolin-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



To 6,7-dichloro-3-isothiocyanatoisoquinoline (0.13 g, 0.510 mmol) in DMF (10 mL) was added cesium carbonate (0.42 g, 1.27 mmol) and (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (0.118 g, 0.515 mmol) at room temperature. The reaction was stirred at 70°C for 2 hours. The reaction was cooled to room temperature and concentrated *in vacuo*. The crude urea was purified by chromatography (Biotage: 85% $CHCl_3$, 14% MeOH, 1% NH_4OH). The product was then treated with DMF (10 mL) and N,N'-diisopropylcarbodiimide (0.238 mL, 1.529 mmol). The reaction was heated to 90°C for 18 hours. The reaction was cooled to room temperature and concentrated to yield the crude product, which was purified by chromatography (Biotage: 85% $CHCl_3$, 14% MeOH, 1% NH_4OH) to yield (R)-N-(6,7-dichloroisoquinolin-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.12 g, 0.312 mmol, 61.2 % yield). 1H NMR (500 MHz, *$CDCl_3$*) δ ppm 9.03 (s, 1 H), 8.87 (s, 1 H), 7.96 (s, 1 H), 7.83 (s, 1 H), 7.24 (s, 1 H), 3.88 - 4.06 (m, 1 H), 3.60 - 3.74 (m, 1 H), 3.42 (d, *J*=14.65 Hz, 1 H), 2.82 - 3.15 (m, 5 H), 2.23 - 2.34 (m, 1 H), 2.18 (s, 1 H), 1.72 - 1.87 (m, 1 H), 1.48 - 1.70 (m, 2 H). MS (LC/MS) R.T. = 1.63; $[M+H]^+ = 377.1$.

EXAMPLE 281

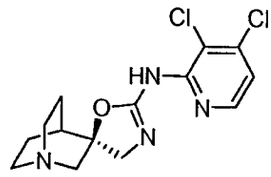
(R)-N-(5,6-Dichloroisoquinolin-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



To 5,6-dichloro-3-isothiocyanatoisoquinoline (0.11 g, 0.431 mmol) in DMF (10 mL) was added cesium carbonate (0.351 g, 1.078 mmol) and (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (0.100 g, 0.435 mmol) at room temperature. The reaction was stirred at 70°C for 2 hours. The reaction was cooled to room temperature and concentrated *in vacuo*. The crude urea was purified by chromatography (Biotage: 85% $CHCl_3$, 14% MeOH, 1% NH_4OH). The product was then treated with DMF (10 mL) and N,N'-diisopropylcarbodiimide (0.202 mL, 1.293 mmol). The reaction was heated to 90°C for 18 hours. The reaction was cooled to room temperature and concentrated to yield the crude product. The crude product was purified by chromatography (Biotage: 85% $CHCl_3$, 14% MeOH, 1% NH_4OH) to yield (R)-N-(5,6-dichloroisoquinolin-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.084 g, 0.218 mmol, 50.6 % yield) as a yellow powder. 1H NMR (500 MHz, *CDCl*$_3$) δ ppm 9.09 (s, 1 H), 8.93 (s, 1 H), 7.63 - 7.82 (m, 2 H), 7.40 (d, *J*=8.55 Hz, 1 H), 3.99 (d, *J*=9.16 Hz, 1 H), 3.78 (d, *J*=8.85 Hz, 1 H), 3.51 (d, *J*=14.65 Hz, 1 H), 3.30 (d, *J*=14.65 Hz, 1 H), 2.90 - 3.23 (m, 4 H), 2.33 - 2.48 (m, 1 H), 2.29 (s, 1 H), 1.83 - 1.94 (m, 1 H), 1.62 - 1.83 (m, *J*=42.12 Hz, 2 H). MS (LC/MS) R.T. = 1.57; $[M+H]^+$ = 377.1.

EXAMPLE 282

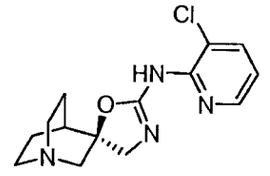
(R)-N-(3,4-Dichloropyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



(R)-N-(3,4-Dichloropyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was prepared by the method of Example 267, starting from 2-amino-3,4-dichloropyridine. 1H NMR (500 MHz, *DMSO-D6*) δ ppm 9.10 (s, 1 H), 8.08 (d, *J*=5.49 Hz, 1 H), 7.13 (d, *J*=5.49 Hz, 1 H), 3.86 (d, *J*=9.77 Hz, 1 H), 3.60 (d, *J*=9.77 Hz, 1 H), 2.96 - 3.05 (m, 2 H), 2.77 (t, *J*=7.63 Hz, 2 H), 2.66 (t, *J*=7.78 Hz, 2 H), 1.97 - 2.05 (m, 1 H), 1.86 - 1.94 (m, 1 H), 1.54 - 1.63 (m, 2 H), 1.43 - 1.51 (m, 1 H). MS (LC/MS) R.T. = 0.78; $[M+H]^+$ = 327.0.

EXAMPLE 283

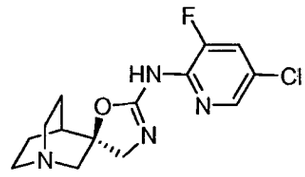
(R)-N-(3-Chloropyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



(R)-N-(3-Chloropyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was prepared by the method of Example 267, starting from 2-amino-3-chloropyridine. 1H NMR (500 MHz, *DMSO-D6*) δ ppm 9.06 (s, 1 H), 8.14 - 8.19 (m, 1 H), 7.74 - 7.79 (m, *J*=7.78, 1.83, 1.83, 1.68 Hz, 1 H), 6.86 - 6.91 (m, 1 H), 3.81 - 3.89 (m, 1 H), 3.55 - 3.63 (m, 1 H), 2.96 - 3.04 (m, 2 H), 2.78 (t, *J*=7.63 Hz, 2 H), 2.67 (t, *J*=7.63 Hz, 2 H), 1.96 - 2.02 (m, 1 H), 1.86 - 1.92 (m, *J*=5.65, 3.20 Hz, 1 H), 1.54 - 1.63 (m, *J*=6.87, 3.66, 3.51 Hz, 2 H), 1.42 - 1.49 (m, 1 H). MS (LC/MS) R.T. = 0.26; $[M+H]^+$ = 293.0.

EXAMPLE 284

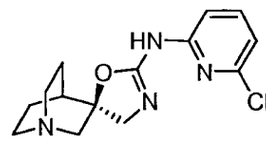
(R)-N-(5-Chloro-3-fluoropyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



(R)-N-(5-Chloro-3-fluoropyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was prepared by the method of Example 267, starting from 2-amino-3-fluoro-5-chloropyridine. 1H NMR (500 MHz, *DMSO-D6*) δ ppm 8.81 (s, 1 H), 8.05 (s, 1 H), 7.79 (d, *J*=10.07 Hz, 1 H), 3.83 (d, *J*=9.46 Hz, 1 H), 3.58 (d, *J*=9.46 Hz, 1 H), 2.99 (s, 2 H), 2.71 - 2.80 (m, 2 H), 2.61 - 2.70 (m, 2 H), 2.00 (s, 1 H), 1.83 - 1.92 (m, 1 H), 1.53 - 1.62 (m, 2 H), 1.41 - 1.50 (m, 1 H). MS (LC/MS) R.T. = 0.52; $[M+]^+$ = 311.0.

EXAMPLE 285

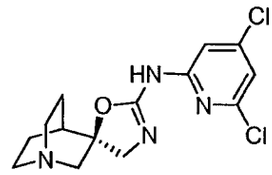
(R)-N-(6-Chloropyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



(R)-N-(6-Chloropyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was prepared by the method of Example 267, starting from 2-amino-6-chloropyridine. 1H NMR (500 MHz, *DMSO-D6*) δ ppm 8.33 - 8.42 (m, 1 H), 7.60 - 7.68 (m, 1 H), 6.94 (d, *J*=7.02 Hz, 1 H), 6.72 - 6.81 (m, 1 H), 3.86 (d, *J*=9.46 Hz, 1 H), 3.57 (d, *J*=10.07 Hz, 1 H), 2.97 (s, 2 H), 2.69 - 2.78 (m, 2 H), 2.63 - 2.68 (m, *J*=7.63, 7.63 Hz, 2 H), 1.95 - 2.03 (m, 1 H), 1.83 - 1.92 (m, 1 H), 1.53 - 1.62 (m, 2 H), 1.41 - 1.49 (m, 1 H). MS (LC/MS) R.T. = 0.43; $[M+H]^+$ = 293.0.

EXAMPLE 286

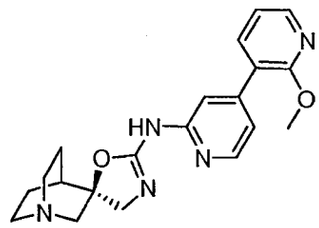
(R)-N-(4,6-Dichloropyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



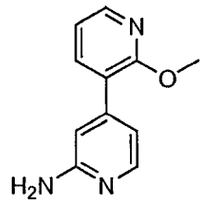
(R)-N-(4,6-Dichloropyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine was prepared by the method of Example 267, starting from 2-amino-4,6-dichloropyridine. 1H NMR (500 MHz, *DMSO-D6*) δ ppm 8.43 (s, 1 H), 7.13 (s, 1 H), 6.84 (s, 1 H), 3.86 (d, *J*=9.77 Hz, 1 H), 3.59 (d, *J*=10.07 Hz, 1 H), 2.98 (s, 2 H), 2.58 - 2.86 (m, 4 H), 1.94 - 2.13 (m, 1 H), 1.78 - 1.95 (m, 1 H), 1.36 - 1.65 (m, 3 H). MS (LC/MS) R.T. = 0.87; $[M+H]^+$ = 327.0.

EXAMPLE 287

(R)-N-(2-Methoxy-3-4'-bipyridin-2'-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



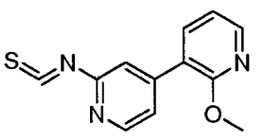
Step A: N-(2,4-Dichlorobenzyl)-2,2-diethoxyacetimidamide



To 4-bromopyridin-2-amine (0.5 g, 2.8 mmol), 2-methoxypyridin-3-ylboronic acid (0.52 g, 3.4 mmol) in DMF (25 mL) was added 1N sodium carbonate (10 mL, 2.3 mmol), followed by 1,1'-bis(diphenylphosphino)ferrocene-

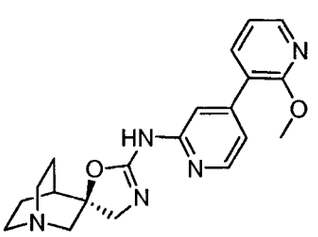
palladium(II)dichloride dichloromethane complex (0.21 g, 0.26 mmol). The reaction mixture was stirred for 3 hours at 85 °C and then cooled to room temperature. The product was extracted with ethyl acetate (2 x 50 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by chromotography (Biotage: 100 to 90/10% ethyl acetate-ethyl acetate/methanol) to yield 2-methoxy-3,4'-bipyridin-2'-amine (0.53 g, 2.63 mmol, 93 % yield) as a brown powder. The product was taken directly to the next step.

Step B: 2'-Isothiocyanato-2-methoxy-3,4'-bipyridine



To 2-methoxy-3,4'-bipyridin-2'-amine (0.53 g, 2.63 mmol) in dichloromethane (20 mL) was added 1,1'-thiocarbonyldipyridin-2(1H)-one (0.62 g, 2.7 mmol) and the reaction mixture was stirred at 40 °C for 4 hours. The reaction was cooled to room temperature and chromatographed (Biotage: 10-100% ethyl acetate/hexanes) to yield 2'-isothiocyanato-2-methoxy-3,4'-bipyridine (0.46 g, 1.9 mmol, 71.8 % yield). 1H NMR (500 MHz, *DMSO-D6*) δ ppm 8.67 (d, *J*=2.44 Hz, 1 H), 8.26 (dd, *J*=4.88, 1.53 Hz, 1 H), 8.15 (dd, *J*=8.24, 2.44 Hz, 1 H), 7.89 (dd, *J*=7.32, 1.53 Hz, 1 H), 7.48 (d, *J*=8.24 Hz, 1 H), 7.15 (dd, *J*=7.32, 4.88 Hz, 1 H), 3.91 (s, 3 H). MS (LC/MS) R.T. = 2.87; $[M+H]^+$ = 244.9.

Step D: (R)-N-(2-Methoxy-3-4'-bipyridin-2'-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

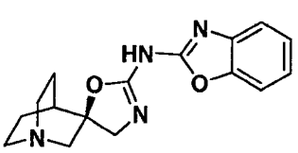


To 2'-isothiocyanato-2-methoxy-3,4'-bipyridine (0.09 g, 0.37 mmol) in DMF (20 mL) was added Et_3N (0.11 mL, 0.81 mmol) and (S)-3-(aminomethyl)quinuclidin-

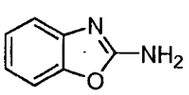
3-ol dihydrochloride (0.09 g, 0.37 mmol) at room temperature. The reaction was stirred at 70 °C for 2 hours. The reaction was cooled to room temperature and concentrated *in vacuo*. The crude urea was purified by chromatography (biotage: 85% $CHCl_3$, 14% MeOH, 1% NH_4OH) to yield the pure urea intermediate. The product was then treated with DMF (20 mL) and N,N'-diisopropylcarbodiimide (0.17 mL, 1.1 mmol). The reaction was heated to 90 °C for 18 hours. The reaction was cooled to room temperature and concentrated to yield the crude product. The crude product was purified by chromatography (Biotage: 85% $CHCl_3$, 14% MeOH, 1% NH_4OH) and the product-containing fractions were combined. LC/MS and 1HNMR indicated some impurities may be present. The impure product was subjected to reverse phase HPLC to yield (R)-N-(2-methoxy-3,4'-bipyridin-2'-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.02 g, 0.05 mmol, 14.05 % yield) as a white powder. 1H NMR (500 MHz, *DMSO-D6*) δ ppm 9.07 (s, 1 H), 8.43 (s, 1 H), 8.17 (dd, *J*=4.73, 1.68 Hz, 1 H), 7.79 (d, *J*=7.32 Hz, 2 H), 7.10 (dd, *J*=7.32, 4.88 Hz, 1 H), 6.79 - 6.92 (m, 1 H), 3.76 - 3.97 (m, 4 H), 3.51 - 3.66 (m, 1 H), 2.92 - 3.09 (m, 2 H), 2.59 - 2.82 (m, 4 H), 1.85 - 2.03 (m, 2 H), 1.53 - 1.71 (m, 2 H), 1.35 - 1.49 (m, 1 H). MS (LC/MS) R.T. = 1.05; $[M+H]^+$ = 366.1.

EXAMPLE 288

(R)-N-(Benzo[d]oxazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



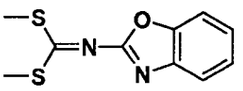
Step A: Benzo[d]oxazol-2-amine



An oven dried round bottom flask was charged with di(1H-imidazol-1-yl)methanimine (500 mg, 3.10 mmol), 2-aminophenol (188 mg, 1.724 mmol) and

anhydrous THF (20ml) at room temperature. The resulting suspension was refluxed under N_2 for 2 hr to give complete conversion based on LC/MS. The solvent was removed *in vacuo* and the residue was purified on a Biotage Flash Collector, eluting with 30-80% EtOAc/Hexane (1200ml) to afford the expected product, benzo[d]oxazol-2-amine (200 mg, 1.5 mmol, 87 % yield), as a white solid. 1H NMR (400 MHz, *CDCl3*) δ ppm 6.20 (br. s., 2 H) 7.02 - 7.11 (m, 1 H) 7.17 - 7.22 (m, 1 H) 7.29 (d, *J*=7.53 Hz, 1 H) 7.36 (d, *J*=7.03 Hz, 1 H). MS (LC/MS) R.T. = 1.05; $[M+H]^+$ = 134.96.

Step B: Dimethyl benzo[d]oxazol-2-ylcarbonimidodithioate



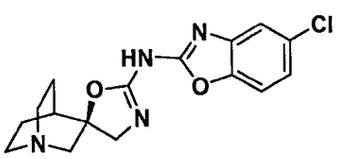
To a colorless solution of benzo[*d*]oxazol-2-amine (200 mg, 1.491 mmol) in DMF (10ml) was added sodium hydroxide (20N, 149 µL, 2.98 mmol), to give a green suspension. The mixture was stirred for 15 min at room temperature. Carbon disulfide (225 µL, 3.73 mmol) was added to give a dark brown solution. The reaction was stirred for 15 min at room temperature, followed by the addition of sodium hydroxide (20N, 149 µL, 2.98 mmol) and stirred for an additional 10 min. Iodomethane(224 µL, 3.58 mmol) was then added dropwise. A green solid precipitated after 12min. The reaction stirred for a further 2 hr. The solid was collected by filtration, washed with DMF (2x1ml), H_2O (2x1ml), dried under the house vacuum for 30 min and further dried in an oven *in vacuo* over night to afford the expected product, dimethyl benzo[*d*]oxazol-2-ylcarbonimidodithioate (258.5mg, 1.085 mmol, 72.7 % yield), as a white solid. 1H NMR (400 MHz, *CDCl3*) δ ppm 2.70 (s, 6 H) 7.24 - 7.34 (m, 2 H) 7.45 - 7.50 (m, 1 H) 7.66 - 7.74 (m, 1 H). MS (LC/MS) R.T. = 1.76, $[M+H]^+$ = 238.96.

Step C: (R)-N-(Benzo[d]oxazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

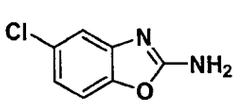
A 10 ml-vial was charged with (S)-3-(aminomethyl)quinuclidin-3-ol•2 HCl salt (69.5 mg, 0.361 mmol) , DMF (2ml), DIEA (0.063 mL, 0.361 mmol)and Cs_2CO_3 (235 mg, 0.722 mmol) at room temperature, followed by dimethyl benzo[d]oxazol-2-ylcarbonimidodithioate (86mg, 0.361 mmol). The resulting suspension was stirred at room temperature for 1 hr. LC/MS then indicated consumption of starting material. The mixture was diluted with MeOH and purified by preparative HPLC to afford the expected product, (R)-N-(benzo[d]oxazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (101.5 mg, 0.323 mmol, 90 % yield), as a tan gum. 1H NMR (400 MHz, Acetone-d_6) δ ppm 2.07 - 2.14 (m, 2 H) 2.20 (ddd, *J*=8.78, 5.27, 3.26 Hz, 2 H) 2.33 - 2.45 (m, 1 H) 2.62 (d, *J*=2.26 Hz, 1 H) 3.34 - 3.47 (m, 3 H) 3.48 - 3.58 (m, 1 H) 3.75 - 3.88 (m, 2 H) 4.15 (d, *J*=10.54 Hz, 1 H) 4.32 (d, *J*=10.54 Hz, 1 H) 7.13 - 7.26 (m, 2 H) 7.41 (td, *J*=3.70, 1.63 Hz, 1 H) 9.24 (br, s, 1H). MS (LC/MS) R.T. = 0.792, $[M+H]^+$ = 299.17.

EXAMPLE 289

(R)-N-(5-Chlorobenzo[d]oxazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



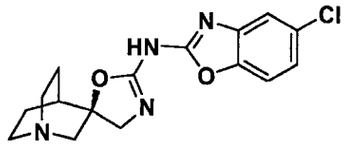
Step A: Dimethyl 5-chlorobenzo[d]oxazol-2-ylcarbonimidodithioate



To a brown solution of 5-chlorobenzo[d]oxazol-2-amine (700mg, 4.15 mmol) in DMF (5ml) was added sodium hydroxide (20N, 415 μL, 8.30 mmol) to give a grey suspension. The mixture was stirred for 15 min at room temperature. Carbon

disulfide (626 μL, 10.38 mmol) was added at room temperature to give a brown solution. The mixture was stirred for 15 min at room temperature, then sodium hydroxide (20N, 208 μL, 4.16mmol) was added. After 10 min, iodomethane (623 μL, 9.97 mmol) was added dropwise. A grey solid came out from solution. The reaction was further stirred at room temperature for 2 hr. The solid was collected by filtration, washed with DMF/H_2O(50:50, 2x2ml), dried under house vacuum for 30 min and further dried in an oven at 65 °C under vacuum for 1 1/2 hr to afford the expected product, dimethyl 5-chlorobenzo[d]oxazol-2-ylcarbonimidodithioate (780mg, 2.86 mmol, 68.9 % yield), as an off-white solid which was pure enough to be used in next step. 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.69 (s, 6 H) 7.37 (dd, *J*=8.53, 2.26 Hz, 1 H) 7.66 (d, *J*=9.03 Hz, 1 H) 7.75 (d, *J*=1.76 Hz, 1 H). MS (LC/MS) R.T. = 1.44; $[M+H]^+$ = 272.9.

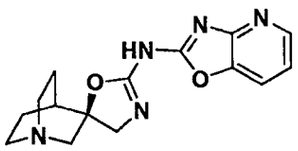
Step B: (R)-N-(5-Chlorobenzo[d]oxazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



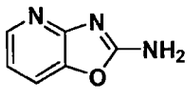
A 10 ml vial was charged with (S)-3-(aminomethyl)quinuclidin-3-ol•2 HCl salt (106 mg, 0.550 mmol), DMF (2ml), DIEA (0.096 mL, 0.550 mmol), and Cs_2CO_3(358 mg, 1.100 mmol) at room temperature, followed by dimethyl 5-chlorobenzo[d]oxazol-2-ylcarbonimidodithioate (150mg, 0.550 mmol). The resulting suspension was stirred at room temperature for 1 hr. LC/MS then indicated consumption of starting material. The reaction mixture was diluted with MeOH and purified by preparative HPLC to afford the expected product, (R)-N-(5-chlorobenzo[d]oxazol-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (106.5 mg, 0.3 mmol, 53.0 % yield), as a white solid. 1H NMR (400 MHz, Acetone-d_6) δ ppm 2.08 - 2.30 (m, 3 H) 2.35 - 2.48 (m, 1 H) 2.60 - 2.73 (m, 1 H) 3.48 (qd, *J*=7.53, 7.28 Hz, 3 H) 3.54 - 3.68 (m, 1 H) 3.79 - 4.00 (m, 2 H) 4.18 (d, *J*=10.54 Hz, 1 H) 4.35 (d, *J*=10.54 Hz, 1 H) 7.19 (dd, *J*=8.53, 2.01 Hz, 1 H) 7.30 - 7.47 (m, 2 H) 9.10 (br. s., 1 H). MS(LC/MS) R.T. = 1.56; $[M+H]^+$ = 333.13.

EXAMPLE 290

(R)-N-(Oxazolo[4,5-b]pyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

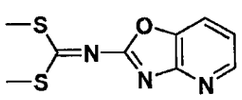


Step A: Oxazolo[4,5-b]pyridin-2-amine



An oven dried round bottom flask was charged with di(1H-imidazol-1-yl)methanimine (500 mg, 3.10 mmol), 2-aminopyridin-3-ol (171 mg, 1.551 mmol) and anhydrous THF (20ml) at room temperature. The resulting suspension was refluxed under N_2 for 1hr. LC/MS indicated complete consumption of starting material. The solvent was removed *in vacuo* and the residue was used in the next step without further purification. MS(LC/MS) R.T. = 0.235; $[M+H]^+$ = 136.09.

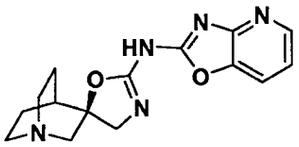
Step B: Dimethyl oxazolo[4,5-b]pyridin-2-ylcarbonimidodithioate



To the crude oxazolo[4,5-b]pyridin-2-amine (811 mg, 6 mmol) from step A, in DMF (12ml), was added NaOH (20 N, 600 µL, 12.00 mmol) to give a tan solution which was stirred for 15 min at room temperature. Carbon disulfide (904 µL, 15.00 mmol) was then added to give an orange solution. The mixture was stirred for 15 min at room temperature, then NaOH (20 N, 600 µL, 12.00 mmol) was added and the stirring continued for 10 min to give a dark red solution. Iodomethane (900 µL, 14.40 mmol) was added dropwise, resulting in a yellow solid precipitating after 1 hr to give ~80% conversion. The mixture was diluted with MeOH and purified via

preparative HPLC to afford the expected product, dimethyl oxazolo[4,5-*b*]pyridin-2-ylcarbonimidodithioate (35 mg, 0.146 mmol, 2.4 % yield), as a white solid. 1H NMR (400 MHz, *CDCl*$_3$) δ ppm 2.71 (s, 6 H) 7.22 (dd, *J*=8.03, 5.02 Hz, 1 H) 7.72 (dd, *J*=8.03, 1.25 Hz, 1 H) 8.49 (dd, *J*=5.02, 1.51 Hz, 1 H). MS (LC/MS) R.T. = 1.358; [M+H] = 240.04.

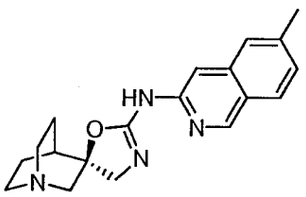
Step C: (R)-N-(Oxazolo[4,5-b]pyridin-2-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine



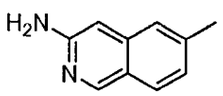
A 10 ml vial was charged with (S)-3-(aminomethyl)quinuclidin-3-ol•2 HCl salt (8.53 mg, 0.044 mmol), DMF (2 ml), DIEA (7.74 µL, 0.04 mmol) and Cs_2CO_3(28.9 mg, 0.089 mmol) at room temperature, followed by dimethyl oxazolo[4,5-*b*]pyridin-2-ylcarbonimidodithioate (10.6 mg, 0.044 mmol). The resulting suspension was stirred at room temperature for 1hr. LC/MS indicated complete consumption of starting material. The reaction mixture was diluted with MeOH and purified via preparative HPLC to afford the expected product, (R)-N-(oxazolo [4, 5-*b*] pyridin-2-yl)-4H-1'-azaspiro [oxazole-5, 3'-bicyclo [2.2.2] octan]-2-amine (13 mg, 0.038 mmol, 86 % yield), as a white solid. 1H NMR (400 MHz, Acetone-d_6) δ ppm 1.54 - 1.60 (m, 1 H) 1.71 - 1.77 (m, 2 H) 2.16 - 2.24 (m, 1 H) 2.77 - 2.82 (m, 2 H) 2.89 (t, *J*=7.91 Hz, 4 H) 3.13 - 3.25 (m, 2 H) 3.90 (d, *J*=10.29 Hz, 1 H) 4.22 (d, *J*=10.29 Hz, 1 H) 7.13 (dd, *J*=8.03, 5.02 Hz, 1 H) 7.70 (dd, *J*=7.91, 1.13 Hz, 1 H) 8.27 (dd, *J*=5.14, 1.13 Hz, 1 H) 9.11 (br. s., 1 H). MS (LC/MS) R.T. = 0.443; $[M+H]^+$ = 300.16.

EXAMPLE 291

(2R)-N-(6,8-Dimethyl-3-isoquinolinyl)-4'H-spiro[4-azabicyclo[2.2.2]octane-2,5'-[1,3]oxazol]-2'-amine

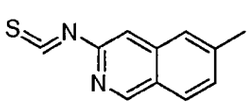


Step A: 6-Methylisoquinolin-3-amine



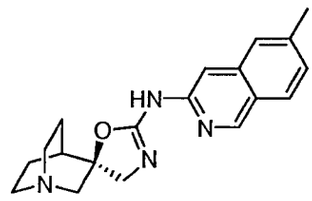
To a solution of methyl 2,2-diethoxyacetimidate (1.1 g, 6.82 mmol) in methanol (8 mL) was added p-tolylmethanamine (0.788 g, 6.50 mmol) dropwise at ambient temperature. The reaction flask was then placed into a preheated oil-bath and stirred at 70 °C for 16 h, then removed and allowed cooled. The volatiles were removed under reduced pressure and the crude material was added dropwise to sulfuric acid (5 mL) at ambient temperature. The reaction mixture was stirred for 72 h, then the flask was placed into an ice-water bath, diluted with water (50 mL), and slowly neutralized to pH = 10 with sodium hydroxide (10 N). As the reaction mixture became basic, a grey precipitate formed. This precipitate was filtered, washed with water, and dried to afford 6-methylisoquinolin-3-amine (0.65g, 63%), as a grey powder. 1H NMR (400 MHz, DMSO-d_6) δ ppm 8.73 (s, 1 H), 7.69 (d, J=8.28 Hz, 1 H),7.29 (s, 1 H), 7.00 (d, J=8.28 Hz, 1 H), 5.81 (s, 1 H), 2.40 (s, 3 H). MS (LC/MS) R.T. = 1.37; $[M+H]^+$ = 159.10.

Step B: 3-Isothiocyanato-6-methylisoquinoline



To a solution of 1,1'-thiocarbonyldipyridin-2(1H)-one (220mg, 0.948 mmol) in dichloromethane (10 mL) at ambient temperature was added 6-methylisoquinolin-3-amine (125 mg, 0.790 mmol). The reaction mixture was placed into a preheated oil-bath and stirred at 40 °C for 18 h,then removed from the oil-bath and cooled to ambient temperature. The mixture was concentrated and the crude material was purified by silica gel chromatography (5-30 % ethyl acetate in hexanes) to afford 3-isothiocyanato-6-methylisoquinoline (75 mg, 0.375 mmol, 47.4 % yield), as an off-white solid.1H NMR (400 MHz, $CDCl_3$) δ ppm 9.03 (s, 1 H), 7.88 (d, *J*=8.24 Hz, 1 H), 7.56 (s, 1 H), 7.46 (dd, *J*=8.24, 1.53 Hz, 1 H) , 7.39 (s, 1 H) 2.57 (s, 3 H). MS (LC/MS) R.T. = 1.92; $[M+H]^+$ = 201.13.

Step C: (R)-N-(6-Methylisoquinolin-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

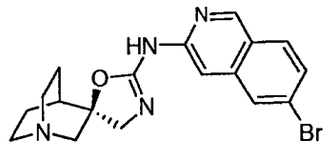


To (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (65.8 mg, 0.285 mmol) in N,N-dimethylformamide (6 mL) was added triethylamine (0.090 mL, 0.63 mmol) and 3-isothiocyanato-6-methylisoquinoline (57 mg, 0.285 mmol). The suspension was placed into a preheated oil-bath and stirred at 70 °C for 2 h and 30 min. N,N'-diisopropylcarbodiimide (0.177 mL, 1.14 mmol) was then added and the mixture was stirred at 85 °C for 16 h. The mixture was concentrated and purified by silica gel chromatography (0-40 % [9:1 methanol:ammonium hydroxide] in chloroform) followed by purification by reverse phase preparatory HPLC (0-40 % TFA-methanol-water). The solution of product was filtered through UCT Clean-up CHQAX15M25 cartridge with MeOH (3x10ml) and concentrated to afford the expected product, (S)-1-((3-hydroxyquinuclidin-3-yl)methyl)-3-(6-methylisoquinolin-3-yl)thiourea, as a tan gum. 1H NMR (400 MHz, MeOD) δ ppm 9.11 (s, 1 H), 8.02 (d, *J*=8.53 Hz, 1 H), 7.80 (s, 1 H), 7.74 (s, 1 H), 7.47 (d, *J*=8.53 Hz, 1 H), 4.47 (d, *J*=10.54 Hz, 1 H), 4.31 (d, *J*=10.54 Hz, 1 H), 4.10 (d, *J*=14.81 Hz,

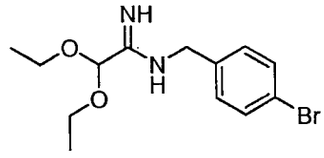
1 H), 3.92 (d, *J*=14.81 Hz, 1 H), 3.53 - 3.71 (m, 2 H), 3.27 - 3.51 (m, 3 H), 2.84 (br.s, 1 H), 2.55 (s, 3H), 2.48 (m, 1 H),) 2.10 – 2.30 (m, 3H). MS (LC/MS) R.T. = 1.24; $[M+H]^+$ = 323.2.

Example 292

(R)-N-(6-Bromoisoquinolin-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

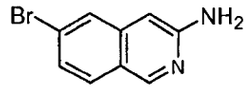


Step A: N-(4-Bromobenzyl)-2,2-diethoxyacetimidamide



(4-Bromophenyl)methanamine hydrochloride (2.359 g, 10.39 mmol) and sodium methoxide (2.376 mL, 10.39 mmol) were added to a solution of methyl 2,2-diethoxyacetimidate (3.35 g, 20.78 mmol) in methanol (10 ml). The cloudy mixture was heated at 70 C for 1.5 h and the resulting yellow mixture was concentrated. The residue was purified by silica gel with 100% ethyl acetate to give a yellow viscous oil (2.04 g, 62%). ^{1}H NMR (400 MHz, *CDCl*$_3$) δ ppm 7.47 (2 H, d, *J*=8.56 Hz), 7.23 (2 H, d, *J*=8.06 Hz), 6.76 (1 H, br. s.), 5.31 (1 H, br. s.), 4.94 (1 H, br. s.), 4.45 (2 H, br. s.), 3.47 - 3.77 (4 H, m), 1.26 (6 H, t, *J*=7.05 Hz). LCMS:R.T. = 2.12; $[M+2]^+$ = 317.2.

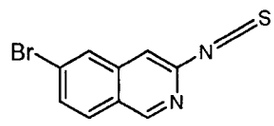
Step B: 6-Bromoisoquinolin-3-amine



N-(4-bromobenzyl)-2,2-diethoxyacetimidamide (1.53 g, 4.85 mmol) in sulfuric acid (4 mL, 95-98 %) was heated at 40 C for 14 h. The mixture was neutralized with 1 M NaOH to pH 7 and the resulting suspension was filtered. The

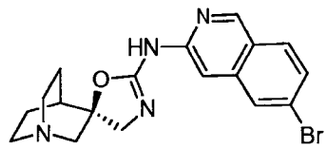
residue was purified by silica gel chromatography with 20-55% ethyl acetate in hexanes. The desired fractions were concentrated to give a brownish yellow solid (0.434 g, 40%). LCMS:R.T. = 1.62; $[M+2]^+ = 225.1$.

Step C: 6-Bromo-3-isothiocyanatoisoquinoline



To a solution of 1,1'-thiocarbonyldipyridin-2(1H)-one (0.251 g, 1.080 mmol) in dichloromethane at room temperature was added 6-bromoisoquinolin-3-amine (0.241 g, 1.080 mmol). The solution was stirred at room temperature for 3 hours. LC/MS indicated formation of the desired product. The deep orange solution was purified by silica gel chromatography (0-10% ethyl acetate-hexanes) to afford: 6-bromo-3-isothiocyanatoisoquinoline (0.1 g, 0.377 mmol, 35 % yield) as a yellow oil. R.T. = 2.54; $[M+H]^+ = 267.04$.

Step D: (R)-N-(6-bromoisoquinolin-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

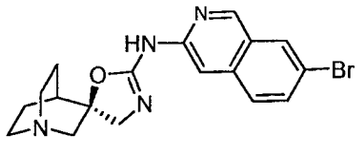


To (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (0.086 g, 0.377 mmol) in N,N-dimethylformamide (15 mL) was added Cs_2CO_3 (0.307 g, 0.943 mmol) and 6-bromo-3-isothiocyanatoisoquinoline (0.1 g, 0.377 mmol). The suspension was stirred at room temperature for 30 minutes. N,N'-Diisopropylcarbodiimide (0.176 mL, 1.132 mmol) was then added and the mixture was stirred for a further 18 hours. The mixture was concentrated and purified by silica gel chromatography (5-25 % [9.5:0.5 methanol:ammonium hydroxide]-ethyl acetate) to afford (R)-N-(6-bromoisoquinolin-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.054 g, 0.135 mmol, 36 % yield) as a yellow solid. ^1H NMR (400 MHz, *MeOD*) δ ppm 9.04 (1 H, s), 7.80 - 8.05 (2 H, m), 7.55 (1 H, dd,

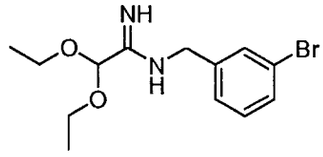
J=8.81, 1.76 Hz), 7.37 (1 H, br. s.), 4.10 (1 H, d, *J*=10.58 Hz), 3.87 (1 H, d, *J*=10.83 Hz), 3.68 - 3.77 (1 H, m), 3.56 - 3.67 (1 H, m), 3.29 - 3.49 (4 H, m), 2.45 (1 H, br. s.), 2.28 - 2.41 (1 H, m), 1.86 - 2.15 (3 H, m). LCMS:R.T. = 1.76; $[M+]^+$ = 387.21.

Example 293

(R)-N-(7-Bromoisoquinolin-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

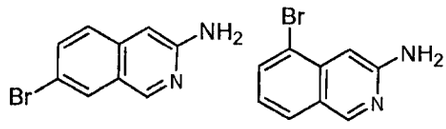


Step A: N-(3-Bromobenzyl)-2,2-diethoxyacetimidamide



(3-Bromophenyl)methanamine hydrochloride (3.62 g, 15.64 mmol) and sodium methoxide (3.58 mL, 15.64 mmol) were added to a solution of methyl 2,2-diethoxyacetimidate (5.042 g, 31.3 mmol) in methanol (15 mL). The cloudy mixture was heated at 70 C for 1.5 h and the resulting yellow mixture was concentrated. The residue was purified by silica gel chromatography with 100% ethyl acetate. The desired fractions were concentrated to give a yellow viscous oil (2.5 g, 51%). LCMS:R.T. = 2.11; $[M+2]^+$ = 317.06.

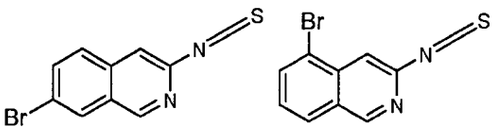
Step B: 7-Bromoisoquinolin-3-amine and 5-bromoisoquinolin-3-amine



N-(3-Bromobenzyl)-2,2-diethoxyacetimidamide (2.5 g, 7.93 mmol)in sulfuric acid (5 mL, 95-98 %) was heated at 40 C for 54 h. The mixture was neutralized with 10 M NaOH aqueous to pH 7 and the resulting suspension was filtered. The residue was purified by silica gel chromatography with 20-55% ethyl acetate in hexanes, then

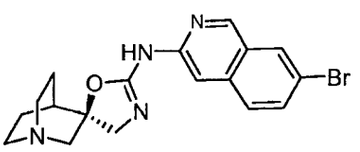
100% ethyl acetate. The fractions were concentrated to give a brown solid containing a mixture of products. (1.0 g, 57%). LCMS:R.T. = 1.56; $[M+2]^+ = 225.1$. The mixture was used as is for the next step.

Step C: 7-Bromo-3-isothiocyanatoisoquinoline and 5-bromo-3-Isothiocyanatoisoquinoline



To a solution of 1,1'-thiocarbonyldipyridin-2(1H)-one 1.145 g, 4.93 mmol) in dichloromethane at room temperature was added the mixture of 7-bromoisoquinolin-3-amine and 5-bromoisoquinolin-3-amine from step B (1.0 g, 4.5 mmol). The orange solution was stirred at room temperature for 18 hours. LCMS indicated the formation of product. The deep orange solution was purified by silica gel chromatography (0-5 % ethyl acetate-hexanes). The first product fractions were combined and concentrated *in vacuo* to afford 7-bromo-3-isothiocyanatoisoquinoline (0.27 g, 0.377 mmol, 22 % yield) as a yellow solid. ^{1}H NMR (400 MHz, *Acetone*) δ ppm 9.19 (1 H, s), 8.41 (1 H, s), 7.86 - 8.02 (2 H, m), 7.76 (1 H, s). R.T. = 4.28; $[M+H]^+ = 267.04$. The second product fractions were combined and concentrated *in vacuo* to afford 5-bromo-3-isothiocyanatoisoquinoline (0.25 g, 0.377 mmol, 21 % yield) as a yellow solid. ^{1}H NMR (400 MHz, *Acetone*) δ ppm 9.24 (1 H, s), 8.23 (1 H, d), 8.15 (1 H, d), 7.81 (1 H, s), 7.64 (1 H, t). LCMS:R.T. = 4.61; $[M+H]^+ =$ 267.04.

Step D:(R)-N-(7-Bromoisoquinolin-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

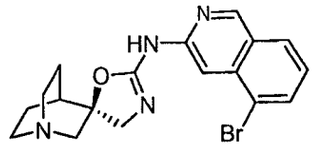


To (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (0.207 g, 0.905 mmol) in N,N-dimethylformamide (20 mL) was added Cs_2CO_3 (0.737 g, 2.263

mmol) and 7-bromo-3-isothiocyanatoisoquinoline (0.24 g, 0.905 mmol). The suspension was stirred at room temperature for 30 minutes. N,N'-Diisopropylcarbodiimide (0.423 mL, 2.72 mmol) was then added and the mixture was stirred at room temperature for 18 hours. The mixture was concentrated and purified by silica gel chromatography using 5-15% [9:1 methanol:ammonium hydroxide] in ethyl acetate. The desired fractions were concentrated and further purified using 5-15% [9.5:0.5 methanol:ammonium hydroxide] in ethyl acetate to afford ((R)-N-(7-bromoisoquinolin-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.061 g, 0.156 mmol, 17 % yield) as a yellow solid. ^{1}H NMR (400 MHz, *MeOD*) δ ppm 8.96 (1 H, s), 8.12 (1 H, s), 7.66 (2 H, s), 7.32 (1 H, s), 4.01 (1 H, d), 3.73 (1 H, d), 3.35 - 3.42 (1 H, m), 3.22 - 3.29 (1 H, m), 2.84 - 3.17 (4 H, m), 2.13 - 2.35 (2 H, m), 1.62 - 1.96 (3 H, m). LCMS:R.T. = 1.76; $[M+]^+$ = 387.21.

Example 294

((R)-N-(5-Bromoisoquinolin-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine

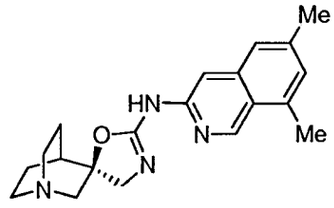


To (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (0.207 g, 0.905 mmol) in N,N-dimethylformamide (20 mL) was added Cs_2CO_3 (0.737 g, 2.263 mmol) and 5-bromo-3-isothiocyanatoisoquinoline (0.24 g, 0.905 mmol). The suspension was stirred at room temperature for 30 minutes. N,N'-Diisopropylcarbodiimide (0.423 mL, 2.72 mmol) was then added and the mixture was stirred at room temperature for 18 hours. The mixture was concentrated and purified by silica gel chromatography (5-15 % [9.5:0.5 methanol:ammonium hydroxide]-ethyl acetate). The desired fractions were concentrated and further purified using 5-15% [9.5:0.5 methanol:ammonium hydroxide] in ethyl acetate to afford (R)-N-(5-bromoisoquinolin-3-yl)-4H-1'-azaspiro[oxazole-5,3'-bicyclo[2.2.2]octan]-2-amine (0.248 g, 0.634 mmol, 70 % yield) as a yellow solid.

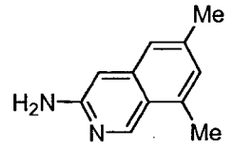
^{1}H NMR (400 MHz, *MeOD*) δ ppm 8.99 (1 H, s), 7.91 (2 H, dd), 7.55 (1 H, br. s.), 7.28 (1 H, t), 3.96 (1 H, d), 3.65 (1 H, d), 3.17 - 3.26 (1 H, m), 3.03 - 3.13 (1 H, m), 2.70 - 2.99 (4 H, m), 2.03 - 2.30 (2 H, m), 1.47 - 1.87 (3 H, m). LCMS:R.T. = 1.69; $[M+2]^+$ = 389.21.

EXAMPLE 295

(2R)-N-(6,8-Dimethyl-3-isoquinolinyl)-4'H-spiro[4-azabicyclo[2.2.2]octane-2,5'-[1,3]oxazol]-2'-amine

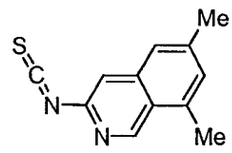


Step A: 6,8-Dimethylisoquinolin-3-amine



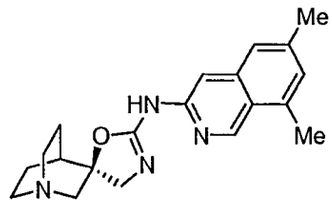
To a solution of methyl 2,2-diethoxyacetimidate (1.5 g, 9.3 mmol) in methanol (4.9 mL) was added (2,4-dimethylphenyl)methanamine (1.2 g, 8.9 mmol) dropwise at ambient temperature. The reaction flask was then placed into a preheated oil-bath and stirred at 70 °C for 16 h, then cooled and the volatiles removed under reduced pressure. The crude material was added dropwise to sulfuric acid (19.7 mL) at ambient temperature and stirred for 72 h. The flask was then placed into an ice-water bath, diluted with water (50 mL), and slowly neutralized to pH = 10 with sodium hydroxide (10 N). As the reaction mixture became basic, an orange precipitate formed. This precipitate was filtered, washed with water, and dried to afford 6,8-dimethylisoquinolin-3-amine (1.37 g, 7.95 mmol, 90 %). 1H NMR (400 MHz, MeOD) δ ppm 8.82 (s, 1 H), 7.17 (s, 1 H), 6.90 (s, 1 H), 6.72 (s, 1 H), 2.61 (s, 3 H), 2.37 (s, 3 H). MS (LC/MS) R.T. = 0.77; $[M+H]^+$ = 173.15.

Step B: 3-Isothiocyanato-6,8-dimethylisoquinoline



To a solution of 1,1'-thiocarbonyldipyridin-2(1H)-one (1.35 g, 5.8 mmol) in dichloromethane (19 mL) at ambient temperature was added 6,8-dimethylisoquinolin-3-amine (1 g, 5.8 mmol). The reaction mixture was placed into a preheated oil-bath and stirred at 40 °C for 18 h, then cooled, concentrated, and the crude material was purified by silica gel chromatography (10-35 % ethyl acetate in hexanes) to afford 3-isothiocyanato-6,8-dimethylisoquinoline (93.7 mg, 0.437 mmol, 8 %) as a yellow solid. 1H NMR (400 MHz, $CDCl_3$) δ ppm 9.20 (s, 1 H), 7.36 - 7.44 (m, 2 H), 7.23 (s, 1 H), 2.75 (s, 3 H), 2.51 (s, 3 H). MS (LC/MS) R.T. = 2.03; $[M+H]^+ = 215.1$.

Step C: (2R)-N-(6,8-Dimethyl-3-isoquinolinyl)-4'H-spiro[4-azabicyclo[2.2.2]octane-2,5'-[1,3]oxazol]-2'-amine



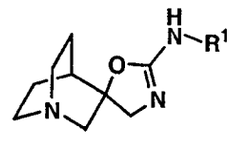
To (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (99 mg, 0.43 mmol) in N,N-dimethylformamide (1.4 mL) was added triethylamine (0.18 mL, 1.3 mmol) and 3-isothiocyanato-6,8-dimethylisoquinoline (93 mg, 0.43 mmol). The suspension was placed into a preheated oil-bath and stirred at 70 °C for 2 h and 30 min. N,N'-Diisopropylcarbodiimide (0.27 mL, 1.7 mmol) was then added and the mixture was stirred at 85 °C for 16 h. The mixture was concentrated and purified by silica gel chromatography (0-40 % [9:1 methanol:ammonium hydroxide] in chloroform) followed by purification by reverse phase preparative HPLC (0-40 % [0.1% TFA]-methanol-water) to afford (2R)-N-(6,8-dimethyl-3-isoquinolinyl)-4'H-spiro[4-

azabicyclo[2.2.2]octane-2,5'-[1,3]oxazol]-2'-amine as the trifluoroacetic acid salt (24 mg, 0.053 mmol, 12 % yield) as a white solid. 1H NMR (400 MHz, MeOD) δ ppm 9.29 (s, 1 H), 7.54 (s, 1 H), 7.43 (s, 1 H), 7.34 (s, 1 H), 4.38 (d, J=11.04 Hz, 1 H), 4.17 (d, J=11.04 Hz, 1 H), 3.94- 4.10 (m, 1 H), 3.86 (dd, J=15.06, 2.26 Hz, 1 H), 3.51 - 3.67 (m, 1 H), 3.37 - 3.51 (m, 3 H), 2.77 (s, 3 H), 2.73 (d, J=3.51 Hz, 1 H), 2.48 - 2.57 (m, 3 H), 2.30 - 2.46 (m, 1 H), 1.94 - 2.28 (m, 3 H). MS (LC/MS) R.T. = 0.90; $[M+H]^+$ = 337.38.

It will be evident to one skilled in the art that the present disclosure is not limited to the foregoing illustrative examples, and that it can be embodied in other specific forms without departing from the essential attributes thereof. It is therefore desired that the examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing examples, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

CLAIMS

1. A compound of formula I, or a stereoisomer thereof,



I

wherein

R^1 is selected from the group consisting of isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, triazinyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, naphthyridinyl, indazolyl, indolyl, 2-indolonyl, benzisoxazolyl, benzoisothiazolyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, furopyridinyl, thienopyridinyl, thienopyrimidinyl, isothiazolopyridinyl, thiazolopyridinyl, thiazolopyridinonyl, thiazolopyrazinyl, thiazolopyrimidinyl, triazolopyridinyl, triazolopyrazinyl, pyrrolotriazinyl, 5,6-dihydrobenzo[h]quinazolinyl, 5H-chromeno[4,3-d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[d]pyrimidinyl, 5,6,7,8-tetrahydroquinazolinyl, 7,8-dihydroquinazolin-5(6H)-onyl, and tetrahydrobenzothiazolyl, and is substituted with 0-3 substituents independently selected from the group consisting of C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}haloalkoxy, C_{3-7}cycloalkoxy, C_{1-4}alkylthio, phenoxy, benzyloxy, halo, hydroxy, cyano, C_{1-4}alkylsulfonyl, NR^2R^3, pyrrolidinonyl, methylenedioxy, furyl, thienyl, triazolyl, pyrimidinyl, naphthyl, C_{1-4}alkylamido, $CONR^2R^3$, pyridyl, phenyl, and benzyl, and where pyridyl, phenyl and benzyl are substituted with 0-2 substituents independently selected from the group consisting of halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, and NR^2R^3;

R^2 is hydrogen, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, or C_{1-4}aminoalkyl;

R^3 is hydrogen, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, or C_{1-4}aminoalkyl;

or R_2 and R_3 taken together with the nitrogen atom to which they are attached is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, N-(C_{1-4}alkyl)piperazinyl, morpholinyl, or homopiperidinyl;

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 where R^1 is selected from the group consisting of dimethylisoxazolyl, (methyl)(phenyl)isoxazolyl, methylpyrazolyl, dimethylpyrazolyl, thienylpyrazolyl, methoxyphenylpyrazolyl, thiazolyl, bromothiazolyl, cyanothiazolyl, methylthiazolyl, dimethylthiazolyl, (methyl)(phenyl)thiazolyl, isopropylthiazolyl, butylthiazolyl, benzylthiazolyl, methoxyphenylmethylthiazolyl, phenylthiazolyl, chlorophenylthiazolyl, methoxyphenylthiazolyl, (methoxyphenyl)(methyl)thiazolyl, pyridinylthiazolyl, (phenyl)(methyl)imidazolyl, methyloxadiazolyl, ethyloxadiazolyl, methylthiadiazolyl, fluorophenylthiadiazolyl, furylthiadiazolyl, (dimethylcarboxamido)(methyl)thiazolyl, (pyrrolidinylCO)thiazolyl, phenyltriazolyl, pyridinyl, bromopyridinyl, chloropyridinyl, (chloro)(fluoro)pyridinyl, (chloro)(methyl)pyridinyl, dichloropyridinyl, fluoropyridinyl, cyanopyridinyl, (cyano)(methyl)pyridinyl, (cyano)(dimethyl)pyridinyl, methoxypyridinyl, (methylpyrrolidinyl)pyridinyl, phenylpyridinyl, methoxypyridinylpyridinyl, pyridazinyl, bromopyridazinyl, chloropyridazinyl, methylpyridazinyl, methoxypyridazinyl, methylthiopyridazinyl, pyrrolidinylpyridazinyl, pyrrolidinonylpyridazinyl, phenylpyridazinyl, pyridinylpyridazinyl, methoxypyridinylpyridazinyl, pyrimidinyl, (bromo)(isopropyl)pyrimidinyl, (bromo)(dimethyl)pyrimidinyl, (bromo)(cyclopropyl)pyrimidinyl, (bromo)(methoxy)pyrimidinyl, (bromo)(phenyl)pyrimidinyl, (bromo)(pyridinyl)pyrimidinyl, chloropyrimidinyl, (chloro)(dimethyl)pyrimidinyl, (methyl)(methoxy)pyrimidinyl, methylpyrimidinyl, ethylpyrimidinyl, (methyl)(phenyl)pyrimidinyl, dimethylpyrimidinyl, butylpyrimidinyl, isopropylpyrimidinyl, cyclopropylpyrimidinyl, methoxypyrimidinyl, dimethoxypyrimidinyl, isopropoxypyrimidinyl, cyclopentoxypyrimidinyl, difluoromethoxypyrimidinyl, trifluoroethoxypyrimidinyl, phenoxypyrimidinyl, methylthiopyrimidinyl, phenylpyrimidinyl, chlorophenylpyrimidinyl, methylphenylpyrimidinyl, methoxyphenylpyrimidinyl,

(phenyl)(triazolyl)pyrimidinyl, pyridinylpyrimidinyl, methoxypyridinylpyrimidinyl, methoxypyrimidinylpyrimidinyl, naphthylpyrimidinyl, pyrazinyl, bromopyrazinyl, (bromo)(methoxy)pyrazinyl, chloropyrazinyl, methylpyrazinyl, dimethylpyrazinyl, butylpyrazinyl, cyanopyrazinyl, methoxypyrazinyl, isopropoxypyrazinyl, trifluoromethylpyrazinyl, and phenylpyrazinyl, and dimethyltriazinyl;

or a pharmaceutically acceptable salt thereof.

3. A compound of claim 1 where R^1 is selected from the group consisting of dimethylpyridinoisoxazolyl, benzoxazolyl, chlorobenzoxazolyl, fluorophenylbenzoxazolyl, ethylphenylbenzoxazolyl, dimethylaminophenylbenzoxazolyl, pyridinylbenzoxazolyl, benzothiazolyl, acetamidobenzothiazolyl, bromobenzothiazolyl, chlorobenzothiazolyl, (chloro)(methyl)benzothiazolyl, (chloro)(methoxy)benzothiazolyl, fluorobenzothiazolyl, difluorobenzothiazolyl, cyanobenzothiazolyl, methylbenzothiazolyl, dimethylbenzothiazolyl, (methyl)(methoxy)benzothiazolyl, ethylbenzothiazolyl, trifluoromethylbenzothiazolyl, hydroxybenzothiazolyl, methoxybenzothiazolyl, ethoxybenzothiazolyl, isopropoxybenzothiazolyl, trifluoromethoxybenzothiazolyl, difluoromethoxybenzothiazolyl, dimethoxybenzothiazolyl, morpholinylbenzothiazolyl, (pyrrolidinylCO)benzothiazolyl, methylsulfonylbenzothiazolyl, chlorothiazolopyridinyl, dimethylthiazolopyridinyl, benzyloxythiazolopyridinyl, difluoromethoxythiazolopyridinyl, benzotriazolyl, indolonyl, indazolyl, bromoindazolyl, chloroindazolyl, fluoroindazolyl, (methyl)(methoxy)indazolyl, methoxyindazolyl, trifluoromethylindazolyl, trifluoromethoxyindazolyl, difluoromethoxyindazolyl, benzimidazolyl, fluorobenzimidazolyl, methylbenzimidazolyl, (methyl)(methoxy)benzimidazolyl, methoxybenzimidazolyl, tetrahydrobenzothiazolyl, furopyridinyl, dimethylfuropyrimidinyl, thienopyrimidinyl, isopropylthienopyrimidinyl, dimethylthienopyrimidinyl, chlorotriazolopyridinyl, methyltriazolopyridinyl, trifluoromethyltriazolopyridinyl, methoxytriazolopyridinyl, triazolopyrazinyl, bromopyrrolotriazinyl, dimethylaminothiazolopyrimidinyl, thiazolopyazinyl, bromothiazolopyazinyl, methoxythiazolopyazinyl, methylthiothiazolopyazinyl, methoxythiazolopyrimidinyl,

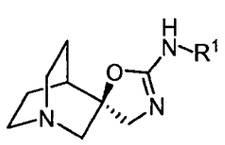
(methyl)(methoxy)thiazolopyrimidinyl, quinolinyl, bromoquinolinyl, fluoroquinolinyl, methylquinolinyl, (methyl)(methoxy)quinolinyl, isoquinolinyl, bromoisoquinolinyl, dichloroisoquinolinyl, methylisoquinolinyl, dimethylisoquinolinyl, quinoxalinyl, chloroquinoxalinyl, methylquinoxalinyl, methoxyquinoxalinyl, quinazolinyl, bromoquinazolinyl, naphthyridinyl, 5,6-dihydrobenzo[h]quinazolinyl, 5H-chromeno[4,3-d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[d]pyrimidinyl, 5,6,7,8-tetrahydroquinazolinyl, and 7,8-dihydroquinazolin-5(6H)-onyl;

or a pharmaceutically acceptable salt thereof.

4. A compound of claim 1 where R^1 is selected from the group consisting of phenylthiazolyl, (chloro)(methyl)pyridinyl, (bromo)(phenyl)pyrimidinyl, methoxypyrimidinyl, difluoromethoxypyrimidinyl, difluoroethoxypyrimidinyl, cyclopentoxypyrimidinyl, (methylphenyl)pyrimidinyl, (methoxyphenyl)pyrimidinyl, bromopyrazinyl, chloropyrazinyl, methylthiopyrazinyl, methoxybenzothiazolyl, ethoxybenzothiazolyl, difluoromethoxybenzothiazolyl, thiazolopyridinonyl, trifluoromethylindazolyl, benzimidazolyl, isoquinoinyl, and quinazolinyl;

or a pharmaceutically acceptable salt thereof.

5. The stereoisomer of claim 1 according to Formula Ia;



Ia

or a pharmaceutically acceptable salt thereof.

6. A compound of claim 5 where R^1 is selected from the group consisting of dimethylisoxazolyl, (methyl)(phenyl)isoxazolyl, methylpyrazolyl, dimethylpyrazolyl, thienylpyrazolyl, methoxyphenylpyrazolyl, thiazolyl, bromothiazolyl, cyanothiazolyl, methylthiazolyl, dimethylthiazolyl, (methyl)(phenyl)thiazolyl, isopropylthiazolyl,

butylthiazolyl, benzylthiazolyl, methoxyphenylmethylthiazolyl, phenylthiazolyl, chlorophenylthiazolyl, methoxyphenylthiazolyl, (methoxyphenyl)(methyl)thiazolyl, pyridinylthiazolyl, (phenyl)(methyl)imidazolyl, methyloxadiazolyl, ethyloxadiazolyl, methylthiadiazolyl, fluorophenylthiadiazolyl, furylthiadiazolyl, (dimethylcarboxamido)(methyl)thiazolyl, (pyrrolidinylCO)thiazolyl, phenyltriazolyl, pyridinyl, bromopyridinyl, chloropyridinyl, (chloro)(fluoro)pyridinyl, (chloro)(methyl)pyridinyl, dichloropyridinyl, fluoropyridinyl, cyanopyridinyl, (cyano)(methyl)pyridinyl, (cyano)(dimethyl)pyridinyl, methoxypyridinyl, (methylpyrrolidinyl)pyridinyl, phenylpyridinyl, methoxypyridinylpyridinyl, pyridazinyl, bromopyridazinyl, chloropyridazinyl, methylpyridazinyl, methoxypyridazinyl, methylthiopyridazinyl, pyrrolidinylpyridazinyl, pyrrolidinonylpyridazinyl, phenylpyridazinyl, pyridinylpyridazinyl, methoxypyridinylpyridazinyl, pyrimidinyl, (bromo)(isopropyl)pyrimidinyl, (bromo)(dimethyl)pyrimidinyl, (bromo)(cyclopropyl)pyrimidinyl, (bromo)(methoxy)pyrimidinyl, (bromo)(phenyl)pyrimidinyl, (bromo)(pyridinyl)pyrimidinyl, chloropyrimidinyl, (chloro)(dimethyl)pyrimidinyl, (methyl)(methoxy)pyrimidinyl, methylpyrimidinyl, ethylpyrimidinyl, (methyl)(phenyl)pyrimidinyl, dimethylpyrimidinyl, butylpyrimidinyl, isopropylpyrimidinyl, cyclopropylpyrimidinyl, methoxypyrimidinyl, dimethoxypyrimidinyl, isopropoxypyrimidinyl, cyclopentoxypyrimidinyl, difluoromethoxypyrimidinyl, trifluoroethoxypyrimidinyl, phenoxypyrimidinyl, methylthiopyrimidinyl, phenylpyrimidinyl, chlorophenylpyrimidinyl, methylphenylpyrimidinyl, methoxyphenylpyrimidinyl, (phenyl)(triazolyl)pyrimidinyl, pyridinylpyrimidinyl, methoxypyridinylpyrimidinyl, methoxypyrimidinylpyrimidinyl, naphthylpyrimidinyl, pyrazinyl, bromopyrazinyl, (bromo)(methoxy)pyrazinyl, chloropyrazinyl, methylpyrazinyl, dimethylpyrazinyl, butylpyrazinyl, cyanopyrazinyl, methoxypyrazinyl, isopropoxypyrazinyl, trifluoromethylpyrazinyl, and phenylpyrazinyl, and dimethyltriazinyl;

or a pharmaceutically acceptable salt thereof.

7. A compound of claim 5 where R^1 is selected from the group consisting of dimethylpyridinoisoxazolyl, benzoxazolyl, chlorobenzoxazolyl,

fluorophenylbenzoxazolyl, ethylphenylbenzoxazolyl, dimethylaminophenylbenzoxazolyl, pyridinylbenzoxazolyl, benzothiazolyl, acetamidobenzothiazolyl, bromobenzothiazolyl, chlorobenzothiazolyl, (chloro)(methyl)benzothiazolyl, (chloro)(methoxy)benzothiazolyl, fluorobenzothiazolyl, difluorobenzothiazolyl, cyanobenzothiazolyl, methylbenzothiazolyl, dimethylbenzothiazolyl, (methyl)(methoxy)benzothiazolyl, ethylbenzothiazolyl, trifluoromethylbenzothiazolyl, hydroxybenzothiazolyl, methoxybenzothiazolyl, ethoxybenzothiazolyl, isopropoxybenzothiazolyl, trifluoromethoxybenzothiazolyl, difluoromethoxybenzothiazolyl, dimethoxybenzothiazolyl, morpholinylbenzothiazolyl, (pyrrolidinylCO)benzothiazolyl, methylsulfonylbenzothiazolyl, chlorothiazolopyridinyl, dimethylthiazolopyridinyl, benzyloxythiazolopyridinyl, difluoromethoxythiazolopyridinyl, benzotriazolyl, indolonyl, indazolyl, bromoindazolyl, chloroindazolyl, fluoroindazolyl, (methyl)(methoxy)indazolyl, methoxyindazolyl, trifluoromethylindazolyl, trifluoromethoxyindazolyl, difluoromethoxyindazolyl, benzimidazolyl, fluorobenzimidazolyl, methylbenzimidazolyl, (methyl)(methoxy)benzimidazolyl, methoxybenzimidazolyl, tetrahydrobenzothiazolyl, furopyridinyl, dimethylfuropyrimidinyl, thienopyrimidinyl, isopropylthienopyrimidinyl, dimethylthienopyrimidinyl, chlorotriazolopyridinyl, methyltriazolopyridinyl, trifluoromethyltriazolopyridinyl, methoxytriazolopyridinyl, triazolopyrazinyl, bromopyrrolotriazinyl, dimethylaminothiazolopyrimidinyl, thiazolopyazinyl, bromothiazolopyazinyl, methoxythiazolopyazinyl, methylthiothiazolopyazinyl, methoxythiazolopyrimidinyl, (methyl)(methoxy)thiazolopyrimidinyl, quinolinyl, bromoquinolinyl, fluoroquinolinyl, methylquinolinyl, (methyl)(methoxy)quinolinyl, isoquinolinyl, bromoisoquinolinyl, dichloroisoquinolinyl, methylisoquinolinyl, dimethylisoquinolinyl, quinoxalinyl, chloroquinoxalinyl, methylquinoxalinyl, methoxyquinoxalinyl, quinazolinyl, bromoquinazolinyl, naphthyridinyl, 5,6-dihydrobenzo[h]quinazolinyl, 5H-chromeno[4,3-d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[d]pyrimidinyl, 5,6,7,8-tetrahydroquinazolinyl, and 7,8-dihydroquinazolin-5(6H)-onyl;

or a pharmaceutically acceptable salt thereof.

8. A compound of claim 5 where R^1 is selected from the group consisting of phenylthiazolyl, (chloro)(methyl)pyridinyl, (bromo)(phenyl)pyrimidinyl, methoxypyrimidinyl, difluoromethoxypyrimidinyl, difluoroethoxypyrimidinyl, cyclopentoxypyrimidinyl, (methylphenyl)pyrimidinyl, (methoxyphenyl)pyrimidinyl, bromopyrazinyl, chloropyrazinyl, methylthiopyrazinyl, methoxybenzothiazolyl, ethoxybenzothiazolyl, difluoromethoxybenzothiazolyl, thiazolopyridinonyl, trifluoromethylindazolyl, benzimidazolyl, isoquinoinyl, and quinazolinyl;

or a pharmaceutically acceptable salt thereof.

9. A compound of claim 5 where R^1 is selected from the group consisting of thiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, benzothiazolyl, thiazolopyridinyl, indazolyl, benzimidazolyl, isoquinoinyl, and quinazolinyl, and is substituted with 0-3 substituents independently selected from the group consisting of C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}haloalkoxy, C_{3-7}cycloalkoxy, C_{1-4}alkylthio, phenoxy, benzyloxy, halo, hydroxy, cyano, C_{1-4}alkylsulfonyl, NR^2R^3, pyrrolidinonyl, methylenedioxy, furyl, thienyl, triazolyl, pyrimidinyl, naphthyl, C_{1-4}alkylamido, $CONR^2R^3$, pyridyl, phenyl, and benzyl, and where pyridyl, phenyl and benzyl are substituted with 0-2 substituents independently selected from the group consisting of halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, and NR^2R^3;

or a pharmaceutically acceptable salt thereof.

10. A compound of claim 9 where R^1 is selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, thiazolopyridinyl, and isoquinoinyl, and is substituted with 0-3 substituents independently selected from the group consisting of C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}haloalkoxy, C_{3-7}cycloalkoxy, C_{1-4}alkylthio, phenoxy, benzyloxy, halo, hydroxy, cyano, C_{1-4}alkylsulfonyl, NR^2R^3, pyrrolidinonyl, methylenedioxy, furyl, thienyl, triazolyl, pyrimidinyl, naphthyl, C_{1-4}alkylamido, $CONR^2R^3$, pyridyl, phenyl, and benzyl, and where pyridyl, phenyl and benzyl are substituted with 0-2 substituents independently selected from the

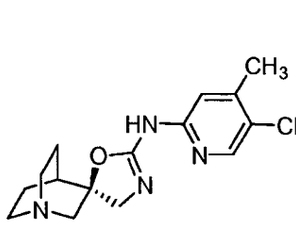
group consisting of halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, and NR^2R^3;

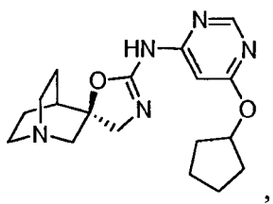
or a pharmaceutically acceptable salt thereof.

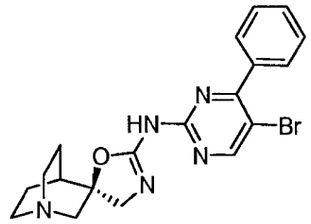
11. A compound of claim 10 where R^1 is selected from the group consisting of pyridinyl and isoquinoinyl, and is substituted with 0-3 substituents independently selected from the group consisting of C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}haloalkoxy, C_{3-7}cycloalkoxy, C_{1-4}alkylthio, phenoxy, benzyloxy, halo, hydroxy, cyano, C_{1-4}alkylsulfonyl, NR^2R^3, pyrrolidinonyl, methylenedioxy, furyl, thienyl, triazolyl, pyrimidinyl, naphthyl, C_{1-4}alkylamido, $CONR^2R^3$, pyridyl, phenyl, and benzyl, and where pyridyl, phenyl and benzyl are substituted with 0-2 substituents independently selected from the group consisting of halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, and NR^2R^3;

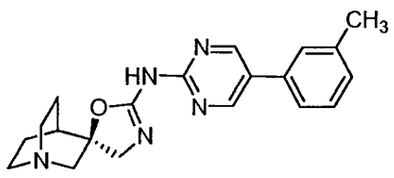
or a pharmaceutically acceptable salt thereof.

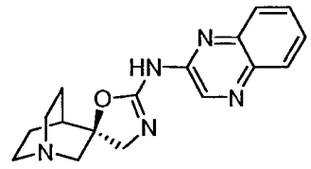
12. A compound selected from the group consisting of

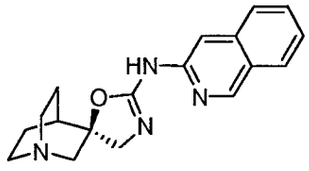


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, and


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COMPUESTOS DE QUINUCLIDINA COMO LIGANDOS DEL RECEPTOR NICOTÍNICO DE ACETILCOLINA ALFA-7

ANTECEDENTES DE LA INVENCIÓN

La revelación se refiere de forma general a compuestos de fórmula I, incluyendo sus sales, así como composiciones y procedimientos de uso de los compuestos. Los compuestos son ligandos para el receptor nicotínico $\alpha 7$ y pueden ser útiles para el tratamiento de diversos trastornos del sistema nervioso central, en especial trastornos afectivos y neurodegenerativos.

La esquizofrenia es un trastorno mental grave que afecta a aproximadamente al 1% de la población. Su curso progresivo da lugar a un importante deterioro del funcionamiento mental y social y con frecuencia conduce al desarrollo de otras patologías. Susceptiblemente cursa con frecuencia en familias y se piensa que son importantes tanto los factores genéticos como ambientales. Solo en los Estados Unidos los costes directos e indirectos de la enfermedad se estiman en miles de millones de dólares al año.

Los pacientes con esquizofrenia tienen un riesgo elevado de suicidio (aproximadamente un 10% de riesgo durante su vida). Estos tienen una mortalidad 2,5 veces superior en todas las causas, dando lugar a una esperanza de vida reducida en un 20%. El inicio de la enfermedad puede dar lugar a una cascada de factores de estilo de vida no saludable y comportamientos que elevan el riesgo de diversos estados patológicos y por consiguiente el riesgo de muerte.

El inicio de la esquizofrenia se da con frecuencia a finales de la adolescencia o al comienzo de la edad adulta y pueden producirse episodios

durante toda la vida. La enfermedad está caracterizada por la expresión de tres dominios sintomatológicos diferenciados: positivo, negativo y cognitivo. Los síntomas psicóticos o positivos incluyen, delirios, alucinaciones, trastorno mental y paranoia. Los síntomas negativos incluyen afecto negativo, abandono social y anhedonia. La disfunción cognitiva incluye deficiencias en la atención, memoria y función cognitiva. La patofisiología de la esquizofrenia no se comprende bien, no obstante, la mayoría de expertos cree que es un trastorno multifactorial en el que desempeñan una función factores biológicos, genéticos y ambientales. La mayoría de las actuales terapias apunta al sistema dopaminérgico y han dado como resultado la sugerencia de que un exceso de neurotransmisión dopaminérgica subyace al menos en ciertos aspectos de la esquizofrenia. Esta teoría recibió un importante apoyo a partir de los descubrimientos de que fármacos que aumentan los niveles de dopamina causan psicosis similares a los síntomas positivos de la enfermedad. Además, el análisis *post mortem* de cerebros de pacientes esquizofrénicos indica niveles mayores de receptores de dopamina D2. Aunque en la década pasada se han introducido agentes antipsicóticos más nuevos, conocidos como antipsicóticos atípicos, que son activos además en otros receptores neurotransmisores, estos agentes todavía comparten eficacia contra el receptor de dopamina D2. Los agentes usados en la actualidad también tienen todos importantes limitaciones. Aunque los síntomas positivos se reducen por lo general en la mayoría de pacientes, estos fármacos aportan poco a la hora de aliviar los síntomas negativos y déficits cognitivos que son comunes y con frecuencia más debilitantes. Además, los agentes antipsicóticos tienen una serie de efectos indeseados y limitantes.

La nicotina está entre los pocos agentes que tienen un efecto positivo sobre la función cognitiva. Muchos esquizofrénicos fuman; la tasa en pacientes es de 2 a 4 veces la de la población general, y hasta el 90% en esquizofrénicos que han sido internados fuman. Este hábito de fumar se ha caracterizado como una forma de automedicación.

La enfermedad de Alzheimer es un trastornos neurodegenerativo progresivo, que da lugar a una pérdida general de las funciones cognitivas. La incidencia aumenta con la edad, hasta el grado de que se estima que del 25-50% de todos los individuos mayores de 85 años sufre algún grado de demencia. Un diagnóstico del Alzheimer conlleva que la esperanza de vida restante se reduce al a mitad al compararla con adultos normales.

Los signos clínicos de la enfermedad de Alzheimer son deterioro cognitivo progresivo, menor capacidad para llevar a cabo las actividades de la vida diaria y síntomas neuropsiquiátricos o cambios en la conducta. En los estadios avanzados de la enfermedad, el deterioro de la musculatura y movilidad pueden conducir a la incapacidad para alimentarse, y finalmente a que el paciente se quede postrado. El lenguaje se convierte drásticamente desorganizado y luego se pierde completamente. Los pacientes no son capaces de llevar a cabo incluso tareas sencillas de forma independiente y requieren supervisión constante. El coste de los cuidados institucionales constituye casi el 70% del coste de la enfermedad. Por tanto, son muy necesarias terapias que aumenten la función cognitiva y retrasen el ingreso del paciente.

Los receptores nicotínicos de la acetilcolina (nAChR) son canales iónicos abiertos por ligandos pentaméricos que se expresan ampliamente a

través del sistema nervioso central y periférico. Estos canales son canales de calcio que se desesibilizan rápidamente los cuales, cuando se abren, aumentan la concentración intracelular del ion Ca^{++}. Aunque hay 12 receptores individuales, la mayoría de los receptores nicotínicos abundantes en el cerebro son $\alpha4\beta2$ y $\alpha7$. El complejo $\alpha4\beta2$ se ha identificado como el sitio nicotínico de "alta afinidad". El receptor homopentamérico $\alpha7$ se une de forma selectiva al producto natural α-bungarotoxina, que ha permitido su localización y medida relativamente fáciles. El receptor $\alpha7$ se expresa fundamentalmente en las regiones de corteza, hipocampo y límbica subcortical y se presenta comúnmente antes de la sinapsis. La localización de a7 nAChr en áreas implicadas con el aprendizaje y la memoria ha conducido a estudios que usan ratones con eliminación génica y manipulación farmacológica. Este se ve implicado en la apertura sensorial, memoria y plasticidad neuronal. Los compuestos que se unen de forma selectiva al receptor $\alpha7$ han demostrado mejorar las funciones de aprendizaje y memoria en animales normales y ancianos, revertir los déficits de memoria inducidos por escopolamina, revertir los déficits de apertura de canales inducidos farmacológicamente y poseer ciertas propiedades ansiolíticas. El receptor $\alpha7$ también ha demostrado que está implicado en la reducción de la inflamación a través del nervio vago.

La enfermedad de Alzheimer ha demostrado en varios estudios que va acompañada por una reducción en receptores nicotínicos en la corteza y el hipocampo. Se ha descrito que inyecciones de nicotina o parches cutáneos de nicotina mejoran significativamente la atención, la memoria y el aprendizaje en pacientes con enfermedad de Alzheimer. Aunque existe una pérdida progresiva de receptores nicotínicos durante el curso de la enfermedad de Alzheimer, las

neuronas α7 están relativamente libres, comparadas con los receptores α4 más abundantes. Recientemente, la administración de agonistas selectivos α7 ha demostrado aumentar la función cognitiva en pacientes con Alzheimer cuando se les dosifica durante 8 semanas.

Las siguientes referencias proporcionan revisiones generales del sistema del receptor nicotínico y los receptores α7 y ligandos: Picciotto and Zoli, *J. Neurobio.* (2002) **53**:641-655; Brening, *et al*, *Ann. Reports in Med. Chem.* (2005) **40**:3-16; Dani and Bertrand, *Ann. Rev. Pharm. Tox.* (2007) **47**:699-729; Olincy and Stevens, *Biochem. Pharmacol.* (2007) **74**:1192-1201; Broad, *et al*, *Drugs Future* (2007) **32** (2):161-70; de Jonge and Ulloa, *Brit. J. Pharmacol.* (2007) **151**:915-929; Romanelli, *et al*, *ChemMedChem* (2007) **2**(6):746-767.

Se han revelado ligandos para el receptor nicotínico α7. Véanse los documentos EP 452,101, EP 337,547, WO 2003/092580, WO 2004/000,469, la publicación de solicitud de patente US 2007004715, y C.J. Swain, *et al.*, *J. Med. Chem.*, (1992) **35**:1019-1031.

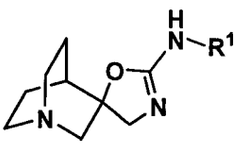
La invención proporciona ventajas técnicas, por ejemplo, los compuestos son novedosos y son eficaces contra la hepatitis C. Además, los compuestos proporcionan ventajas para usos farmacéuticos, por ejemplo, con respecto a uno o más mecanismos de acción, unión, eficacia de inhibición, selectividad de la diana, solubilidad, perfiles de seguridad o biodisponibilidad.

DESCRIPCIÓN DE LA INVENCIÓN

La invención abarca compuestos de fórmula I, incluyendo las sales farmacéuticamente aceptables y composiciones y procedimientos de

tratamiento que usan estos compuestos. Los compuestos pueden ser útiles para el tratamiento de diversos trastornos del sistema nervioso central.

Un aspecto de la invención es un compuesto de fórmula I, o uno de sus estereoisómeros,



I

en la que:

R^1 se selecciona del grupo constituido por isoxazolilo, pirazolilo, oxazolilo, tiazolilo, imidazolilo, oxadiazolilo, tiadiazolilo, triazolilo, piridinilo, pirazinilo, piridazinilo, pirimidinilo, triazinilo, quinolinilo, isoquinolinilo, quinoxalinilo, quinazolinilo, naftiridinilo, indazolilo, indolilo, 2-indolonilo, benzoisoxazolilo, benzoisotiazolilo, benzoxazolilo, benzotiazolilo, bencimidazolilo, furopiridinilo, tienopiridinilo, tienopirimidinilo, isotiazolopiridinilo, tiazolopiridinilo, tiazolopiridinonilo, tiazolopirazinilo, tiazolopirimidinilo, triazolopiridinilo, triazolopirazinilo, pirrolotriazinilo, 5,6-dihidrobenzo[h]quinazolinilo, 5H-cromeno[4,3-d]pirimidinilo, 6,7-dihidro-5H-ciclopenta[d]pirimidinilo, 5,6,7,8-tetrahidroquinazolinilo, 7,8-dihidroquinazolin-5(6H)-onilo, y tetrahidrobenzotiazolilo, y está sustituido con 0-3 sustituyentes seleccionados independientemente del grupo constituido por alquilo C_{1-4}, cicloalquilo C_{3-7}, haloalquilo C_{1-4}, alcoxi C_{1-4}, haloalcoxi C_{1-4}, cicloalcoxi C_{3-7}, (alquil C_{1-4})tio, fenoxi, benciloxi, halo, hidroxi, ciano, (alquil C_{1-4})sulfonilo, NR^2R^3, pirrolidinonilo,

metilenodioxi, furilo, tienilo, triazolilo, pirimidinilo, naftilo, (alquil C_{1-4})amido, $CONR^2R^3$, piridilo, fenilo, y bencilo, y donde piridilo, fenilo y bencilo están sustituidos con 0-2 sustituyentes seleccionados independientemente del grupo constituido por halo, alquilo C_{1-4}, alcoxi C_{1-4}, haloalquilo C_{1-4}, haloalcoxi C_{1-4} y NR^2R^3;

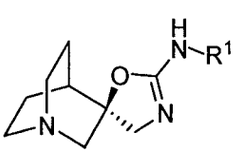
R^2 es hidrógeno, alquilo C_{1-4}, hidroxialquilo C_{1-4}, o aminoalquilo C_{1-4};

R^3 es hidrógeno, alquilo C_{1-4}, hidroxialquilo C_{1-4}, o aminoalquilo C_{1-4};

o R_2 y R_3 tomados junto con el átomo de nitrógeno a los que están unidos es azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, N-(alquil C_{1-4})piperazinilo, morfolinilo u homopiperidinilo;

o una de sus sales farmacéuticamente aceptables.

Otro aspecto de la invención es un estereoisómero de fórmula I de acuerdo con la fórmula Ia.



Ia

Otro aspecto de la invención es un compuesto de fórmula I o Ia en la que R^1 se selecciona del grupo constituido por dimetilisoxazolilo,

(metil)(fenil)isoxazolilo, metilpirazolilo, dimetilpirazolilo, tienilpirazolilo, metoxifenilpirazolilo, tiazolilo, bromotiazolilo, cianotiazolilo, metiltiazolilo, dimetiltiazolilo, (metil)(fenil)tiazolilo, isopropiltiazolilo, butiltiazolilo, benciltiazolilo, metoxifenilmetiltiazolilo, feniltiazolilo, clorofeniltiazolilo, metoxifeniltiazolilo, (metoxifenil)(metil)tiazolilo, piridiniltiazolilo, (fenil)(metil)imidazolilo, metiloxadiazolilo, etiloxadiazolilo, metiltiadiazolilo, fluorofeniltiadiazolilo, furiltiadiazolilo, (dimetilcarboxamida)(metil)tiazolilo, (pirrolidinilCO)tiazolilo, feniltriazolilo, piridinilo, bromopiridinilo, cloropiridinilo, (cloro)(fluoro)piridinilo, (cloro)(metil)piridinilo, dicloropiridinilo, fluoropiridinilo, cianopiridinilo, (ciano)(metil)piridinilo, (ciano)(dimetil)piridinilo, metoxipiridinilo, (metilpirrolidinil)piridinilo, fenilpiridinilo, metoxipiridinilpiridinilo, piridazinilo, bromopiridazinilo, cloropiridazinilo, metilpiridazinilo, metoxipiridazinilo, metiltiopiridazinilo, pirrolidinilpiridazinilo, pirrolidinonilpiridazinilo, fenilpiridazinilo, piridinilpiridazinilo, metoxipiridinilpiridazinilo, pirimidinilo, (bromo)(isopropil)pirimidinilo, (bromo)(dimetil)pirimidinilo, (bromo)(ciclopropil)pirimidinilo, (bromo)(metoxi)pirimidinilo, (bromo)(fenil)pirimidinilo, (bromo)(piridinil)pirimidinilo, cloropirimidinilo, (cloro)(dimetil)pirimidinilo, (metil)(metoxi)pirimidinilo, metilpirimidinilo, etilpirimidinilo, (metil)(fenil)pirimidinilo, dimetilpirimidinilo, butilpirimidinilo, isopropilpirimidinilo, ciclopropilpirimidinilo, metoxipirimidinilo, dimetoxipirimidinilo, isopropoxipirimidinilo, ciclopentoxipirimidinilo, difluorometoxipirimidinilo, trifluoroetoxipirimidinilo, fenoxipirimidinilo, metiltiopirimidinilo, fenilpirimidinilo, clorofenilpirimidinilo, metilfenilpirimidinilo, metoxifenilpirimidinilo, (fenil)(triazolil)pirimidinilo, piridinilpirimidinilo, metoxipiridinilpirimidinilo, metoxipirimidinilpirimidinilo, naftilpirimidinilo, pirazinilo,

bromopirazinilo, (bromo)(metoxi)pirazinilo, cloropirazinilo, metilpirazinilo, dimetilpirazinilo, butilpirazinilo, cianopirazinilo, metoxipirazinilo, isopropoxipirazinilo, trifluorometilpirazinilo y fenilpirazinilo, y dimetiltriazinilo; o una de sus sales farmacéuticamente aceptables.

Otro aspecto de la invención es un compuesto de fórmula I o la en la que R^1 se selecciona del grupo constituido por dimetilpiridinoisoxazolilo, benzoxazolilo, clorobenzoxazolilo, fluorofenilbenzoxazolilo, etilfenilbenzoxazolilo, dimetilaminofenilbenzoxazolilo, piridinilbenzoxazolilo, benzotiazolilo, acetamidabenzotiazolilo, bromobenzotiazolilo, clorobenzotiazolilo, (cloro)(metil)benzotiazolilo, (cloro)(metoxi)benzotiazolilo, fluorobenzotiazolilo, difluorobenzotiazolilo, cianobenzotiazolilo, metilbenzotiazolilo, dimetilbenzotiazolilo, (metil)(metoxi)benzotiazolilo, etilbenzotiazolilo, trifluorometilbenzotiazolilo, hidroxibenzotiazolilo, metoxibenzotiazolilo, etoxibenzotiazolilo, isopropoxibenzotiazolilo, trifluorometoxibenzotiazolilo, difluorometoxibenzotiazolilo, dimetoxibenzotiazolilo, morfolinilbenzotiazolilo, (pirrolidinilCO)benzotiazolilo, metilsulfonilbenzotiazolilo, clorotiazolopiridinilo, dimetiltiazolopiridinilo, benciloxitiazolopiridinilo, difluorometoxitiazolopiridinilo, benzotriazolilo, indolonilo, indazolilo, bromoindazolilo, cloroindazolilo, fluoroindazolilo, (metil)(metoxi)indazolilo, metoxiindazolilo, trifluorometilindazolilo, trifluorometoxiindazolilo, difluorometoxiindazolilo, bencimidazolilo, fluorobencimidazolilo, metilbencimidazolilo, (metil)(metoxi)bencimidazolilo, metoxibencimidazolilo, tetrahidrobenzotiazolilo, furopiridinilo, dimetilfuropirimidinilo, tienopirimidinilo, isopropiltienopirimidinilo,

dimetiltienopirimidinilo, clorotriazolopiridinilo, metiltriazolopiridinilo, trifluorometiltriazolopiridinilo, metoxitriazolopiridinilo, triazolopirazinilo, bromopirrolotriazinilo, dimetilaminotiazolopirimidinilo, tiazolopiazinilo, bromotiazolopiazinilo, metoxitiazolopiazinilo, metiltiotiazolopiazinilo, metoxitiazolopirimidinilo, (metil)(metoxi)tiazolopirimidinilo, quinolinilo, bromoquinolinilo, fluoroquinolinilo, metilquinolinilo, (metil)(metoxi)quinolinilo, isoquinolinilo, bromoisoquinolinilo, dicloroisoquinolinilo, metilisoquinolinilo, dimetilisoquinolinilo, quinoxalinilo, cloroquinoxalinilo, metilquinoxalinilo, metoxiquinoxalinilo, quinazolinilo, bromoquinazolinilo, naftiridinilo, 5,6-dihidrobenzo[h]quinazolinilo, 5H-cromeno[4,3- d]pirimidinilo, 6,7-dihidro-5H-ciclopenta[d]pirimidinilo, 5,6,7,8-tetrahidroquinazolinilo, y 7,8-dihidroquinazolin-5(6H)-onilo; o una de sus sales farmacéuticamente aceptables.

Otro aspecto de la invención es un compuesto de fórmula I o la en la que R^1 se selecciona del grupo constituido por feniltiazolilo, (cloro)(metil)piridinilo, (bromo)(fenil)pirimidinilo, metoxipirimidinilo, difluorometoxipirimidinilo, difluoroetoxipirimidinilo, ciclopentoxipirimidinilo, (metilfenil)pirimidinilo, (metoxifenil)pirimidinilo, bromopirazinilo, cloropirazinilo, metiltiopirazinilo, metoxibenzotiazolilo, etoxibenzotiazolilo, difluorometoxibenzotiazolilo, tiazolopiridinonilo, trifluorometilindazolilo, bencimidazolilo, isoquinoinilo y quinazolinilo o una de sus sales farmacéuticamente aceptables.

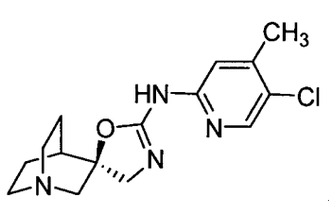
Otro aspecto de la invención es un compuesto de fórmula I o la en la que R^1 se selecciona del grupo constituido por tiazolilo, piridinilo, piridazinilo,

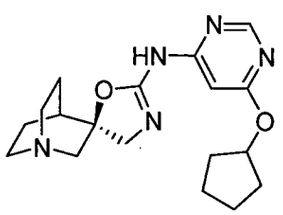
pirimidinilo, pirazinilo, benzotiazolilo, tiazolopiridinilo, indazolilo, bencimidazolilo, isoquinoinilo y quinazolinilo, y está sustituido con 0-3 sustituyentes seleccionados independientemente del grupo constituido por alquilo C_{1-4}, cicloalquilo C_{3-7}, haloalquilo C_{1-4}, alcoxi C_{1-4}, haloalcoxi C_{1-4}, cicloalcoxi C_{3-7}, (alquil C_{1-4})tio, fenoxi, benciloxi, halo, hidroxi, ciano, (alquil C_{1-4})sulfonilo, NR^2R^3, pirrolidinonilo, metilenodioxi, furilo, tienilo, triazolilo, pirimidinilo, naftilo, (alquil C_{1-4})amido, $CONR^2R^3$, piridilo, fenilo y bencilo, y donde piridilo, fenilo y bencilo están sustituidos con 0-2 sustituyentes seleccionados independientemente del grupo constituido por halo, alquilo C_{1-4}, alcoxi C_{1-4}, haloalquilo C_{1-4}, haloalcoxi C_{1-4} y NR^2R^3; o una sal farmacéuticamente aceptable de los mismos.

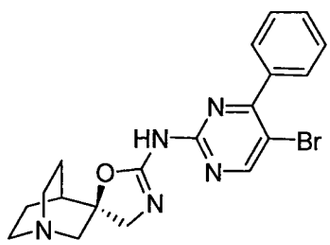
Otro aspecto de la invención es un compuesto o fórmula I o Ia en la que R^1 se selecciona del grupo constituido por piridinilo, pirimidinilo, pirazinilo, tiazolopiridinilo e isoquinoinilo, y está sustituido con 0-3 sustituyentes seleccionados independientemente del grupo constituido por alquilo C_{1-4}, cicloalquilo C_{3-7}, haloalquilo C_{1-4}, alcoxi C_{1-4}, haloalcoxi C_{1-4}, cicloalcoxi C_{3-7}, (alquil C_{1-4})tio, fenoxi, benciloxi, halo, hidroxi, ciano, (alquil C_{1-4})sulfonilo, NR^2R^3, pirrolidinonilo, metilenodioxi, furilo, tienilo, triazolilo, pirimidinilo, naftilo, (alquil C_{1-4})amido, $CONR^2R^3$, piridilo, fenilo y bencilo y donde piridilo, fenilo y bencilo están sustituidos con 0-2 sustituyentes seleccionados independientemente del grupo constituido por halo, alquilo C_{1-4}, alcoxi C_{1-4}, haloalquilo C_{1-4} , haloalcoxi C_{1-4} y NR^2R^3; o una de sus sales farmacéuticamente aceptables.

Otro aspecto de la invención es un compuesto o fórmula I o Ia en la que R^1 se selecciona del grupo constituido por piridinil y isoquinoinilo, y está sustituido con 0-3 sustituyentes seleccionados independientemente del grupo constituido por alquilo C_{1-4}, cicloalquilo C_{3-7}, haloalquilo C_{1-4}, alcoxi C_{1-4}, haloalcoxi C_{1-4}, cicloalcoxi C_{3-7}, (alquil C_{1-4})tio, fenoxi, benciloxi, halo, hidroxi, ciano, (alquil C_{1-4})sulfonilo, NR^2R^3, pirrolidinonilo, metilenodioxi, furilo, tienilo, triazolilo, pirimidinilo, naftilo, (alquil C_{1-4})amido, $CONR^2R^3$, piridilo, fenilo, y bencilo, y donde piridilo, fenilo y bencilo están sustituidos con 0-2 sustituyentes seleccionados independientemente del grupo constituido por halo, alquilo C_{1-4}, alcoxi C_{1-4}, haloalquilo C_{1-4}, haloalcoxi C_{1-4} y NR^2R^3; o una de sus sales farmacéuticamente aceptables.

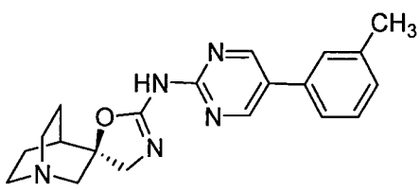
Otro aspecto de la invención es un compuesto seleccionado del grupo constituido por

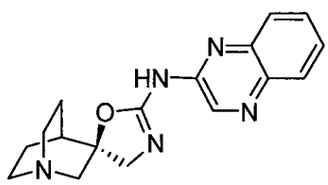


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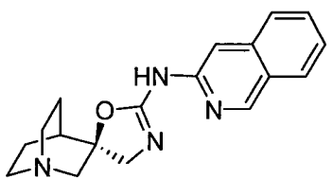
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o una de sus sales farmacéuticamente aceptables.

Otro aspecto de la invención es un compuesto de fórmula I en la que R_1 se selecciona del grupo constituido por tiazol, tiadiazol, isoxazol, oxazol, pirazol, imidazol, piridina, pirazina, piridazina, pirimidina, quinolina, isoquinolina, quinoxalina, indazol, indol, 2-indolona, benzotiazol, bencimidazol, benzoxazol, benzo(d)isotiazol, benzoisoxazol, isotiazolo-[5,4-b]piridina, (1,2,4)-triazolo[1,5-a]piridina, tiazolo[5,4-b]piridina y tetrahidrobenzotiazol en los que cada grupo está opcionalmente sustituido con uno o dos sustituyentes seleccionados del grupo constituido por alquilo C_{1-4}, alcoxi C_{1-4}, halógeno, hidroxi, ciano, trifluorometilo, difluorometilo, fluorometilo, trifluorometoxi, difluorometoxi, (alquil C_{1-4})sulfonilo, furilo, morfolino, metilenodioxi, piridilo, (alquil C_{1-4})fenilo, halofenilo, dimetilaminofenilo, (alquil C_{1-4})amido, $-CONR_2R_3$ donde R_2 y R_3 cada uno de ellos son independientemente, alquilo C_{1-4}, hidroxi alquilo C_{1-4}, amino alquilo C_{1-4} o R_2 y R_3 tomados junto con el átomo de nitrógeno al que están unidos son cicloalquilo C_{3-6}; fenilo, fenilo sustituido, fenilmetilo, fenilmetilo sustituido donde dicho fenilo sustituido y fenilmetilo sustituido están sustituidos con sustituyentes seleccionados independientemente del grupo constituido por halógeno, alquilo C_{1-4}, alcoxi C_{1-4}, trifluorometilo y triflurometoxi; o una de sus sales farmacéuticamente aceptables.

Para un compuesto de fórmula I o Ia, el alcance de cualquiera de los casos de sustituyente variable, incluyendo R^1, R^2, y R^3, se puede usar independientemente con el alcance de cualquier otro caso de un sustituyente

variable. Como tal, la invención incluye combinaciones de los diferentes aspectos.

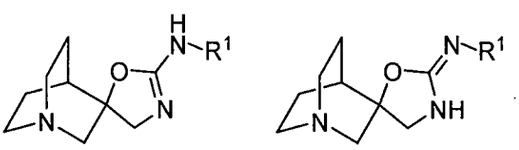
Salvo que se especifique de otra manera, estos términos tienen los siguientes significados. "Alquilo" significa un grupo alquilo lineal o ramificado compuesto de 1 a 4 carbonos. "Alquenilo" significa un grupo alquilo lineal o ramificado compuesto de 2 a 4 carbonos con al menos un doble enlace. "Alquinilo" significa un grupo alquilo lineal o ramificado compuesto de 2 a 4 carbonos con al menos un triple enlace. "Cicloalquilo" significa un sistema de anillo a monocíclico compuesto de 3 a 7 carbonos. "Haloalquilo" y "haloalcoxi" incluyen todos los isómeros halogenados desde monohalo a perhalo. Los términos con un resto hidrocarburo (por ejemplo, alcoxi) incluyen isómeros lineales y ramificados para la parte hidrocarburo. Los términos entre paréntesis y multiparéntesis pretenden clarificar las relaciones de unión para los expertos en la técnica. Por ejemplo, un término tal como ((R)alquilo) significa un sustituyente alquilo sustituido además con el sustituyente R.

La invención incluye todas las formas de sales farmacéuticamente aceptables de los compuestos. Las sales farmacéuticamente aceptables son aquellas en las que los contraiones no contribuyen de manera significativa a la actividad o toxicidad fisiológica de los compuestos y como tal funcionan como equivalentes farmacológicos. Estas sales se pueden preparar de acuerdo con las técnicas orgánicas comunes que emplean reactivos comercialmente disponibles. Algunas formas de sales aniónicas incluyen acetato, acistrato, besilato, bromuro, cloruro, citrato, fumarato, glucuronato, bromhidrato,

clorhidrato, yodhidrato, yoduro, lactato, maleato, mesilato, nitrato, pamoato, fosfato, succinato, sulfato, tartrato, tosilato y xinofoato. Algunas formas de sales catiónicas incluyen amonio, aluminio, benzatina, bismuto, calcio, colina, dietilamina, dietanolamina, litio, magnesio, meglumina, 4-fenilciclohexilamina, piperazina, potasio, sodio, trometamina y cinc.

Algunos de los compuestos de la invención existen en formas estereoisoméricas. La invención incluye todas las formas estereoisoméricas de los compuestos que incluyen enantiómeros y diastereoisómeros. Los procedimientos de preparación y separación de estereoisómeros se conocen en la técnica.

La invención incluye todas las formas tautómeras de los compuestos. Un ejemplo de un par tautómero se muestra a continuación.



Procedimientos de síntesis

Los compuestos se pueden preparar mediante procedimientos conocidos en la técnica que incluyen los descritos más adelante y que incluyen variaciones dentro de la técnica. Algunos reactivos e intermedios se conocen en la técnica. Otros reactivos e intermedios se pueden preparar mediante procedimientos conocidos en la técnica usando materiales fácilmente

disponibles. Las variables (por ejemplo, sustituyentes numerados "R") usadas para describir la síntesis de los compuestos pretenden solamente ilustrar cómo preparar los compuestos y no se han de confundir con las variables usadas en las reivindicaciones o en otras secciones de la memoria descriptiva. Los siguientes procedimientos tienen propósitos ilustrativos y no pretenden limitar el alcance de la invención.

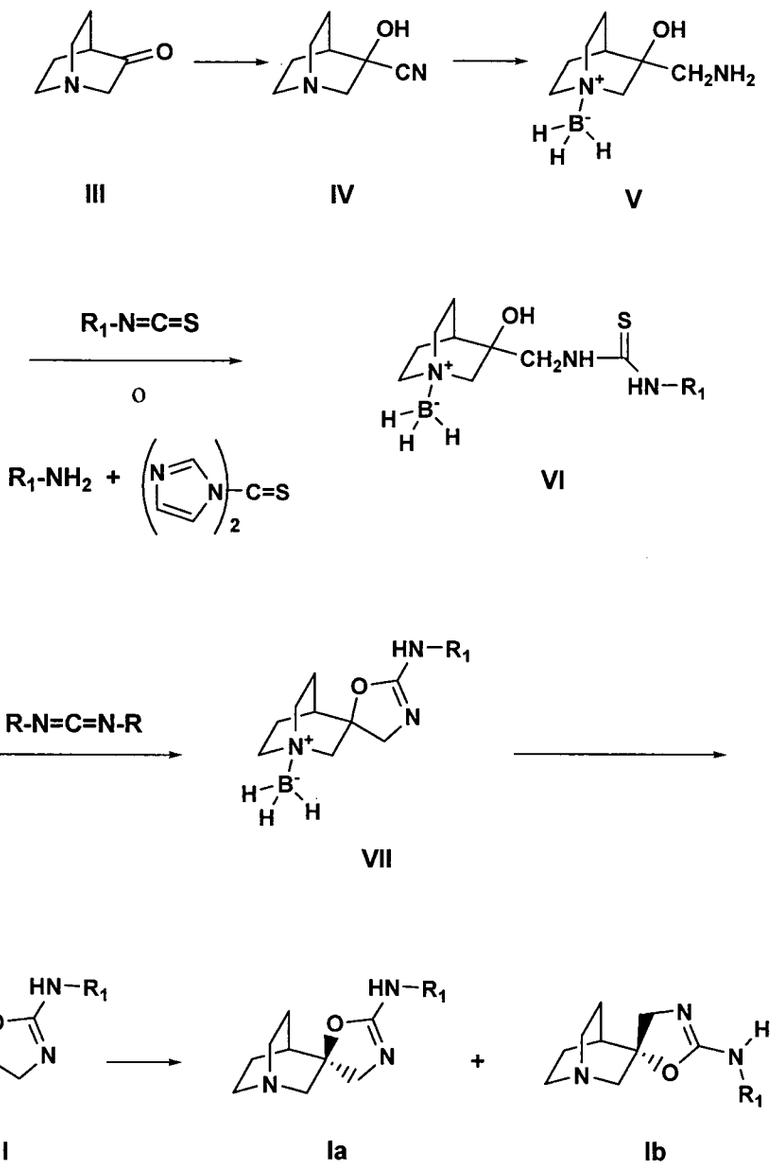
Alguno de los compuestos se puede preparar usando las reacciones y técnicas descritas en esta sección. Las reacciones se realizan en disolventes apropiados para los reactivos y materiales empleados y son adecuadas para las transformaciones que se están efectuando. Los expertos en la técnica de la síntesis orgánica entenderán que la funcionalidad presente en varias partes de la molécula debe ser compatible con los reactivos y reacciones propuestos. Tales restricciones a los sustituyentes que son compatibles con las condiciones de reacción serán fácilmente evidentes por los expertos en la técnica y se deben usar después procedimientos alternativos.

Las abreviaturas usadas en los esquemas en general siguen las convenciones usadas en la técnica. Las abreviaturas químicas usadas en la memoria descriptiva y ejemplos se definen como sigue: "NaHMDS" para bis(trimetilsilil)amida de sodio; "DMF" para N,N-dimetilformamida; "MeOH" para metanol; "NBS" para N-bromosuccinimida; "Ar" para arilo; "TFA" para ácido trifluoroacético; "LAH" para hidruro de litio y aluminio; "BOC", "DMSO" para dimetilsulfóxido; "h" para horas; "t a" para temperatura ambiente, "t r" para tiempo de retención; "min" para minutos; "EtOAc" para acetato de etilo; "THF" para tetrahidrofurano; "EDTA" para ácido etilendiaminatetraacético; "Et_2O" para éter dietílico; "DMAP" para 4-dimetilaminopiridina; "DCE" para 1,2-dicloroetano;

"ACN" para acetonitrilo; "DME" para 1,2-dimetoxietano; "HOBt" para 1-hidroxibenzotriazol hidrato; "DIEA" para diisopropiletilamina, "Nf" para $CF_3(CF_2)_3SO_2$-; y "TMOF" para ortoformiato de trimetilo.

Las abreviaturas que se usan en el presente documento, se definen como sigue: "1 x" para una vez, "2 x" para dos veces, "3 x" para tres veces, "°C" para grados Celsius, "eq" para equivalente o equivalentes, "g" para gramo o gramos, "mg" para miligramo o miligramos, "l" para litro o litros, "ml" para mililitro o mililitros, "µl" para microlitro o microlitros, "N" para normal, "M" para molar, "mmol" para milimol o milimoles, "min" para minuto o minutos, "h" para hora u horas, "t a" para temperatura ambiente, "TR" para tiempo de retención, "atm" para atmósfera, "psi" para libras por pulgada cuadrada, "conc." para concentrado, "sat" o "sat'd " para saturado, "PM" para peso molecular, "pf" para punto de fusión, "ee" para exceso enantiomérico, "MS" o "Mass Spec" para espectrometría de masas, "ESI" para espectroscopía de masas de ionización por electropulverización, "HR" para alta resolución, "HRMS" para espectrometría de masas de alta resolución, "LCMS" para espectrometría de masas de cromatografía líquida, "HPLC" para cromatografía líquida de alta presión, "RP HPLC" para HPLC de fase inversa, "TLC" o "tlc" para cromatografía en capa fina, "RMN" para espectroscopía de resonancia magnética nuclear, "^{1}H" para protón, "δ" para delta, "s" para singlete, "d" para doblete, "t" para triplete, "c" para cuartete, "m" para multiplete, "a" para ancho, "Hz" para hercio y "α", "β", "R", "S", "E", y "Z" son designaciones estereoquímicas familiares para los expertos en la técnica.

Esquema 1.



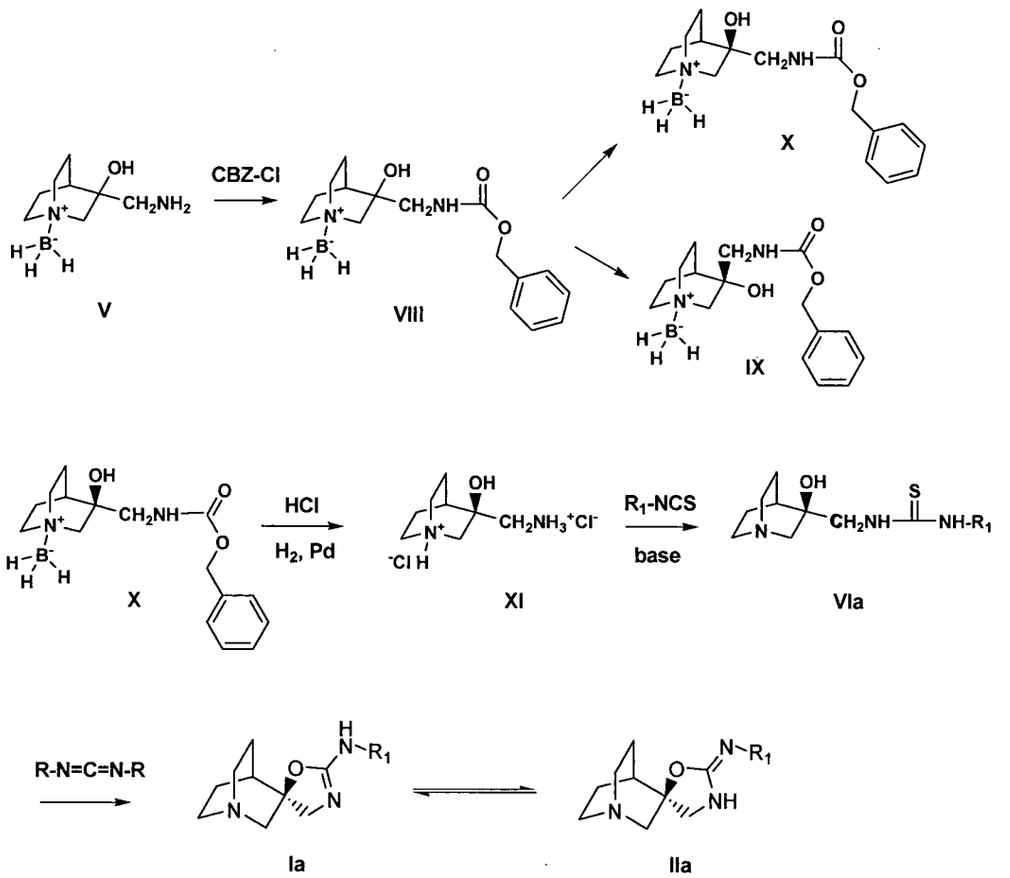
Los compuestos de Fórmula I se preparan como se ilustra en el Esquema de reacción 1. La cetona de Fórmula III (3-quinuclidona) se muestra, está disponible comercialmente, o se puede preparar por procedimientos

conocidos por los expertos en la técnica. La cetona se puede convertir en la cianohidrina correspondiente de Fórmula IV por reacción con cianuro sódico o potásico más un ácido. El compuesto de Fórmula IV se puede reducir al correspondiente compuesto de amino-metilo (complejo de borano) de Fórmula V por reacción con complejo de borano/tetrahidrofurano.

El compuesto de Fórmula V se puede hacer reaccionar con isotiocianatos de heteroarilo directamente en un disolvente inerte para dar las tioureas de Fórmula VI. De forma alternativa, la heteroarilamina se puede hacer reaccionar con tiocarbonil-diimidazol para dar una especie activada que se puede usar sin aislamiento para convertir el compuesto de Fórmula V al compuesto de Fórmula VI. La heteroarilamina se puede preparar por procedimientos conocidos por los expertos en la técnica.

La tiourea de Fórmula VI se puede ciclar usando, por ejemplo, di-isopropilcarbodiimida para dar el oxazolina de Fórmula VII que se puede desproteger por tratamiento con ácido para dar el producto racémico final de Fórmula I. El compuesto de Fórmula I se puede resolver en compuestos enantioméricos puros de Fórmula Ia y Fórmula Ib por medios conocidos en la técnica, por ejemplo, por cromatografía quiral.

Esquema 2.



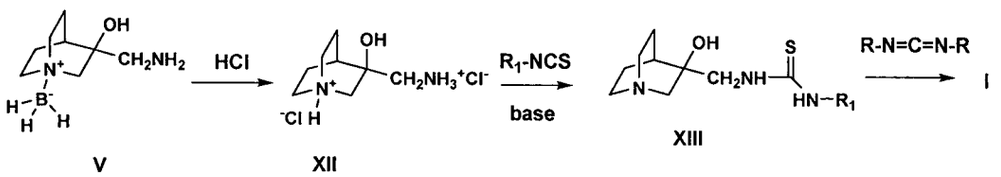
De forma alternativa, el grupo amino libre de la quinuclidina de Fórmula V se puede bloquear con, por ejemplo, carbobenciloxi-cloruro ("CBZ-Cl") para dar el compuesto de Fórmula VIII como se ilustra en el Esquema de reacción 2.

El compuesto racémico de Fórmula VIII se puede resolver en sus enantiómeros, Fórmula IX y Fórmula X por, por ejemplo, cromatografía quiral. Cualquiera del compuesto de Fórmula IX o Fórmula X, y preferiblemente el compuesto de Fórmula X, se pueden llevar como se muestran al Esquema de reacción 2.

El grupo borano en el compuesto de Fórmula X se puede retirar, por

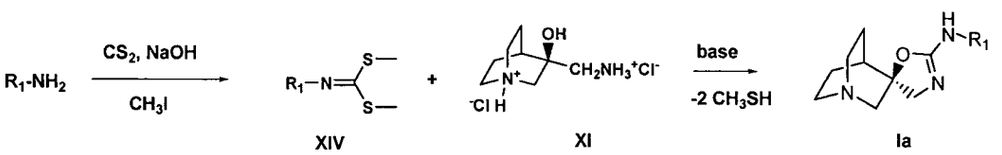
ejemplo, por tratamiento con ácido clorhídrico diluido y el grupo carbobenciloxi se puede retirar, por ejemplo, por hidrogenación catalítica para dar la quinuclidina amina quiral de Fórmula XI. De igual modo al Esquema de reacción 1, la sal de amina de Fórmula XI se puede hacer reaccionar con isotiocianatos para dar la tiourea de Fórmula VIa, que se puede hacer reaccionar con dialquil carbodiimidas o tioureas mixtas (como de la reacción de tiocarbonildiimidazol) para dar los compuestos de oxazolina quinuclidina quirales de Fórmula Ia y su tautómero, Fórmula IIa.

Esquema 2a.



De forma alternativa, el grupo borano de V se puede retirar con ácido clorhídrico para dar sal diclorhidrato XII, que se puede hacer reaccionar en presencia de base con un isotiocianato para dar la tiourea XIII intermedio, que se puede ciclar entonces como en los Esquemas de Reacción 1-2 para dar I. También se puede preparar XII por otros procedimientos, como los que se referencian en la patente de Estados Unidos nº 5.137.895 (8/11/1992).

Esquema 3.



Además, las aminas (hetero)aromáticas se pueden hacer reaccionar con

disulfuro de carbono, hidróxido sódico y yoduro de metilo para dar los carbonimidoditioatos XIV intermedios. Estos se hacen reaccionar con diclorhidrato XI en presencia de base para eliminar dos moles de metanotiol y generar los productos deseados la directamente.

Procedimientos biológicos

I) Unión del receptor nicotínico de acetilcolina α7

Se prepararon membranas para unión usando células HEK293 que expresan de manera estable el receptor nicotínico de acetilcolina α7 de rata (α7 nACr de rata). Se homogeneizaron las células a 4°C en tampón de lisis hipotónico que consta de Tris 10 mM (pH 7,4), EDTA 5 mM e inhibidores de proteasa y se centrifugaron a 32000 x g durante 20 minutos. El sedimento se lavó una vez en tampón de lavado de membrana que consta de Tris 50 mM (pH 7,4), EDTA 1 mM e inhibidores de proteasa y se centrifugaron a 32000 x g durante 20 minutos. Después este sedimento se volvió a suspender en tampón de ensayo que consiste en KH_2PO_4 50 mM (pH 7,4 a 25°C), EDTA 1 mM, Triton X 100 al 0,005% 100 y 0,1% (v/v) de Cóctel Inhibidor de Proteasa de Sigma. Se congelaron después alícuotas en hielo seco/etanol y se mantuvieron a -80°C hasta el día del ensayo.

II) Un ensayo basado en fluorescencia, sensible a Ca^{2+}, para la función de los canales de los receptores nicotínicos de acetilcolina α7 en células de mamífero ("FLIPR")

Sumario: Se evalúan compuestos de plomo para determinar la actividad

agonista en los subtipos α-7, α3β4, α4αβ2 y α1β1δ1ε de los canales de iones del receptor ACh nicotínico expresado en células HEK 293 de mamífero. Se determinan los valores de potencia agonista y eficacia a partir de las mediciones de entrada de Ca^{2+} de fluorescencia cinética realizadas usando un FLIPR (Lector de Placas de Imagen por Fluorescencia) de 384 pocillos. La utilidad de los indicadores de fluorescencia para medir los cambios en las concentraciones de cationes divalentes intracelulares, particularmente Ca^{2+}, para los propósitos de descubrimiento de fármacos está bien documentado (Rudiger, R., *et al.*, Nature Reviews, 2003, **4**: 579 - 586; González J.E., *et al.*, Receptors and Channels, 2002, **8**: 283 - 295). En este ensayo, líneas celulares HEK que expresan el canal sembradas en placas de ensayo de 384 pocillos se cargan con un colorante indicador de Ca^{2+} fluorescente que penetra en las membranas, cuya emisión verde a 510 nm se incrementa en respuesta a la elevación de la concentración de Ca^{2+} intracelular. La fluorescencia basal a partir de las células se controla en tiempo real, seguido de la adición intensa de los compuestos de ensayo. Si el compuesto es un agonista en cualquiera de los canales de catión no selectivos, los últimos se abren y permiten el movimiento de los iones Ca^{2+} extracelulares en el citoplasma de la célula, donde se unen al colorante indicador de Ca^{2+}, y producen un incremento en la señal de salida de fluorescencia, que se detecta mediante una cámara de formación de imágenes CCD refrigerada.

Materiales y Procedimientos: Reactivos: El éster acetometoxi (AM) del colorante indicador de Ca^{2+} Fluo-4 se obtuvo de InVitrogen, (Carlsbad, CA). Acetilcolina y todos los constituyentes de tampón se compraron en Sigma

Chemical Company, St. Louis, MO. G418 y el Medio Mínimo Esencial se compraron en InVitrogen Life Technologies, Carlsbad, CA. Suero Bovino Fetal se compró en (InVitrogen, Carlsbad, CA).

Cultivo de células: Se hicieron crecer células HEK-293 en Medio Mínimo Esencial que contenía 10% (v/v) de suero bovino fetal a 37° C en un incubador de CO_2 al 5%. Las células HEK-293 que expresan de manera estable los canales de ion se hicieron crecer en el mismo medio con la adición de 500 μg/ml G418.

Ensayos de flujo de Ca^{2+} de los canales Ca^{2+} expresados en células HEK-293: Células HEK-293 que expresan los canales de ion de interés se sembraron en placas de 384 pocillos, de pared negra, de fondo transparente, recubiertas con poli-D-lisina a una densidad de ~ 20.000 células/pocillo en 20 μl de Medio Mínimo Esencial que contiene 10% (v/v) de suero bovino fetal y se incubaron durante 2 días a 29° C en un incubador de CO_2 al 5%. Antes del ensayo, las células se cargaron con éter Fluo-4 AM. La carga de células se llevó a cabo retirando el medio de cultivo y reemplazándolo con 30 μl/pocillo del éster AM del colorante (5 μM) mezclado con Solución Salina Equilibrada de Hanks (nº 14175-095) que contiene HEPES 20mM, 2,5 mM de probenecid, $CaCl_2$ 0,5 mM, $MgCl_2$ 1 mM y 10 μM de atropina. Se dejó que la carga del colorante procediera durante 90 minutos a temperatura ambiente momento en el que la solución de la carga del tinte se retiró y se reemplazó con 40 μl/pocillo de tampón Hanks. Las células cargadas con colorante se cargaron sobre FLIPR384 (Molecular Devices, Sunnyvale, CA). Se excitó el colorante Fluo-4

usando la línea de 488 nm de un láser de argón. Se filtró la emisión usando un filtro de paso banda de 540 +/- 30 nm. Para la evaluación de los efectos de los compuestos de ensayo que usa el ensayo de flujo de Ca^{2+}, los compuestos a ensayar se proporcionaron en placas listas para ensayo. Para las células que expresan del ion del receptor nicotínico, se iniciaron los ensayos mediante la adición de 20 µl/pocillo de tampón de Hanks que contenía los compuestos de ensayo. Para todos los ensayos, se recogieron los datos a 1 Hz durante 10 segundos (estado inicial), momento en el que se añadieron los tampones de estímulo que contenían el compuesto, y se recogieron mediciones adicionales a 0,33Hz durante 3 min.

Análisis de datos: La validez estadística de los ensayos de flujo de Ca^{2+} del receptor nicotínico se determina a partir de los pocillos blancos y totales. Los pocillos totales definen la activación del canal máximo para cada placa de ensayo del compuesto (Dosis de eficacia Máxima de acetilcolina), y los pocillos blancos que contenían DMSO coincidente solamente definen la activación del canal cero. Los archivos de datos de unidades de fluorescencia brutas generados en el lector de placas FLIPR se exportan automáticamente y se procesan mediante herramientas de análisis de datos locales. Los datos de activación en porcentaje reducidos para cada concentración del compuesto de ensayo se ajustan usando el motor de ajuste MatiQ (ID Business Solutions Limited, Surrey, Reino Unido). Se analizaron los datos mediante ajuste de amplitudes máximas de cambio en fluorescencia, para flujo de Ca^{2+} para una condición dada del compuesto de ensayo. Potencias (valores de CE_{50}) de los compuestos se calculan a partir de tres pocillos de ensayo a partir de un CRC

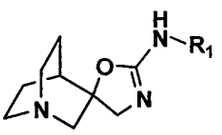
de veinte puntos. Los valores de la eficacia del compuesto de ensayo (valores Ymax) se expresan con relación a una respuesta máxima a acetilcolina en los pocillos totales.

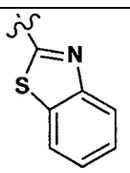
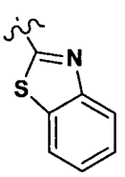
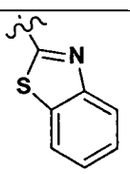
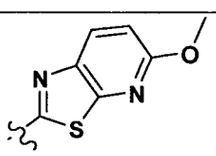
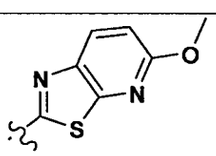
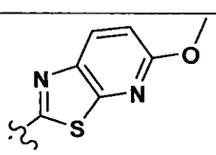
III) Ensayo de cuantificación de Fos: Ratas Wistar macho se tratan con fármaco (1 - 10 mg/kg) o vehículo (2 ml/kg, sc). Dos horas después de los tratamientos, las ratas se decapitan rápidamente y se aíslan las regiones del cerebro discretas de interés sobre hielo y se pesan y se ultracongelan con nitrógeno líquido y se almacenan a -80 °C. El procesamiento posterior del tejido del cerebro para determinar los extractos nucleares así como para la cuantificación Fos están de acuerdo con el protocolo prescrito por un kit de detección de quimioluminiscencia basado en ELISA (nº de catálogo 89860, kit EZ-detect c-Fos Trans, Pierce Biotechnology Inc., Rockford, IL).

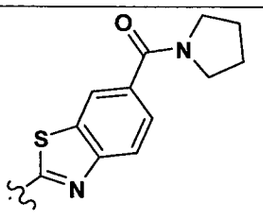
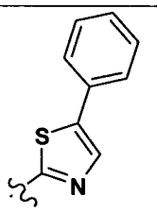
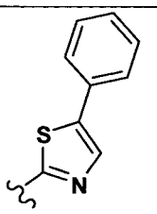
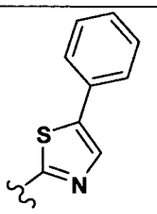
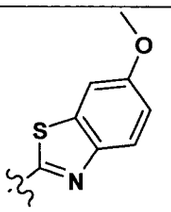
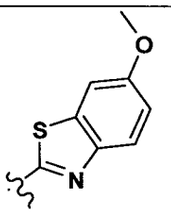
IV) Ensayo de Fijación - Desplazamiento interrumpido de MK-801 en ratas: Este ensayo usa una modificación del protocolo descrito por Stefani et al. (*Behavioral Neuroscience*, 2003, **117**: 728 - 737). Los compuestos de ensayo se evalúan para determinar su capacidad de invertir un déficit del comportamiento inducido por MK - 801 (0,03 mg/kg, i.p., dosis única) en este ensayo.

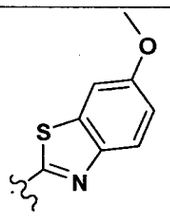
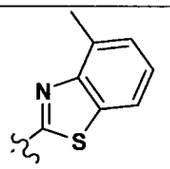
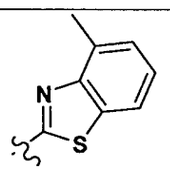
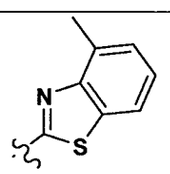
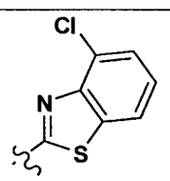
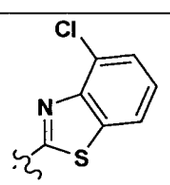
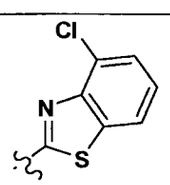
La actividad de compuestos específicos descritos en la presente memoria y ensayados en el ensayo (II) anteriores se proporciona en la Tabla 1.

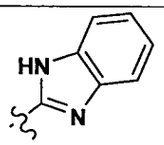
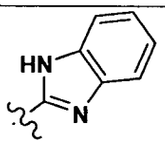
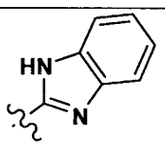
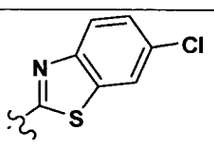
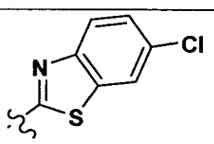
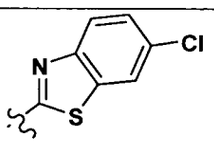
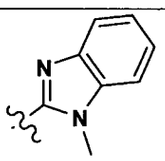
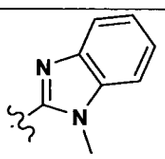
Tabla 1.

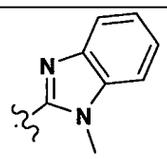
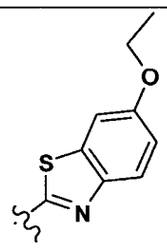
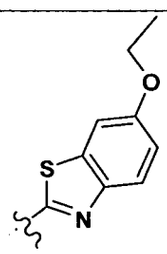
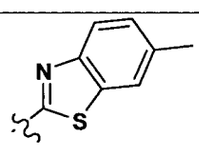
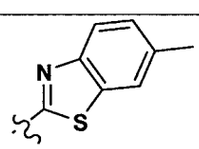
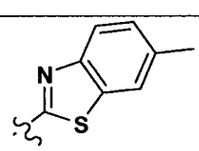
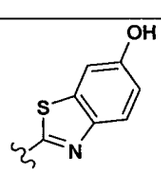


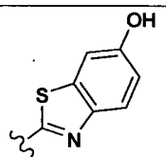
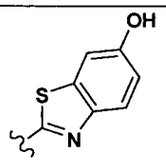
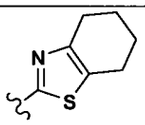
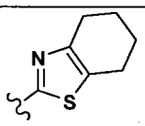
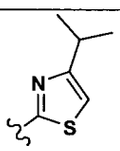
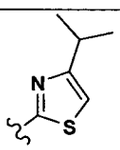
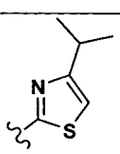
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
1			+++
1a			+
1b			+++
2			++
2a			+
2b			++

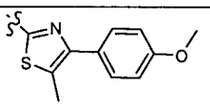
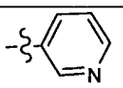
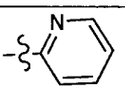
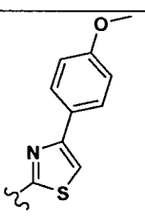
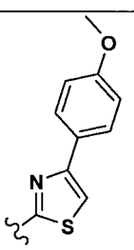
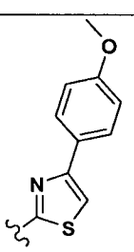
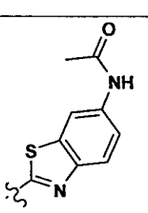
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
3		3840	+
4			+++
4a			+
4b		230	++
5			++
5a			+

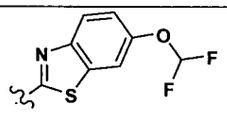
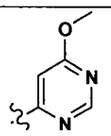
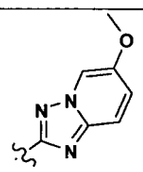
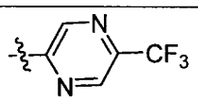
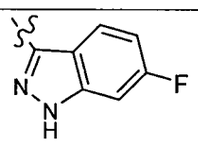
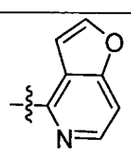
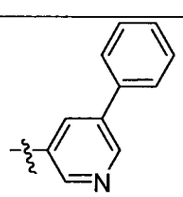
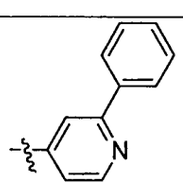
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
5b			+++
6			++
6a		4340	+
6b			+++
7			++
7a			+
7b			+++

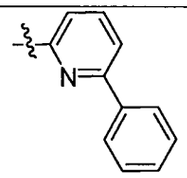
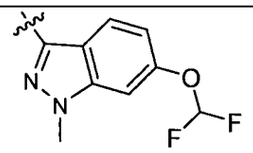
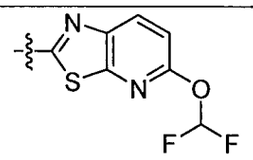
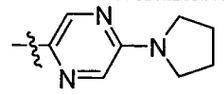
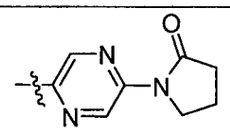
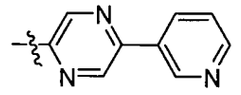
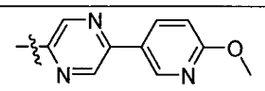
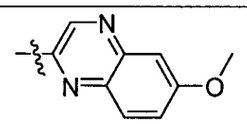
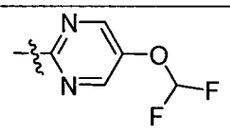
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
8			++
8a		120	++
8b			+
9			++
9a		7315	+
9b			+++
10			++
10a			++

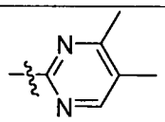
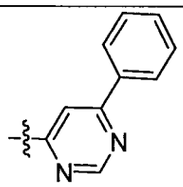
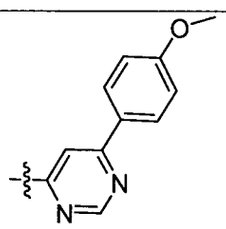
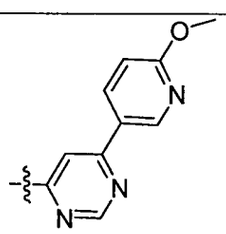
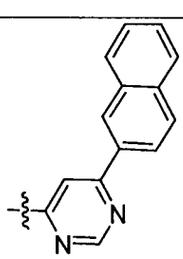
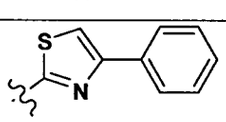
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
10b			++
11			++
11b		213	++
12			++
12a			++
12b			+
13			+++

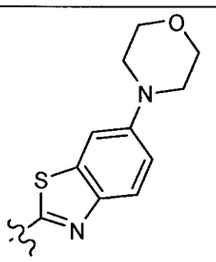
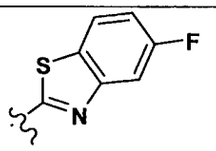
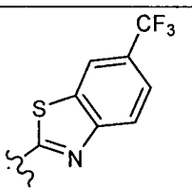
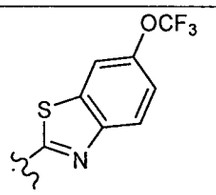
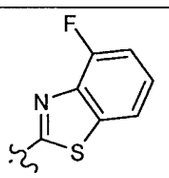
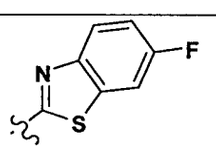
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
13a			++
13b			+++
14			++
14b			++
15			++
15a		6345	+
15b			++
16			++
16a		3174	+

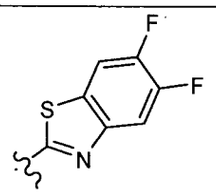
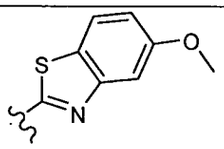
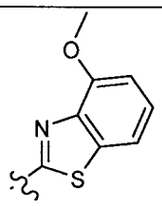
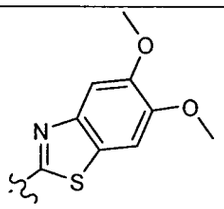
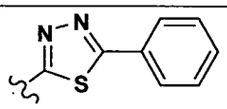
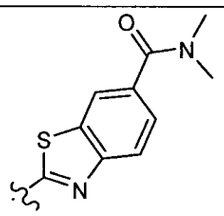
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
16b			++
17			++
18		3930	+
19			++
20			++
20a			++
20b		318	++
21			+++

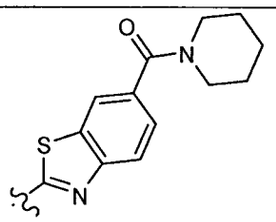
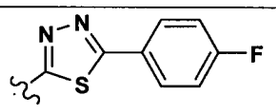
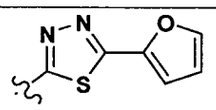
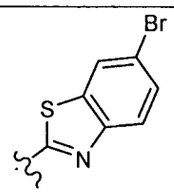
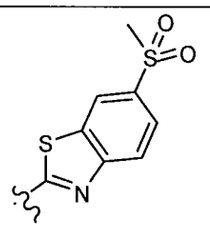
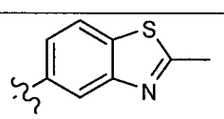
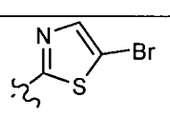
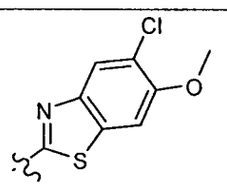
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
22			++
23			+++
24			+++
25		510	++
26			+++
27			+++
28		4010	+
29			++

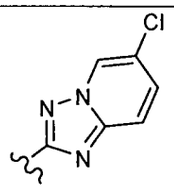
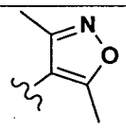
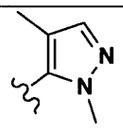
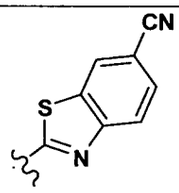
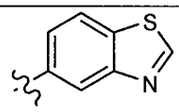
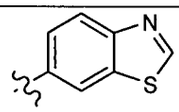
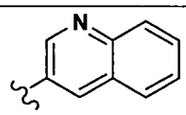
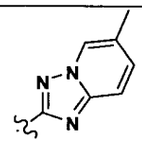
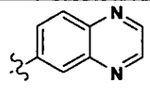
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
30			++
31			++
32			++
34			+
35		4035	+
36			++
37			+
38			+++
39			+++

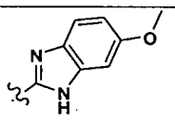
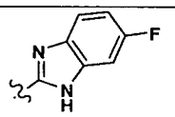
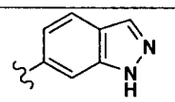
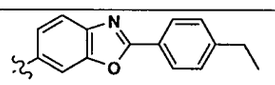
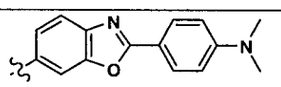
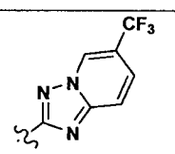
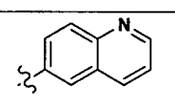
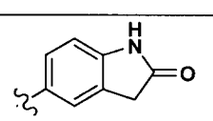
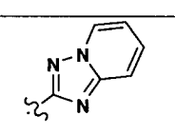
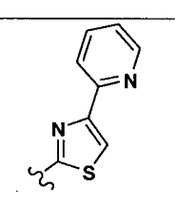
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
40			+++
41			+++
42			+++
43			+++
44			++
45			++

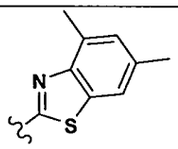
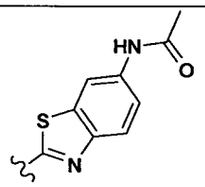
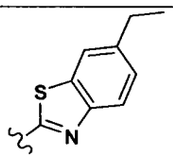
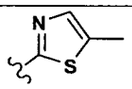
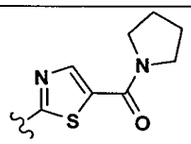
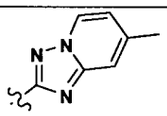
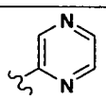
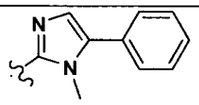
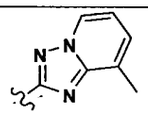
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
46		2000	+
47			+++
48		790	++
49		3330	+
50			+++
51			NE[b]

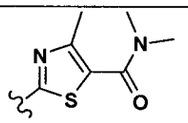
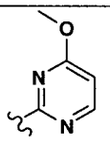
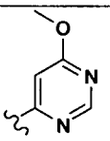
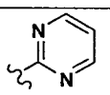
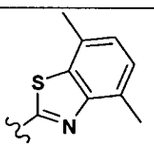
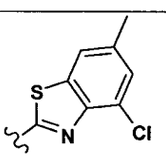
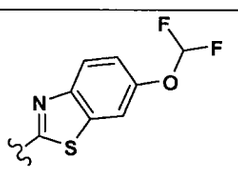
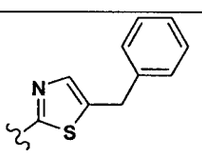
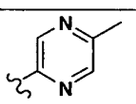
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
52		325	++
53			+
54			+
55			+
56			+
57		3900	+

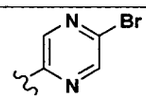
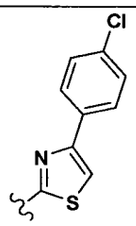
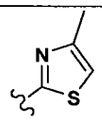
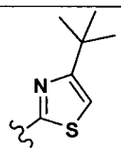
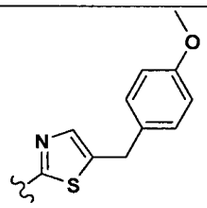
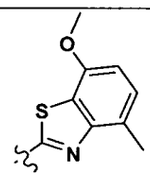
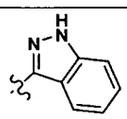
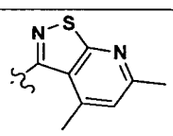
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
58			+
59		4240	+
60		2550	+
61			++
62			+
63		2600	+
64			+++
65			+

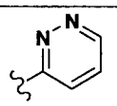
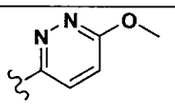
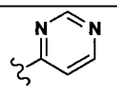
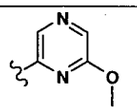
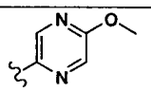
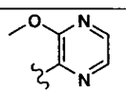
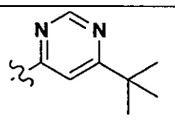
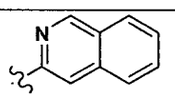
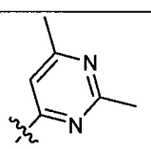
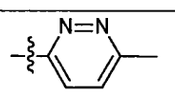
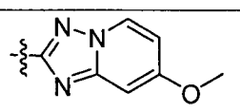
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
66		360	++
67			+
68			+
70			++
71			+
72			+
73		7550	+
74			+++
75			+

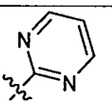
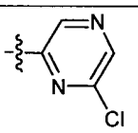
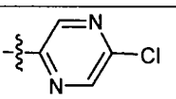
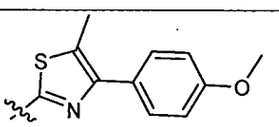
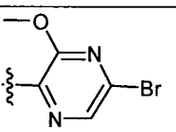
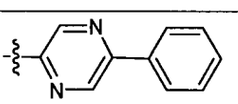
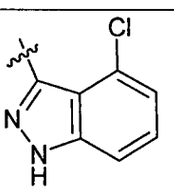
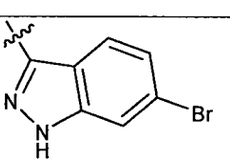
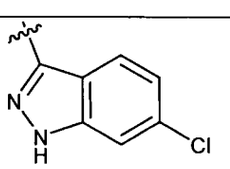
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
76			++
77		355	++
78			+
81			NE[b]
82			NE[b]
83		240	++
85			+
86			+
87			+++
88			++

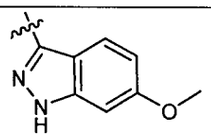
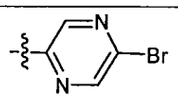
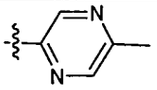
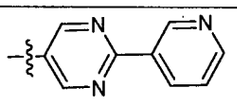
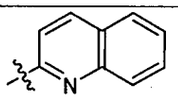
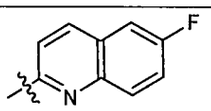
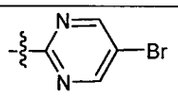
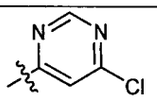
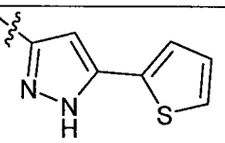
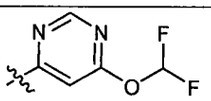
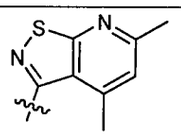
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
89			+++
90		130	++
91			++
92			+++
93			++
94			+++
95			++
96			+
97			++

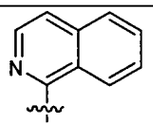
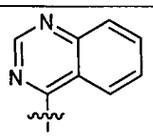
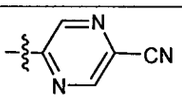
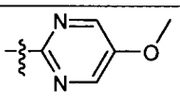
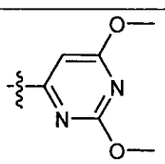
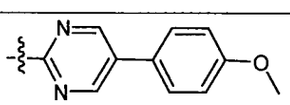
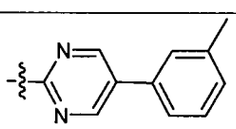
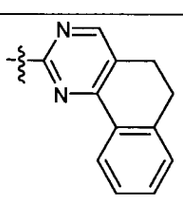
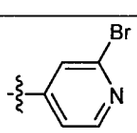
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
98			+
99			++
100			+++
101			++
102			+++
103		280	++
104			++
105			++
106			++

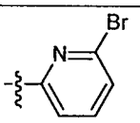
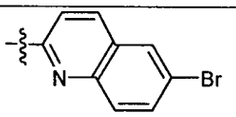
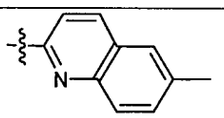
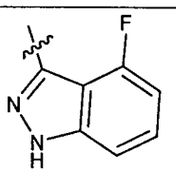
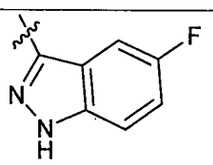
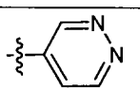
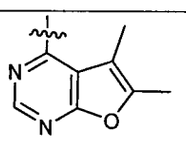
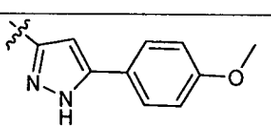
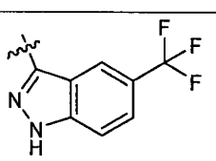
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
107			++
108			NE[b]
109			++
110		450	++
111			++
112			+++
113			+++
114			++

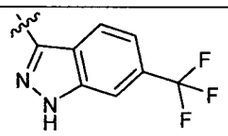
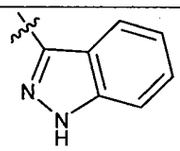
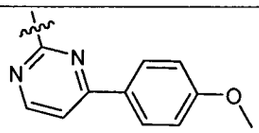
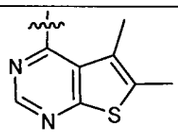
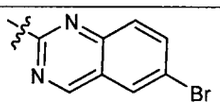
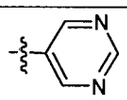
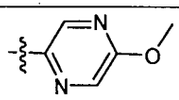
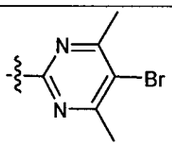
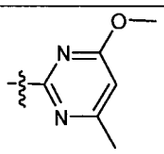
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
115			+
116			+
117			++
118			+
119			+++
120		875	++
121			+
122			+++
123			+
124			+
125		17	+++

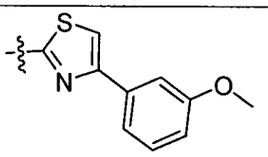
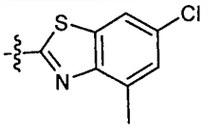
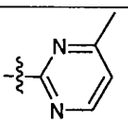
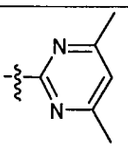
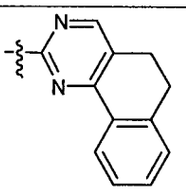
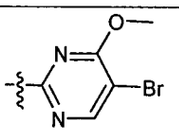
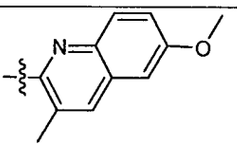
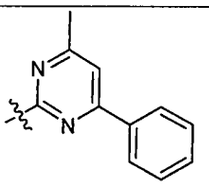
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
126			+++
127			+
128			+++
129			++
130			++
131			+
132			++
133			+++
134			+++

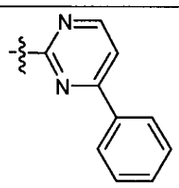
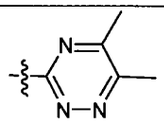
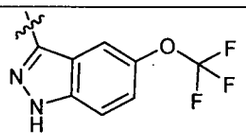
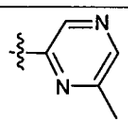
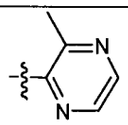
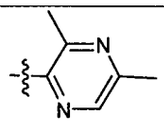
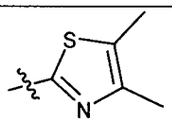
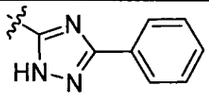
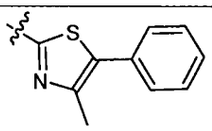
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
135			+++
136			+++
137		137	++
138			+
139		16	+++
140			++
141		4	+++
142			++
143			++
144			+++
145			+

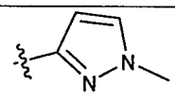
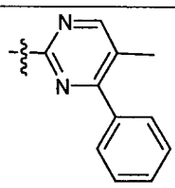
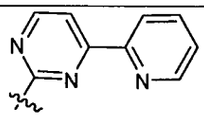
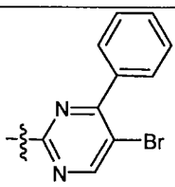
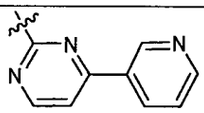
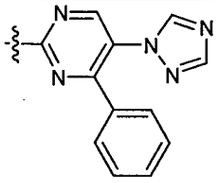
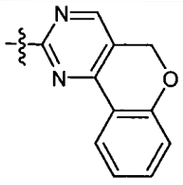
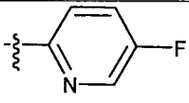
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
146			++
147			++
148			+
149		17	+++
150			++
151			++
152		233	++
153			++
154			+

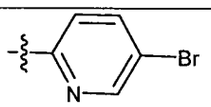
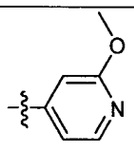
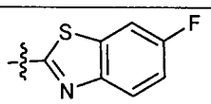
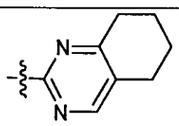
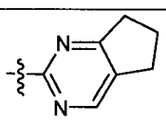
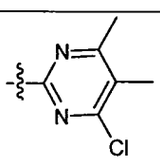
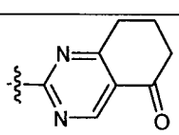
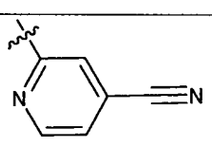
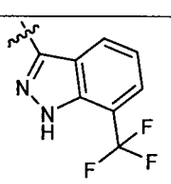
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
155			++
156			++
157			++
158		135	++
159			+++
160			+
161			+
162			+
163			+++

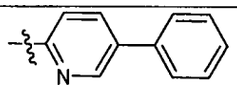
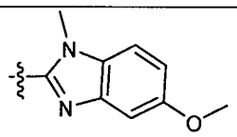
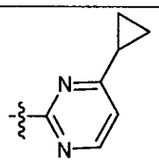
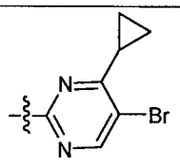
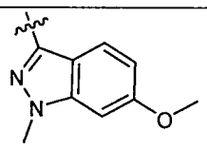
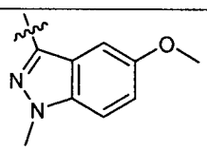
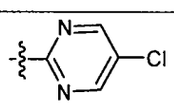
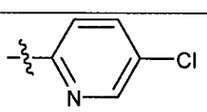
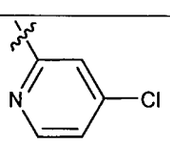
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
164			++
165		13	+++
166		11	+++
167			+
168			+++
169			+
170			+++
171			+++
172			++

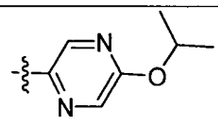
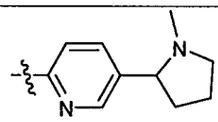
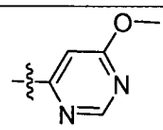
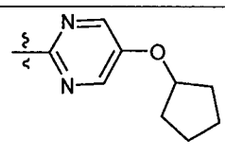
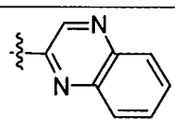
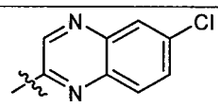
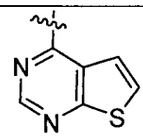
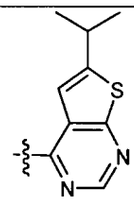
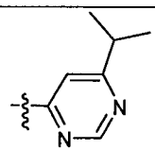
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
173			++
174		245	++
175			++
176			++
177			+++
178		17	+++
179			++
180			++

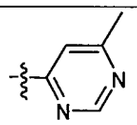
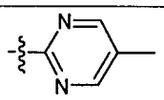
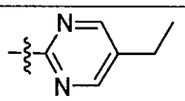
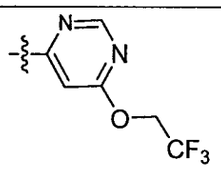
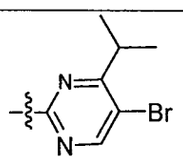
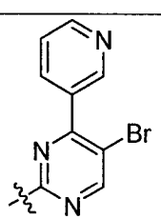
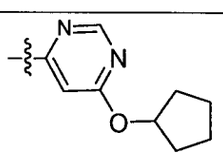
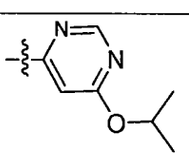
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
181		13	+++
182			++
183			+++
184			+
185			+
186			++
187		424	++
188			+
189			++

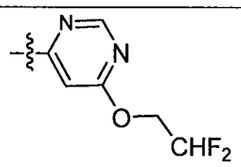
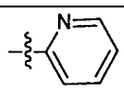
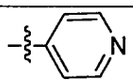
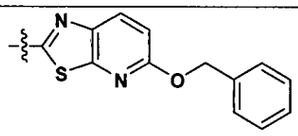
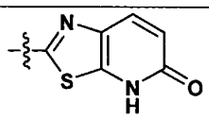
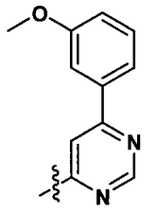
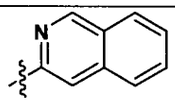
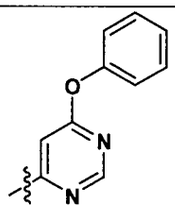
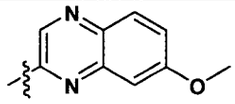
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
190			+
191			+++
192			++
193		17	+++
194		18	+++
195			+
196		13	+++
197			+++

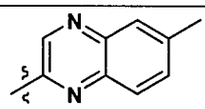
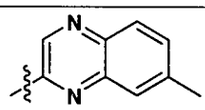
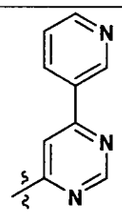
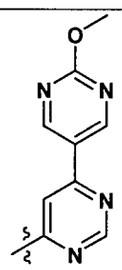
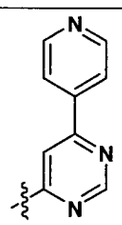
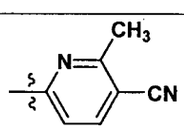
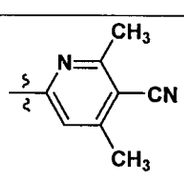
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
198		15	+++
199			+
200			+++
201			+++
202		16	+++
203			+++
204			++
205			++
206			+

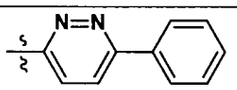
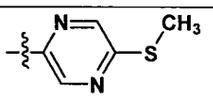
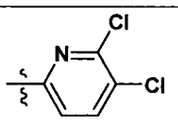
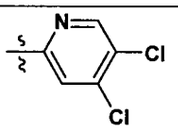
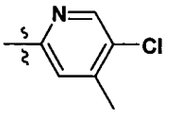
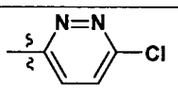
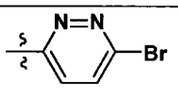
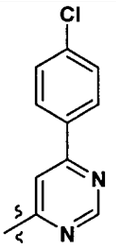
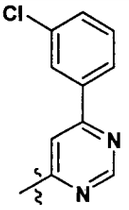
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
207			++
208			+
209			+++
210		9	+++
211			++
212			+
213		9	+++
214			+++
215			+++

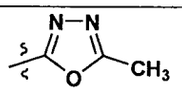
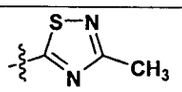
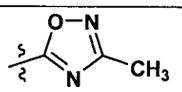
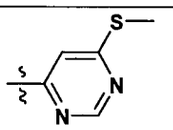
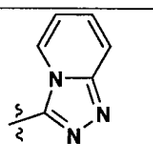
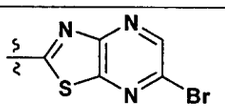
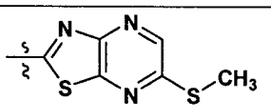
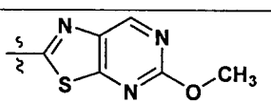
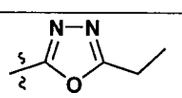
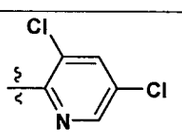
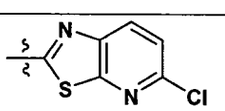
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
216			+
217			+
218		285	++
219			+
220			+++
221			++
222			++
223			++
224			++

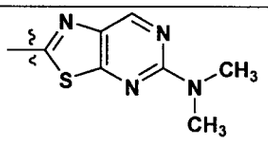
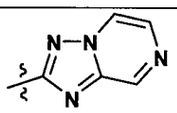
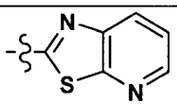
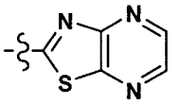
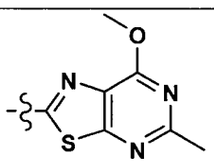
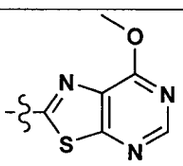
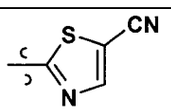
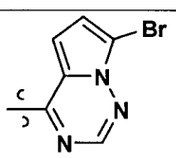
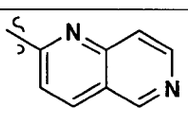
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
225			++
226			+++
227			++
228			+++
229			+++
230			+++
231			++
232			++

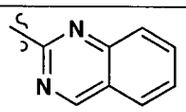
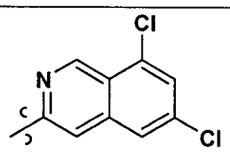
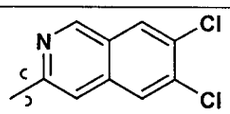
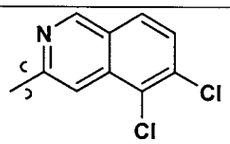
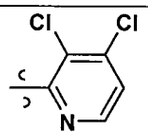
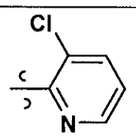
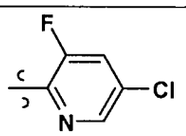
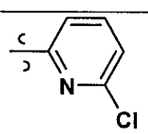
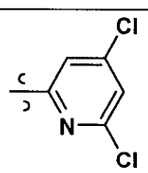
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
233			+++
234			+++
235			+
236			+
237			+++
238		16	+++
239		15	+++
240			++
241			+

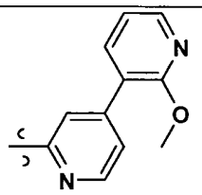
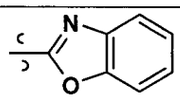
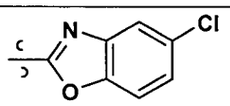
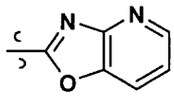
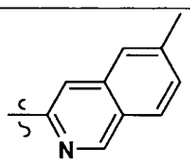
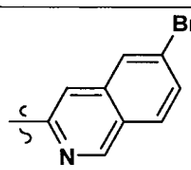
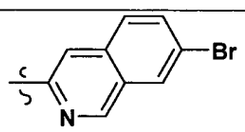
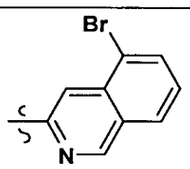
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
242			++
243			+
244			+++
245			+++
246			+++
247			++
248			++

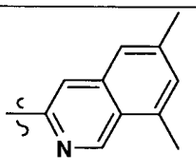
Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
249			+
250			+++
251			+++
252			+++
253			+++
254			++
255			++
256			+++
257			+++

Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
258			+
259			+
260			++
261			+++
262			+
263			+++
264			++
265			+++
266			+
267			+++
268			+++

Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
269			+
270			+++
271			+++
272			+++
273			+
274			+
275			++
276			+++
277			+++

Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
278			+++
279			++
280			
281			+++
282			++
283			++
284			+++
285			++
286			++

Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
287			++
288			+++
289			+++
290			+++
291			+++
292			+++
293			++
294			+++

Ejemplo Número	R_1	FLIPR α7–HI (CE_{50}, nM)	FLIPR α7–HI (CE_{50}, nM)
295			++

[a] Actividad basada en valores de CE_{50} nM:

+++ = < 100 nM

++ = 100 - 1000 nM

\+ = 1000 - 100000 nM

[b] NE = No ensayado

NA = No activo (> 1000000 nM)

Composiciones farmacéuticas y procedimientos de tratamiento

Los compuestos de fórmula I se unen a alfa 7 y pueden ser útiles en el tratamiento de trastornos afectivos y trastornos neurodegenerativos. Por tanto, otro aspecto de la invención es una composición que comprende un compuesto de fórmula I o una de sus sales farmacéuticamente aceptables, y un vehículo farmacéuticamente aceptable.

Otro aspecto de la invención es el uso de un compuesto de fórmula I en la fabricación de un medicamento para el tratamiento de trastornos afectivos o trastornos neurodegenerativos.

Otro aspecto de la invención es el uso de un compuesto de fórmula I en la fabricación de un medicamento para el tratamiento de esquizofrenia o enfermedad de Alzheimer.

Otro aspecto de la invención es un procedimiento para tratar trastornos afectivos o trastornos neurodegenerativos que comprende administrar a un paciente una cantidad terapéuticamente eficaz de un compuesto de fórmula I.

Otro aspecto de la invención es un procedimiento para tratar esquizofrenia o enfermedad de Alzheimer que comprende administrar a un paciente una cantidad terapéuticamente eficaz de un compuesto de fórmula I.

Otro aspecto de la invención es un procedimiento para tratar esquizofrenia que comprende administrar a un paciente una cantidad terapéuticamente eficaz de un compuesto de fórmula I.

Otro aspecto de la invención es un procedimiento para tratar enfermedad de Alzheimer que comprende administrar a un paciente una cantidad terapéuticamente eficaz de un compuesto de fórmula I.

"Paciente" significa una persona adecuada para terapia tal como se entiende por los expertos en el campo de los trastornos afectivos y trastornos neurodegenerativos.

"Tratamiento," "terapia," y términos relacionados se usan tal como se entiende por los expertos en el campo de los trastornos afectivos y trastornos neurodegenerativos.

Los compuestos de esta invención se administran por lo general como composiciones farmacéuticas compuestas por una cantidad terapéuticamente eficaz de un compuesto o su sal farmacéuticamente aceptable y un vehículo farmacéuticamente aceptable y puede contener excipientes convencionales. Vehículos farmacéuticamente aceptables son aquellos vehículos conocidos de forma convencional que tienen perfiles de seguridad aceptables. Las composiciones abarcan todas las formas sólidas y líquidas comunes incluyendo

por ejemplo, cápsulas, comprimidos, tabletas y polvos, así como suspensiones líquidas, jarabes, elixires y soluciones. Las composiciones se preparan usando técnicas de formulación convencionales y por lo general para las composiciones se usan excipientes convencionales (tales como ligantes y humectantes) y vehículos (tales como agua y alcoholes). Véase, por ejemplo, *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Easton, PA, 17ª edición, 1985.

Las composiciones sólidas se formulan normalmente en unidades de dosis y se prefieren composiciones que proporcionan de aproximadamente 1 a 1000 mg de ingrediente activo por dosis. Algunos ejemplos de dosificaciones son 1 mg, 10 mg, 100 mg, 250 mg, 500 mg y 1000 mg. Por lo general, estarán presentes otros agentes en un intervalo de unidades similar a agentes de dicha clase usados clínicamente. De forma típica, esto es 0,25-1000 mg/unidad.

Normalmente las composiciones líquidas se usan en intervalos de unidades de dosis. Por lo general, la composición líquida estará en un intervalo de dosis unitaria de 1-100 mg/ml. Algunos ejemplos de dosificaciones son 1 mg/ml, 10 mg/ml, 25 mg/ml, 50 mg/ml y 100 mg/ml. En general estarán presentes otros agentes en un intervalo de unidades similar a agentes de dicha clase usados clínicamente. De forma típica, esto es 1-100 mg/ml.

La invención abarca todos los modos convencionales de administración; se prefieren los procedimientos oral y parenteral. Por lo general la pauta de dosificación será similar a otros agentes usados clínicamente. De forma típica la dosis diaria será de 1-100 mg/kg de peso corporal al día. En general, por vía oral se requiere más compuesto y menos por vía parenteral. La pauta de dosificación específica se determinará, no obstante, por el médico usando el

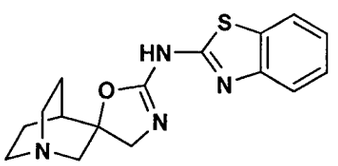
criterio médico habitual.

DESCRIPCIÓN DE REALIZACIONES ESPECÍFICAS

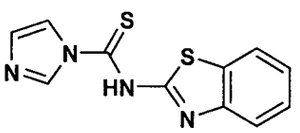
Los espectros de RMN de ^{1}H se ejecutaron en un aparato Bruker 500, 400 o 300 MHz y los desplazamientos químicos se expresan en ppm (δ) con referencia a tetrametilsilano (δ=0,0). Todas las evaporaciones se llevaron a cabo a presión reducida. A no ser que se indique de otro modo, los análisis de LC/MS se llevaron a cabo en un aparato Shimadzu usando una columna de fase inversa Phenomenex-Luna de 4,6x50 mm S 10 que emplea un caudal de 4 ml/min usando gradiente de TFA al 0,1% en metanol/agua [0-100% en 3 min, con 4 min de ejecución] y un detector UV ajustado a 220 nm o una columna de fase inversa Gemini C18 de 4,6x50 mm 5u que emplea un caudal de 5 ml/min usando un gradiente de acetato amónico 10 mM acetonitrilo/agua [5-95% en 3 min, con 4 min de ejecución] y un detector UV ajustado a 220 nm (espectrometría de masas de ion negativo). A no ser que se indique de otro modo, la purificación se podía realizar por columna C-18 preparativa empleando gradientes de metanol-agua que contenían 0,1% de ácido trifluoracético (TFA) y usando un Sistema de cromatografía líquida de alta resolución preparativa Shimadzu que emplea una columna S5 XTERRA de 30x100 mm a 40 ml/min de caudal con un gradiente de 12 minutos.

EJEMPLO 1

N-(benzo[d]tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

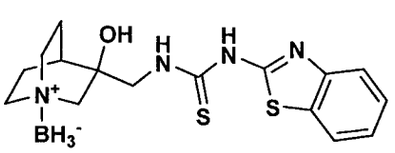


Etapa A: N-(Benzo[d]tiazol-2-il)- ^{1}H-imidazol-1-carbotioamida



A benzo[d]tiazol-2-amina (20 g, 133 mmol) en acetonitrilo (300 ml) se añadió 1,1'- tiocarbonildiimidazol (30,8 g, 173 mmol). La reacción se agitó a 50 ºC durante 24 horas. La reacción se enfrió hasta temperatura ambiente y el precipitado se filtró y se lavó con acetonitrilo (2 x 50 ml). El polvo amarillo se secó en un horno de vacío (40ºC) durante 2 horas. El producto, N-(benzo[d]tiazol-2-il)- ^{1}H-imidazol-1-carbotioamida (28,9 g, 111 mmol), se llevó directamente a la etapa siguiente sin purificación posterior.

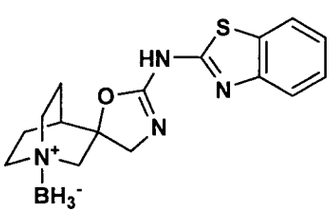
Etapa B: (3-((3-Benzo[d]tiazol-2-iltioureido)metil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato



A N-(benzo[d]tiazol-2-il)- ^{1}H-imidazol-1-carbotioamida (9,2 g, 35 mmol) en N,N-dimetilformamida (100 ml) se añadió (3-(aminometil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (6,0 g, 35 mmol) que se sintetizó de acuerdo con Swain C.J., et. al., *J. Med. Chem.*, **35**:1019-1031 (1992). La reacción se agitó a 65 ºC durante 15 horas. La reacción se enfrió y se

concentró proporcionando el producto bruto. El material bruto se purificó por cromatografía ultrarrápida (acetato de etilo al 50-100%/hexanos) proporcionando las primeras manchas/fracciones detectadas por TLC como producto. Las fracciones se reunieron y concentraron proporcionando (3-((3-benzo[d]tiazol-2-iltioureido)metil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (10,6 g, 29,1 mmol, 83 % de rendimiento) como un polvo blanquecino. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 11,88 (s, 1 H), 10,30 (s, 1 H), 7,94 (d, *J*=7,63 Hz, 1 H), 7,55 - 7,74 (m, 1 H), 7,37 - 7,53 (m, *J*=7,32, 7,32 Hz, 1 H), 7,16 - 7,37 (m, *J*=7,63, 7,63 Hz, 1 H), 5,39 (s, 1 H), 3,85 (d, 2 H), 2,65 - 3,08 (m, 6 H), 1,99 - 2,22 (m, 1 H), 1,79 - 1,97 (m, 2 H), 1,66 - 1,79 (m, 1 H), 1,08 - 1,63 (m, 4 H). MS (LC/MS) T. R. = 3,40; $[M+H]^+$ = 363,1

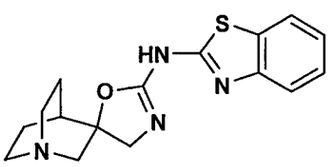
Etapa C: (2-(Benzo[d]tiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato



A (3-((3-benzo[d]tiazol-2-iltioureido)metil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (10,6 g, 29,1 mmol) en N,N-dimetilformamida (100 ml) se añadió N,N'-diisopropilcarbodiimida (11,4 ml, 72,8 mmol). La reacción se agitó a 70 °C durante 4 horas. La reacción se concentró proporcionando un residuo bruto. Se añadió una pequeña cantidad de acetato de etilo (20 ml) y la suspensión se sometió a ultrasonidos. Los sólidos se filtraron y se lavaron con pequeñas porciones de acetato de etilo (2 x 10 ml). Los sólidos se secaron en un horno de vacío (80 °C) proporcionando (2-

(benzo[d]tiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato (6,83 g, 20,8 mmol, 72 % de rendimiento) como un polvo blanco. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 9,09 (s ancho, 1 H) 7,81 (d, *J*=7,63 Hz, 1 H) 7,63 (d, *J*=7,93 Hz, 1 H) 7,30 - 7,40 (m, 1 H) 7,15 - 7,24 (m, 1 H) 3,88 (d, *J*=10,38 Hz, 1 H) 3,77 (d, *J*=10,38 Hz, 1 H) 3,25 - 3,37 (m, 1 H) 3,17 (dd, *J*=14,95, 1,83 Hz, 1 H) 2,99 - 3,10 (m, 1 H) 2,79 - 2,98 (m, 3 H) 2,27 (s ancho, 1 H) 1,98 - 2,11 (m, 1 H) 1,71 - 1,88 (m, 3 H) 1,45 (s ancho, 3 H). MS (LC/MS) T. R. = 2,44; $[M+H-BH_3]^+$ = 315,1.

Etapa D: N-(Benzo[d]tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



A (2-(benzo[d]tiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato (6,6 g, 20,1 mmol) en acetona (9 ml) se añadió HCl 3M (50,3 ml, 151 mmol). La reacción se agitó a temperatura ambiente durante 4 horas. La reacción se completó por TLC (mancha inferior). Se añadió acetato de etilo y se separó entonces la fase acuosa. La fase acuosa se neutralizó con hidróxido sódico 1N. El producto se extrajo con acetato de etilo (2 x 150 ml). Los orgánicos se reunieron, se secaron con sulfato de magnesio, se filtraron y concentraron a vacío proporcionando un polvo blanco. Se añadió al polvo una pequeña cantidad de acetato de etilo (20 ml). Los sólidos se sometieron a ultrasonidos y se filtraron proporcionando N-(benzo[d]tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

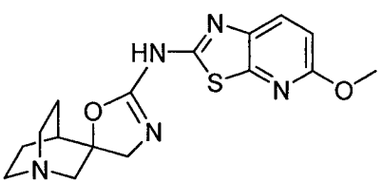
racémica (5,13 g, 16,3 mmol, 81 % de rendimiento) como un polvo blanco. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 9,02 (s ancho, 1 H) 7,79 (d, *J*=7,02 Hz, 1 H) 7,62 (d, *J*=7,63 Hz, 1 H) 7,29 - 7,38 (m, 1 H) 7,15 - 7,22 (m, 1 H) 3,90 (d, *J*=10,07 Hz, 1 H) 3,65 (d, *J*=10,07 Hz, 1 H) 2,98 - 3,10 (m, 2 H) 2,73 - 2,88 (m, 2 H) 2,67 (t, *J*=7,78 Hz, 2 H) 2,07 (s ancho, 1 H) 1,93 (s ancho, 1 H) 1,42 - 1,67 (m, 3 H). MS (LC/MS) T. R. = 1,15; $[M+H]^+$ = 315,3.

Los enantiómeros se separaron usando una columna a Chiralpak AD-H (3x25 cm, 5 uM) con una fase móvil constituida por CO_2/(metanol/ACN/DEA = 70/30/0,1 (v/v/v)) = 77/23. La longitud de onda se fijó a 300 nM. Los picos separados se concentraron a vacío proporcionando polvos blancos. El primer pico que salió de la columna fue (S)-N-(benzo[d]tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (1,45 g, 4,61 mmol, 29,4 % de rendimiento). (1a; isómero S): RMN de ^{1}H (400 MHz, DMSO-d_6) δ ppm 9,03 (s ancho, 1 H) 7,78 (d, *J*=7,05 Hz, 1 H) 7,61 (d, *J*=7,55 Hz, 1 H) 7,27 - 7,37 (m, 1 H) 7,11 - 7,23 (m, 1 H) 3,89 (d, *J*=10,07 Hz, 1 H) 3,64 (d, *J*=10,07 Hz, 1 H) 2,96 - 3,09 (m, 2 H) 2,71 - 2,88 (m, 2 H) 2,66 (t, *J*=7,81 Hz, 2 H) 2,02 - 2,11 (m, 1 H) 1,85 - 1,97 (m, 1 H) 1,41 - 1,65 (m, 3 H). MS (LC/MS) T. R. = 1,15; $[M+H]^+$ = 315,3. Rotación óptica (1,23 mg/ml, DMSO) = +5,20°. El segundo pico fue (R)-N-(benzo[d]tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (1,21 g, 3,85 mmol, 24,5 % de rendimiento). (1b; isómero R): RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 9,02 (s ancho, 1 H) 7,79 (d, *J*=7,32 Hz, 1 H) 7,62 (d, *J*=7,63 Hz, 1 H) 7,33 (t, *J*=7,63 Hz, 1 H) 7,18 (t, *J*=7,48 Hz, 1 H) 3,90 (d, *J*=10,07 Hz, 1 H) 3,65 (d, *J*=10,07 Hz, 1 H) 2,98 - 3,10 (m, 2 H) 2,73 - 2,87 (m, 2 H) 2,67 (t, *J*=7,63 Hz, 2 H) 2,08 (s ancho, 1 H) 1,93 (s ancho, 1 H) 1,42 - 1,67 (m, 3 H). MS (LC/MS) T. R. = 1,15; $[M+H]^+$ = 315,3; Rotación óptica (3,9 mg/ml,

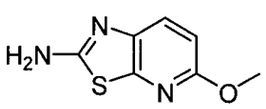
DMSO) = -3,92°.

EJEMPLO 2

N-(5-Metoxitiazolo[5,4-b]piridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



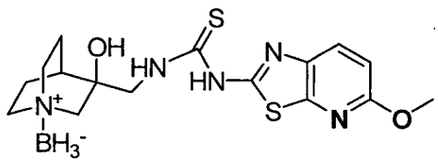
Etapa A: 5-Metoxitiazolo[5,4-b]piridin-2-amina



En un matraz de tres bocas de 500 ml equipado con un agitador mecánico, embudo de adición y termómetro, se añadió ácido acético (100 ml) y se enfrió en un baño de hielo. Se añadieron a la mezcla de reacción tiocianato potásico (40 g, 412 mmol) y 6-metoxipiridin-3-amina (6,2 g, 49,9 mmol). La reacción se enfrió en un baño de hielo-sal hasta que la temperatura de reacción alcanzó <0 °C. Se añadió gota a gota durante 2 horas a una velocidad que mantenía la temperatura de reacción <0 °C una solución de bromo (8 ml, 156 mmol) en ácido acético (30,0 ml). Se requirió agitación mecánica. Después de completar la adición, se dejó agitar la mezcla y se dejó calentar lentamente hasta temperatura ambiente durante la noche. Se añadió entonces agua (30 ml) y la mezcla se calentó hasta 85 °C en un baño de aceite. Esta mezcla se filtró entonces mientras estaba todavía caliente. La torta de filtro naranja se devolvió al matraz de reacción, y se añadieron otros 50 ml de ácido acético. La

mezcla de calentó de nuevo hasta 85 °C, y luego se filtró mientras estaba todavía caliente una vez más. Los filtrados reunidos se enfriaron en un baño de hielo y se neutralizó hasta pH 8 con hidróxido amónico concentrado. Un precipitado púrpura formado que se que se recogió por filtración proporcionó 5 g de material bruto. Este material bruto se recristalizó en metanol (40 ml) proporcionando 5-metoxitiazolo[5,4-b]piridin-2-amina (3 g, 16,55 mmol, 33,1 % de rendimiento) como cristales púrpura. RMN de ^{1}H (300 MHz, DMSO-d_6) δ ppm 7,60 (1 H, d, *J*=8,42 Hz), 7,41 (2 H, s), 6,67 (1 H, d, *J*=8,78 Hz), 3,81 (3 H, s).

Etapa B: (3-Hidroxi-3-((3-(5-metoxitiazolo[5,4-b]piridin-2-il)tioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato

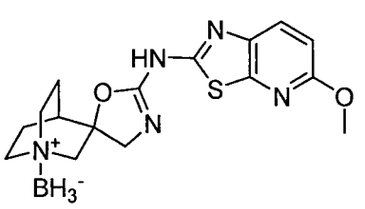


Se dividió 5-metoxitiazolo[5,4-b]piridin-2-amina (2,4g, 13,24 mmol) en 5 viales con tapa a rosca de 20 ml. Se añadió a cada vial acetonitrilo (10 ml) y tiocarbonil diimidazol (600 mg). Todos los viales se calentaron a 60 °C durante la noche. Los viales de reacción se combinaron y concentraron proporcionando N-(5-metoxitiazolo[5,4-b]piridin-2-il)-1H-imidazol-1-carbotioamida producto bruto.

Este producto bruto se suspendió en N,N-dimetilformamida (50ml) y se añadió entonces (3-(aminometil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (2,7g, 15,88 mmol). La reacción se calentó a 70 °C durante 4 horas. La LC/MS mostró conversión básicamente completa. La reacción se

enfrió hasta temperatura ambiente y luego se vertió en agua. El producto se extrajo primero con tolueno, y luego con cloroformo. Los orgánicos se reunieron, se lavaron con agua y salmuera, se secaron sobre sulfato sódico, se filtraron y se concentraron a vacío proporcionando material bruto. Este material bruto se purificó por cromatografía ultrarrápida (acetato de etilo de 20-100%-hexano). Las fracciones de producto se recogieron y se concentraron a vacío proporcionando (3-hidroxi-3-((3-(5-metoxitiazolo[5,4-b]piridin-2-il)tioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (1,36 g, 3,46 mmol, 26,1 % de rendimiento). La RMN de ^{1}H mostró una relación molar 1:0,55 de (3-hidroxi-3-((3-(5-metoxitiazolo[5,4-b]piridin-2-il)tioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (1,36 g, 3,46 mmol, 26,1 % de rendimiento) a 5-metoxitiazolo[5,4-b]piridin-2-amina (,34 g, 1,876 mmol, 14,17 % de rendimiento). La mezcla se llevó directamente a la etapa siguiente sin purificación posterior. MS (LC/MS) T. R. = 3,23; $[M+H]^+$ = 392,1.

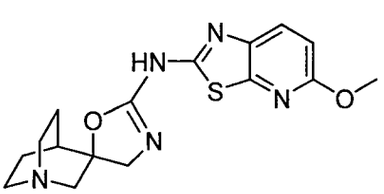
Etapa C: (2-(5-Metoxi-3a,7a-dihidrotiazolo[5,4-b]piridin-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato



A (3-hidroxi-3-((3-(5-metoxitiazolo[5,4-b]piridin-2-il)tioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (1,7 g, 3,46 mmol) en N,N-dimetilformamida (10 ml) se añadió N,N'-diisopropilcarbodiimida (1,89 ml, 12,10 mmol). La reacción se agitó a 70 °C durante 2 horas. La mezcla se enfrió y luego se vertió en agua. El producto se extrajo con tolueno y cloroformo. Las

fases orgánicas se reunieron, se lavaron con salmuera, se secaron sobre sulfato sódico, se filtraron y se concentraron a vacío proporcionando material bruto. Este material sólido se trituró con éter. Los sólidos se filtraron entonces y se secaron proporcionando (2-(5-metoxi-3a,7a-dihidrotiazolo[5,4-b]piridin-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato (700 mg, 1,94 mmol, 56,0 % de rendimiento). RMN de ^{1}H (300 MHz, DMSO-d_6) δ ppm 8,98 (1 H, s), 7,86 (1 H, d, *J*=8,78 Hz), 6,81 (1 H, d, *J*=8,42 Hz), 3,87 (3 H, s), 3,83 (1 H, s), 3,68 - 3,78 (1 H, m), 3,31 (1 H, s), 3,15 - 3,29 (1 H, m), 2,78 - 3,14 (4 H, m), 2,26 (1 H, s ancho), 2,04 (1 H, s ancho), 1,63 - 1,89 (3 H, m).

Etapa D: N-(5-Metoxitiazolo[5,4-b]piridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



A (2-(5-metoxitiazolo[5,4-b]piridin-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato (780 mg, 2,17 mmol) en acetona (10 ml) se añadió HCl 3M (10 ml, 329 mmol). La reacción se agitó a temperatura ambiente durante 2 horas. Se añadieron cloroformo y agua y se separó

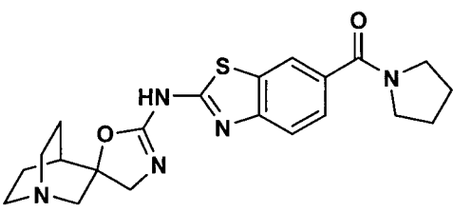
entonces la fase acuosa. La fase acuosa se neutralizó con bicarbonato sódico. El producto se extrajo con cloroformo (2x). Los orgánicos se reunieron, se secaron sobre sulfato sódico, se filtraron y se concentraron a vacío proporcionando N-(5-metoxitiazolo[5,4-b]piridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina racémica (588 mg, 1,70 mmol, 78 % de rendimiento) como un polvo blanco. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 8,90 (1 H, s ancho), 7,82 - 7,86 (1 H, m), 6,80 (1 H, d, *J*=8,85 Hz), 3,84 - 3,89 (4 H, m), 3,61 (1 H, d, *J*=10,07 Hz), 3,03 (2 H, d, *J*=5,19 Hz), 2,73 - 2,86 (2 H, m), 2,66 (2 H, t, *J*=7,78 Hz), 2,07 (1 H, s ancho), 1,92 (1 H, s ancho), 1,45 - 1,65 (3 H, m). MS (LC/MS) T. R. = 1,29; $[M+H]^+$ = 346,1.

Los enantiómeros se separaron usando una columna Chiralpak AD-H (30 x 250mm, 5μm) con una fase móvil constituida por 35% de metanol (0,1% de DEA) en CO_2. La longitud de onda se fijó a 300 nM. Los picos separados se concentraron a vacío proporcionando polvos blancos. El primer pico que salió de la columna fue (S)-N-(5-metoxitiazolo[5,4-b]piridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (212 mg, 0,61 mmol, 36,1 % de rendimiento). (2a; isómero S): RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 8,89 (1 H, s ancho), 7,84 (1 H, d, *J*=8,85 Hz), 6,77 - 6,82 (1 H, m), 3,84 - 3,89 (4 H, m), 3,61 (1 H, d, *J*=10,07 Hz), 3,03 (2 H, d, *J*=5,19 Hz), 2,74 - 2,86 (2 H, m), 2,66 (2 H, t, *J*=7,63 Hz), 2,06 (1 H, s ancho), 1,92 (1 H, s ancho), 1,44 - 1,65 (3 H, m). MS (LC/MS) T. R. = 1,47; $[M+H]^+$ = 346,2. Rotación óptica (3,57 mg/ml, DMSO) = -2,58°. El segundo pico fue (R)-N-(5-metoxitiazolo[5,4-b]piridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (242 mg, 0,70 mmol, 41,2 % de rendimiento). (2b; isómero R): RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 8,89 (1 H, s ancho), 7,84 (1 H, d, *J*=8,85 Hz), 6,79 (1 H, d, *J*=8,55 Hz),

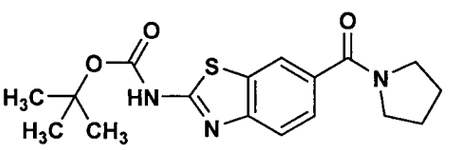
3,82 - 3,90 (4 H, m), 3,61 (1 H, d, *J*=10,07 Hz), 3,03 (2 H, d, *J*=5,49 Hz), 2,74 - 2,86 (2 H, m), 2,66 (2 H, t, *J*=7,78 Hz), 2,06 (1 H, s ancho), 1,92 (1 H, s ancho), 1,42 - 1,67 (3 H, m). MS (LC/MS) T. R. = 1,30; $[M+H]^+$ = 346,2. Rotación óptica (3,29 mg/ml, DMSO) = +2,43°.

EJEMPLO 3

(2-(5H-1'-Azaspiro[oxazol-4,3'-biciclo[2.2.2]octano]-2-ilamina)benzo[d]tiazol-6-il)pirrolidin-1-il)metanona



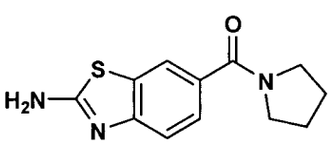
Etapa A: 6-(pirrolidin-1-carbonil)benzo[d]tiazol-2-ilcarbamato de terc-butilo



En un matraz de 250 ml se añadió ácido 2-(*terc*-butoxicarbonil-amino)benzo[d]tiazol-6-carboxílico (1,0 g, 3,4 mmol) y pirrolidina (0,559 ml, 6,8 mmol) en tetrahidrofurano (50 ml). A esta solución se añadió EDC (1,3 g, 6,8 mmol), 1-hidroxibenzotriazol (1,041 g, 6,8 mmol) y base de Hunig (2,37 ml, 13,59 mmol). La reacción se agitó a 25 °C durante 1 hora. A continuación la reacción se vertió en agua y diclorometano. El agua se extrajo tres veces con diclorometano y las fases orgánicas se reunieron y concentraron. El residuo se suspendió en una pequeña cantidad de diclorometano y precipitó con éter dietílico/hexanos. El matraz se colocó en el congelador durante 1 hora y se

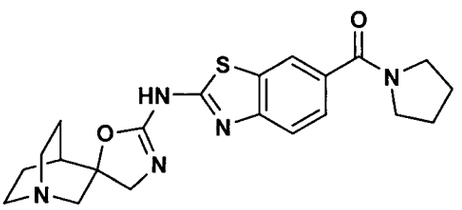
filtró. El precipitado blanco se recogió proporcionando 6-(pirrolidin-1-carbonil)benzo[d]tiazol-2-ilcarbamato de *terc*-butilo (1,09 g, 3,14 mmol, 92 % de rendimiento). RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 11,95 (s, 1 H), 8,14 (s, 1 H), 7,61 - 7,77 (m, *J*=8,39, 1,98 Hz, 1 H), 7,46 - 7,63 (m, 1 H), 3,39 - 3,63 (m, 4 H), 1,74 - 2,00 (m, 4 H), 1,45 - 1,62 (m, 9 H). MS (LC/MS) T. R. = 3,40; $[M+H]^+$ = 363,1.

Etapa B: (2-Aminobenzo[d]tiazol-6-il)(pirrolidin-1-il)metona



Se disolvió 6-(pirrolidin-1-carbonil)benzo[d]tiazol-2-ilcarbamato *de terc*-butilo (1,09 g, 3,14 mmol) en diclorometano (10 ml) y TFA (3 ml, 38,9 mmol) y la reacción se agitó a 25 °C durante la noche. La reacción se vertió en un embudo de separación y se neutralizó cuidadosamente con bicarbonato sódico. El líquido se extrajo 3 veces con cloroformo/metanol (4:1). Las fases orgánicas se concentraron hasta un residuo blanco y se trituraron con éter dietílico. El precipitado se recogió proporcionando (2-aminobenzo[d]tiazol-6-il)(pirrolidin-1-il)metona (0,497 g, 2,0 mmol, 64 %). RMN de ^{1}H (400 MHz, DMSO-d_6) δ ppm 7,86 (d, *J*=1,51 Hz, 1 H), 7,65 (s, 2 H), 7,35 - 7,46 (m, 1 H), 7,26 - 7,35 (m, 1 H), 3,41 - 3,57 (m, 4 H), 1,64 - 1,97 (m, 4 H). MS (LC/MS) T. R. = 1,39; $[M+H]^+$ = 248,1.

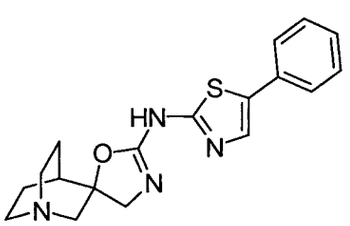
Etapa C: (2-(5H-1'-Azaspiro[oxazol-4,3'-biciclo[2.2.2]octano]-2-ilamina)benzo[d]tiazol-6-il)pirrolidin-1-il)metanona



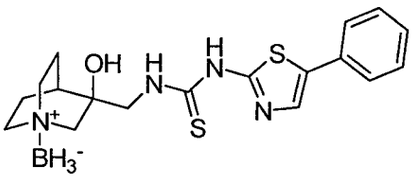
(2-(5H-1'-Azaspiro[oxazol-4,3'-biciclo[2.2.2]octano]-2-ilamina)benzo-[d]tiazol-6-il)pirrolidin-1-il)metanona se preparó siguiendo los procedimientos generales del Ejemplo 1, Etapas A-D y usando (2-aminobenzo[d]tiazol-6-il)(pirrolidin-1-il)metona (Ejemplo 3, Etapa B) como material de partida. RMN de ^{1}H (400 MHz, DMSO-d_6) δ ppm 9,05 (s ancho, 1 H) 7,99 (d, *J*=1,76 Hz, 1 H) 7,60 (d, *J*=8,31 Hz, 1 H) 7,48 (dd, *J*=8,31, 1,76 Hz, 1 H) 3,90 (d, *J*=10,07 Hz, 1 H) 3,65 (d, *J*=10,07 Hz, 1 H) 3,42 - 3,52 (m, 4 H) 3,04 (s, 2 H) 2,75 - 2,87 (m, 2 H) 2,67 (t, *J*=7,81 Hz, 2 H) 2,08 (s ancho, 1 H) 1,76 - 1,98 (m, 5 H) 1,41 - 1,65 (m, 3 H). MS (LC/MS) T. R. = 1,33; $[M+H]^+$ = 412,2.

EJEMPLO 4

N-(5-Feniltiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

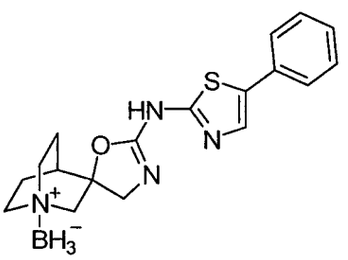


Etapa A: (3-Hidroxi-3-((3-(5-feniltiazol-2-il)tioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato



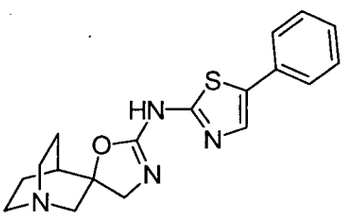
A 5-feniltiazol-2-amina (0,52 g, 2,9 mmol) en acetonitrilo (6 ml) se añadió 1,1'-tiocarbonildiimidazol (0,68 g, 3,8 mmol). La mezcla de reacción se agitó a 65 ºC durante 2 horas. El precipitado se filtró y se lavó con acetonitrilo (2 x 20 ml) proporcionando el intermedio N-(5-feniltiazol-2-il)-^{1}H-imidazol-1-carbotioamida. El intermedio se suspendió en N,N-dimetilformamida (30 ml) y se trató con (3-(aminometil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (0,5 g, 2,9 mmol). La mezcla de reacción se agitó durante 5 horas a 65 °C. La reacción se concentró a vacío y se purificó por cromatografía sobre gel de sílice (acetato de etilo al 30-100%/hexano). Las fracciones de producto se reunieron y concentraron a vacío proporcionando (3-hidroxi-3-((3-(5-feniltiazol-2-il)tioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (,85 g, 2,19 mmol, 74,4 % de rendimiento) como un polvo blanco. La LC/MS confirmó producto con pérdida de BH_3 en las condiciones de LC/MS: tiempo de retención 3,26 (M+1-BH_3= 375,33).

Etapa B: (2-(5-Feniltiazol-2-ilamino)-4H-1'-amoniospiro-[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato



A (3-hidroxi-3-((3-(5-feniltiazol-2-il)tioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (0,8 g, 2,1 mmol) en N,N-dimetilformamida (20 ml) se añadió N,N'-diisopropilcarbodiimida (1,12 ml, 7,2 mmol). La mezcla de reacción se agitó a 70 ºC durante 4 horas. La reacción se concentró a vacío y se purificó por cromatografía sobre gel de sílice (acetato de etilo de 40-100%/hexano). Las fracciones de producto reunidas se concentraron a vacío proporcionando (2-(5-feniltiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato (0,51 g, 1,44 mmol, 70 % de rendimiento) como un polvo blanco. LCMS - masa corresponde a la pérdida de BH_3 en las condiciones de LC/MS: tiempo de retención 2,46 (M+1-BH_3 = 341,36).

Etapa C: N-(5-Feniltiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



A (2-(5-feniltiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato (0,56 g, 1,58 mmol) en acetona (9 ml) se añadió HCl 3 M (3,95 ml, 11,86 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 4 horas y luego se neutralizó con hidróxido sódico 1N. El producto se extrajo con acetato de etilo (2 x 20 ml), seguido por cloroformo (2 x 20 ml). Los orgánicos se reunieron, se secaron con sulfato de magnesio, se filtraron y se concentraron a vacío proporcionando un polvo

blanco. El producto bruto se purificó por HPLC de fase inversa (Phenomenex Luna 30 X 100mm; 220 de longitud de onda; tiempo de gradiente 10 min; caudal 40 ml/min; disolvente A; 10% de metanol-90% de agua-0,1% de TFA, disolvente B; 90% de metanol-10% de agua-0,1% de TFA). Las fracciones se reunieron, se neutralizaron con hidróxido sódico 1N y se extrajo con acetato de etilo (2 x 30 ml) y cloroformo (2 x 30 ml). Los orgánicos se reunieron, se secaron con sulfato de magnesio, se filtraron y concentraron a vacío proporcionando N-(5-feniltiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,4 g, 1,175 mmol, 74,3 % de rendimiento) como un polvo blanco. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 8,63 (1 H, s ancho), 7,71 (1 H, s), 7,52 (2 H, d, *J*=7,32 Hz), 7,37 (2 H, t, *J*=7,78 Hz), 7,25 (1 H, t, *J*=7,32 Hz), 3,82 (1 H, d, *J*=10,07 Hz), 3,57 (1 H, d, *J*=9,77 Hz), 3,02 (2 H, d, *J*=4,27 Hz), 2,79 (2 H, t, *J*=7,63 Hz), 2,66 (2 H, t, *J*=7,63 Hz), 2,04 (1 H, s ancho), 1,92 - 1,97 (1 H, m), 1,44 - 1,65 (3 H, m). MS (LC/MS) T. R. = 1,52; $[M+H]^+$ = 341,3.

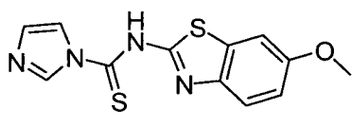
Los enantiómeros se separaron usando una columna Chiralpak AS-H (30 x 250mm, 5μm) con una fase móvil constituida por 30% de metanol (0,1% de DEA) en CO_2 y control UV a 300 nm. Los picos separados se concentraron a vacío proporcionando polvos blancos. El primer pico que salió de la columna proporcionó 0,4 g, 1,15 mmol, 32,7 % (4a, isómero S): RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 8,69 (s, 1 H), 7,69 - 7,87 (m, 1 H), 7,52 - 7,66 (m, *J*=10,99 Hz, 2 H), 7,37 - 7,51 (m, 2 H), 7,21 - 7,38 (m, 2 H), 3,52 - 4,00 (m, 2 H), 2,98 - 3,23 (m, 2 H), 2,78 - 2,94 (m, 2 H), 2,64 - 2,78 (m, 2 H), 1,88 - 2,19 (m, *J*=60,43 Hz, 2 H), 1,40 - 1,77 (m, 3 H). MS (LC/MS) T. R. = 1,77; $[M+H]^+$ = 341,1. El segundo pico proporcionó 0,4 g, 1,15 mmol, 32,7 %. (4b, isómero R): L P.F.

187-9 °C. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 8,64 (s, 1 H), 7,62 - 7,84 (m, 1 H), 7,44 - 7,61 (m, 2 H), 7,33 - 7,46 (m, 2 H), 7,18 - 7,31 (m, 1 H), 3,50 - 3,99 (m, 2 H), 2,94 - 3,14 (m, 2 H), 2,74 - 2,91 (m, 2 H), 2,61 - 2,72 (m, 2 H), 2,05 (s, 1 H), 1,82 - 2,00 (m, 1 H), 1,34 - 1,72 (m, 3 H). MS (LC/MS) T. R. = 1,78; $[M+H]^+$ = 341,1.

EJEMPLO 5

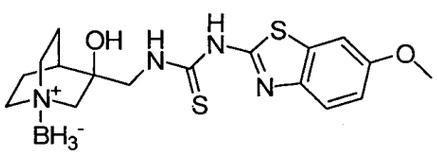
N-(6-Metoxibenzo[d]tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

Etapa A: N-(6-Metoxibenzo[d]tiazol-2-il)-^{1}H-imidazol-1-carbotioamida



A 6-metoxibenzo[d]tiazol-2-amina (0,53 g, 2,94 mmol) en acetonitrilo (20 ml) se añadió 1,1'-tiocarbonildiimidazol (0,681 g, 3,82 mmol). La mezcla de reacción se agitó a 65 °C durante 24 horas. El precipitado se filtró y se lavó con acetonitrilo (2 x 20 ml) proporcionando el producto. El producto se llevó directamente a la etapa siguiente sin purificación o caracterización posterior.

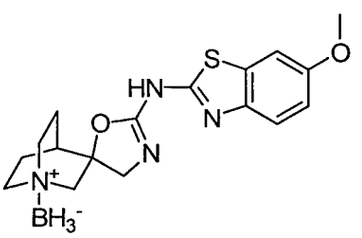
Etapa B: (3-Hidroxi-3-((3-(6-metoxibenzo[d]tiazol-2-il)-tioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato



A N-(6-metoxibenzo[d]tiazol-2-il)- ^{1}H-imidazol-1-carbotioamida (0,82 g,

2,82 mmol) en N,N-dimetilformamida (20 ml) se añadió (3-(aminometil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (0,48 g, 2,82 mmol). La mezcla de reacción se agitó a 65ºC durante 6 horas. La reacción se concentró a vacío y luego se purificó por cromatografía sobre gel de sílice (acetato de etilo del 30-100%/hexanos). Las fracciones puras se reunieron y se concentraron proporcionando (3-hidroxi-3-((3-(6-metoxibenzo[d]tiazol-2-il)tioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (0,7 g, 1,78 mmol, 63,2 % de rendimiento) como un polvo blanco. La LC/MS confirmó producto cuando se perdió el BH_3 en las condiciones de LC/MS: tiempo de retención 3,11 (M+1-BH_3 = 379,4).

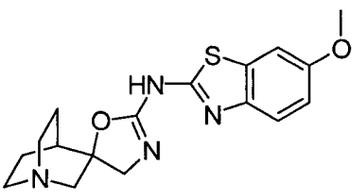
Etapa C: (2-(6-Metoxibenzo[d]tiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato



A (3-hidroxi-3-((3-(6-metoxibenzo[d]tiazol-2-il)tioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (0,68 g, 1,73 mmol) en N,N-dimetilformamida (20 ml) se añadió N,N'-diisopropilcarbodiimida (0,95 ml, 6,1 mmol). La mezcla de reacción se agitó a 70 ºC durante 4 horas. La reacción se concentró y purificó por cromatografía sobre gel de sílice (acetato de etilo de 40-100%/hexano). Las fracciones de producto se reunieron y concentraron a vacío proporcionando (2-(6-metoxibenzo[d]tiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato (0,35 g, 0,98

mmol, 56,4 % de rendimiento) como un polvo blanco. LC/MS MH^+ - BH_3 = 345,2.

Etapa D: N-(6-Metoxibenzo[d]tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



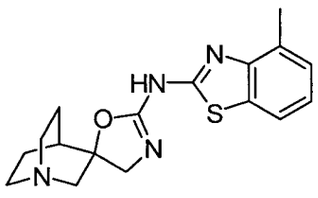
A (2-(6-metoxibenzo[d]tiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato (0,33 g, 0,921 mmol) en acetona (9 ml) se añadió HCl 3 M (2,30 ml, 6,91 mmol). La reacción se agitó a temperatura ambiente durante 4 horas y luego se neutralizó con hidróxido sódico 1N. El producto se extrajo con acetato de etilo (2 x 20 ml), seguido por cloroformo (2 x 20 ml). Los orgánicos se reunieron, se secaron con sulfato de magnesio, se filtraron y se concentraron a vacío proporcionando un polvo blanco. El producto bruto se purificó por HPLC de fase inversa (Phenomenex Luna 30 X 100mm; 220 de longitud de onda; tiempo de gradiente 10 min; caudal 40 ml/min; disolvente A; 10% de metanol-90% de agua-0,1% de TFA, disolvente B; 90% de metanol-10% de agua-0,1% de TFA). Las fracciones se reunieron, se neutralizaron con hidróxido sódico 1N y se extrajeron con acetato de etilo (2 x 30 ml). Los orgánicos se reunieron, se secaron con sulfato de magnesio, se filtraron y concentraron a vacío proporcionando N-(6-metoxibenzo[d]tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,25 g, 0,73 mmol, 79 % de rendimiento) como un polvo blanco. RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 8,88 (1 H, d, J=1,22 Hz), 7,48 - 7,52 (1 H, m), 7,40 (1 H, d, J=2,75 Hz),

6,92 (1 H, dd, *J*=8,70, 2,59 Hz), 3,87 (1 H, d, *J*=9,77 Hz), 3,77 (3 H, s), 3,61 (1 H, d, *J*=9,77 Hz), 3,03 (2 H, s), 2,75 - 2,86 (2 H, m), 2,67 (2 H, t, *J*=7,78 Hz), 2,06 (1 H, s ancho), 1,91 (1 H, s ancho), 1,41 - 1,65 (3 H, m). MS (LC/MS) T. R. = 1,44; $[M+H]^+$ = 345,3.

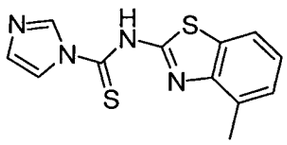
Los enantiómeros se separaron usando una columna Chiralpak AD-H (30 x 250mm, 5μm) con una fase móvil constituida por 23% de metanol (0,1% de DEA) en CO_2 y control UV a 220 nm. Los picos separados se concentraron a vacío proporcionando polvos blancos. El primer pico que salió de la columna proporcionó 205,5 mg, 0,60 mmol, 34,1 %. (5a, isómero S): RMN de ^1H (400 MHz, DMSO-d_6) δ ppm 8,88 (1 H, s ancho), 7,50 (1 H, d, *J*=8,81 Hz), 7,40 (1 H, d, *J*=2,52 Hz), 6,92 (1 H, dd, *J*=8,81, 2,77 Hz), 3,87 (1 H, d, *J*=9,82 Hz), 3,77 (3 H, s), 3,58 - 3,65 (1 H, m), 3,02 (2 H, s), 2,74 - 2,86 (2 H, m), 2,66 (2 H, t, *J*=7,68 Hz), 2,03 - 2,08 (1 H, m), 1,91 (1 H, s ancho), 1,39 - 1,65 (3 H, m). MS (LC/MS) T. R. = 1,40; $[M+H]^+$ = 345,2. El segundo pico proporcionó 206,9 mg, 0,6 mmol, 34 %. (5b, isómero R): RMN de ^1H (400 MHz, DMSO-d_6) δ ppm 8,88 (1 H, s ancho), 7,50 (1 H, d, *J*=8,56 Hz), 7,40 (1 H, d, *J*=2,52 Hz), 6,93 (1 H, dd, *J*=8,81, 2,52 Hz), 3,87 (1 H, d, *J*=10,07 Hz), 3,77 (3 H, s), 3,62 (1 H, d, *J*=10,07 Hz), 3,02 (2 H, s), 2,75 - 2,86 (2 H, m), 2,67 (2 H, t, *J*=7,68 Hz), 2,04 - 2,09 (1 H, m), 1,92 (1 H, s ancho), 1,42 - 1,66 (3 H, m). MS (LC/MS) T. R. = 1,70; $[M+H]^+$ = 345,1.

EJEMPLO 6

N-(4-Metilbenzo[d]tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

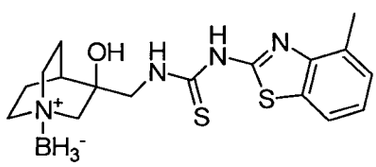


Etapa A: N-(4-Metilbenzo[d]tiazol-2-il)-^{1}H-imidazol-1-carbotioamida



A 4-metilbenzo[d]tiazol-2-amina (1,1 g, 6,7 mmol) en acetonitrilo (30 ml) se añadió 1,1'-tiocarbonildiimidazol (1,552 g, 8,71 mmol). La mezcla de reacción se agitó a 50ºC durante 18 horas. La reacción se enfrió hasta temperatura ambiente y el precipitado se filtró y se lavó con acetonitrilo (2 x 50 ml). El polvo amarillo se secó en un horno de vacío (50 ºC) durante 1 hora proporcionando N-(4-metilbenzo[d]tiazol-2-il)-^{1}H-imidazol-1-carbotioamida (900 mg, 3,28 mmol, 49 % de rendimiento) y luego se usó en la etapa siguiente sin purificación o caracterización posterior.

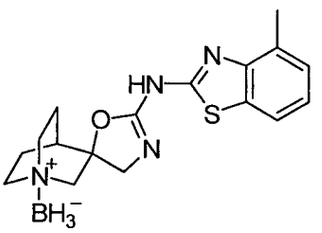
Etapa B: (3-Hidroxi-3-((3-(4-metilbenzo[d]tiazol-2-il)tioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato



A N-(4-metilbenzo[d]tiazol-2-il)-^{1}H-imidazol-1-carbotioamida (0,71 g, 2,59 mmol) en N,N-dimetilformamida (20 ml) se añadió (3-(aminometil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (0,44 g, 2,59 mmol). La mezcla de reacción se agitó a 70 ºC durante 4 horas. La reacción se concentró y purificó

por cromatografía sobre gel de sílice (acetato de etilo de 40-100%/hexanos). Las fracciones de producto se concentraron a vacío proporcionando (3-hidroxi-3-((3-(4-metilbenzo[d]tiazol-2-il)tioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (0,65 g, 1,73 mmol, 66,7 % de rendimiento) como un polvo blanco. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 11,93 (1 H, s), 7,74 (1 H, d, *J*=7,63 Hz), 7,22 - 7,26 (1 H, m), 7,19 (1 H, t, *J*=7,63 Hz), 3,75 - 3,93 (2 H, m), 2,72 - 2,95 (6 H, m), 2,56 (3 H, s), 2,03 - 2,14 (1 H, m), 1,95 (1 H, s ancho), 1,78 - 1,87 (1 H, m), 1,73 (1 H, ddd, *J*=13,81, 9,23, 5,04 Hz), 1,56 (1 H, td, *J*=9,99, 7,78 Hz), 1,38 (2 H, s ancho). (LC/MS) T. R. = 3,70; $[M+H]^+$ = 375,2.

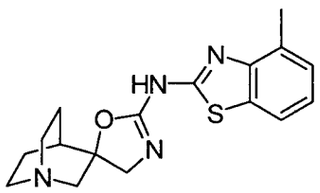
Etapa C: (2-(4-Metilbenzo[d]tiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato



A (3-hidroxi-3-((3-(4-metilbenzo[d]tiazol-2-il)tioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (0,62 g, 1,65 mmol) en N,N-dimetilformamida (20 ml) se añadió N,N'-diisopropilcarbodiimida (0,33 ml, 2,14 mmol). La mezcla de reacción se agitó a 70 °C durante 4 horas. La reacción se concentró y purificó por cromatografía sobre gel de sílice (acetato de etilo de 40-100%/hexanos). Las fracciones de producto se concentraron a vacío proporcionando (2-(4-metilbenzo[d]tiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato (0,4 g, 1,17 mmol, 70,9 % de rendimiento) como un polvo blanco. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm

8,90 (s, 1 H), 7,61 (d, *J*=7,63 Hz, 1 H), 7,13 - 7,17 (m, 1 H), 7,09 (t, *J*=7,48 Hz, 1 H), 3,90 (d, *J*=10,38 Hz, 1 H), 3,77 (d, *J*=10,38 Hz, 1 H), 3,32 (s, 3 H), 3,30 (d, *J*=1,53 Hz, 1 H), 3,13 - 3,20 (m, 2 H), 3,00 - 3,09 (m, 1 H), 2,85 - 2,94 (m, 4 H), 2,57 (s, 4 H), 2,28 (s, 1 H), 2,06 (s, 1 H), 1,75 - 1,83 (m, 4 H), 1,45 (s, 1 H). (LC/MS) T. R. = 2,73; $[M+H]^+$ = 343,2.

Etapa D: N-(4-Metilbenzo[d]tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

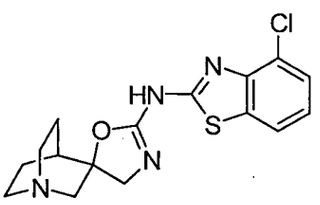


A (2-(4-metilbenzo[d]tiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato (0,38 g, 1,11 mmol) en acetona (9 ml) se añadió HCl 3 M (2,78 ml, 8,33 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 4 horas. Se añadió acetato de etilo y la fase acuosa se recogió y neutralizó con hidróxido sódico 1N. El producto se extrajo con acetato de etilo (2 x 40 ml). Los orgánicos se reunieron, se secaron con sulfato de magnesio, se filtraron y concentraron a vacío proporcionando N-(4-metilbenzo[d]tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,195 g, 0,594 mmol, 53,5 % de rendimiento) como un polvo blanco. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 8,84 (s, 1 H), 7,60 (d, *J*=7,32 Hz, 1 H), 7,13-7,17 (m, 1 H), 7,08 (t, *J*=7,63 Hz, 1 H), 3,92 (d, *J*=10,07 Hz, 1 H), 3,66 (d, *J*=9,77 Hz, 1 H), 3,04 (s, 2 H), 2,76 - 2,85 (m, 2 H), 2,68 (t, *J*=7,48 Hz, 2 H), 2,56 (s, 3 H), 2,09 (s, 1 H), 1,93 (s, 1 H), 1,61 (d, *J*=3,05 Hz, 1 H), 1,60 (s, 1 H), 1,50 (dd, *J*=7,17, 2,59 Hz, 1 H). (LC/MS) T. R. = 1,76; $[M+H]^+$ = 329,2.

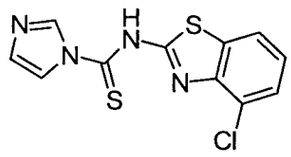
Los enantiómeros se separaron usando una columna Chiralcel OJ-H (30 x 250mm, 5μm) con una fase móvil constituida por 30% de metanol (0,1% de DEA) en CO_2 y control UV a 300 nm. Los picos separados se concentraron a vacío proporcionando polvos blancos. El primer pico que salió de la columna proporcionó 0,07 g, 0,21 mmol, 38,9 %. (6a, isómero S): RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 8,83 (s ancho, 1 H) 7,59 (d, *J*=7,63 Hz, 1 H) 7,11 - 7,18 (m, 1 H) 7,08 (t, *J*=7,63 Hz, 1 H) 3,92 (d, *J*=10,38 Hz, 1 H) 3,66 (d, *J*=9,77 Hz, 1 H) 3,04 (s, 2 H) 2,73 - 2,89 (m, 2 H) 2,61 - 2,72 (m, 2 H) 2,56 (s, 3 H) 2,09 (s ancho, 1 H) 1,93 (s ancho, 1 H) 1,43 - 1,71 (m, 3 H). MS (LC/MS) T. R. = 1,75; $[M+H]^+$ = 329,1. El segundo pico proporcionó 0,07 g, 0,21 mmol, 38,1 %. (6b, isómero R): RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 8,84 (s ancho, 1 H) 7,59 (d, *J*=7,63 Hz, 1 H) 7,15 (d, *J*=7,20 Hz, 1 H) 7,08 (t, *J*=7,48 Hz, 1 H) 3,92 (d, *J*=9,77 Hz, 1 H) 3,66 (d, *J*=10,07 Hz, 1 H) 3,00 - 3,09 (m, 2 H) 2,73 - 2,87 (m, 2 H) 2,62 - 2,72 (m, 2 H) 2,56 (s, 3 H) 2,05 - 2,12 (m, 1 H) 1,93 (s ancho, 1 H) 1,56 - 1,67 (m, 2 H) 1,45 - 1,55 (m, 1 H). MS (LC/MS) T. R. = 1,75; $[M+H]^+$ = 329,1.

EJEMPLO 7

N-(4-Clorobenzo[d]tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

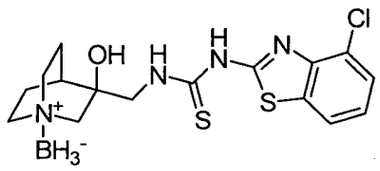


Etapa A: N-(4-Clorobenzo[d]tiazol-2-il)-^{1}H-imidazol-1-carbotioamida



A 4-clorobenzo[d]tiazol-2-amina (1,12 g, 6,07 mmol) en acetonitrilo (30 ml) se añadió 1,1'-tiocarbonildiimidazol (1,405 g, 7,89 mmol). La mezcla de reacción se agitó a 50 ºC durante 18 horas. La reacción se enfrió hasta temperatura ambiente y el precipitado se filtró y se lavó con acetonitrilo (2 x 50 ml). El polvo amarillo se secó en un horno de vacío (40 ºC) durante 1 hora proporcionando N-(4-clorobenzo[d]tiazol-2-il)-^{1}H-imidazol-1-carbotioamida (0,33 g, 1,12 mmol, 18,5 % de rendimiento) y luego se usó en la etapa siguiente sin purificación o caracterización posterior.

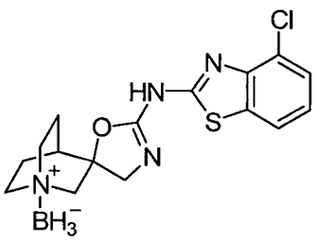
Etapa B: (3-((3-(4-Clorobenzo[d]tiazol-2-il)tioureido)metil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato



A N-(4-clorobenzo[d]tiazol-2-il)-^{1}H-imidazol-1-carbotioamida (0,3 g, 1,018 mmol) en N,N-dimetilformamida (20 ml) se añadió (3-(aminometil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (0,173 g, 1,018 mmol). La mezcla de reacción se agitó a 70 ºC durante 4 horas. La reacción se concentró y purificó por cromatografía sobre gel de sílice (acetato de etilo del 60-100%/hexanos). Las fracciones de producto se concentraron a vacío proporcionando (3-((3-(4-clorobenzo[d]tiazol-2-il)tioureido)metil)-3-hidroxi-1-

amoniobiciclo[2.2.2]octan-1-il)trihidroborato (0,25 g, 0,63 mmol, 61,9 % de rendimiento) como un polvo blanco. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 12,19 (s, 1 H) 9,72 (s ancho, 1 H) 7,93 (d, *J*=7,93 Hz, 1 H) 7,51 (d, *J*=7,93 Hz, 1 H) 7,26 - 7,32 (m, 1 H) 5,32 (s, 1 H) 3,88 (dd, *J*=13,73, 4,88 Hz, 1 H) 3,75 (dd, *J*=13,73, 4,88 Hz, 1 H) 2,73 - 2,95 (m, 6 H) 2,08 (s ancho, 1 H) 1,96 (s ancho, 1 H) 1,79 - 1,89 (m, 1 H) 1,68 - 1,78 (m, 1 H) 1,52 - 1,61 (m, 1 H) 1,39 (s ancho, 3 H).

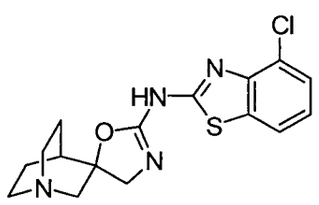
Etapa C: (2-(4-Clorobenzo[d]tiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato



A (3-((3-(4-clorobenzo[d]tiazol-2-il)tioureido)metil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (0,23 g, 0,58 mmol) en N,N-dimetilformamida (20 ml) se añadió N,N'-diisopropilcarbodiimida (0,117 ml, 0,75 mmol). La mezcla de reacción se agitó a 70 ºC durante 4 horas. La reacción se concentró y purificó por cromatografía sobre gel de sílice (acetato de etilo de 40-100%/hexanos). Las fracciones de producto se concentraron a vacío proporcionando (2-(4-clorobenzo[d]tiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato (0,1 g, 0,27 mmol, 47,6 % de rendimiento) como un polvo blanco. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 8,95 (s, 1 H) 7,79 (d, *J*=7,93 Hz, 1 H) 7,42 (d, *J*=7,63 Hz, 1 H) 7,18 (t, *J*=7,93 Hz, 1 H) 3,92 (d, *J*=10,38 Hz, 1 H) 3,77 (d, *J*=10,38 Hz, 1 H) 3,26 - 3,38 (m, 1

H) 3,19 (dd, *J*=15,26, 1,53 Hz, 1 H) 3,01 - 3,11 (m, 1 H) 2,81 - 3,00 (m, 3 H) 2,31 (s ancho, 1 H) 2,03 - 2,15 (m, 1 H) 1,70 - 1,89 (m, 3 H) 1,45 (s ancho, 3 H).

Etapa D: N-(4-Clorobenzo[d]tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



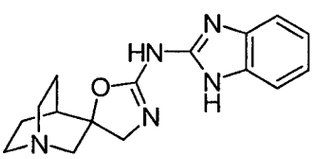
A (2-(4-clorobenzo[d]tiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato (0,08 g, 0,221 mmol) en acetona (9 ml) se añadió HCl 3 M (0,551 ml, 1,654 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 4 horas. Se añadió acetato de etilo y la fase acuosa se recogió y neutralizó con hidróxido sódico 1N. El producto se extrajo con acetato de etilo (2 x 40 ml). Los orgánicos se reunieron, se secaron con sulfato de magnesio, se filtraron y concentraron a vacío proporcionando N-(4-clorobenzo[d]tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,05 g, 0,14 mmol, 65,0 % de rendimiento) como un polvo blanco. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 8,90 (s ancho, 1 H) 7,77 (dd, *J*=7,78, 1,07 Hz, 1 H) 7,41 (dd, *J*=7,78, 1,07 Hz, 1 H) 7,17 (t, *J*=7,78 Hz, 1 H) 3,94 (d, *J*=10,07 Hz, 1 H) 3,67 (d, *J*=10,07 Hz, 1 H) 3,00 - 3,11 (m, 2 H) 2,76 - 2,88 (m, 2 H) 2,68 (t, *J*=7,63 Hz, 2 H) 2,11 (s ancho, 1 H) 1,91 - 2,00 (m, 1 H) 1,47 - 1,67 (m, 3 H). MS (LC/MS) T. R. = 2,11; $[M+H]^+$ = 349,1.

Los enantiómeros se separaron usando una columna Chiralcel OJ-H (30 x 250mm, 5μm) con una fase móvil constituida por 30% de metanol (0,1% de

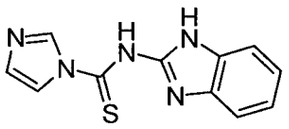
DEA) en CO_2. La longitud de onda se fijó a 220 nM. Los picos separados se concentraron a vacío proporcionando polvos blancos. El primer pico que salió de la columna fue (S)-N-(4-clorobenzo[d]tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,11 g, 0,30 mmol, 34,8 % de rendimiento). (7a, isómero S): RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 8,90 (s ancho, 1 H) 7,77 (d, *J*=7,32 Hz, 1 H) 7,41 (d, *J*=7,93 Hz, 1 H) 7,17 (t, *J*=7,93 Hz, 1 H) 3,94 (d, *J*=10,07 Hz, 1 H) 3,67 (d, *J*=10,07 Hz, 1 H) 3,00 - 3,11 (m, 2 H) 2,76 - 2,90 (m, 2 H) 2,68 (t, *J*=7,78 Hz, 2 H) 2,11 (s ancho, 1 H) 1,91 - 2,01 (m, 1 H) 1,47 - 1,68 (m, 3 H). MS (LC/MS) T. R. = 2,06; $[M+H]^+$ = 349,1. El segundo pico fue (R)-N-(4-clorobenzo[d]tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,11 g, 0,30 mmol, 35,2 % de rendimiento). (7b, isómero R): RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 8,89 (s ancho, 1 H) 7,77 (d, *J*=7,93 Hz, 1 H) 7,40 (d, *J*=7,93 Hz, 1 H) 7,16 (t, *J*=7,93 Hz, 1 H) 3,94 (d, *J*=10,07 Hz, 1 H) 3,67 (d, *J*=10,07 Hz, 1 H) 2,99 - 3,11 (m, 2 H) 2,74 - 2,88 (m, 2 H) 2,68 (t, *J*=7,78 Hz, 2 H) 2,11 (s ancho, 1 H) 1,90 - 2,01 (m, 1 H) 1,44 - 1,68 (m, 3 H). MS (LC/MS) T. R. = 2,07; $[M+H]^+$ = 349,1.

EJEMPLO 8

N-(1H-Benzo[d]imidazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

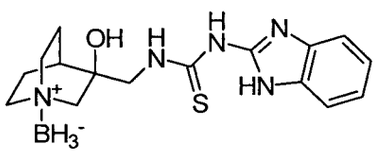


Etapa A: N-(¹H-Benzo[d]imidazol-2-il)-¹H-imidazol-1-carbotioamida



A ¹H-benzo[d]imidazol-2-amina (1,28 g, 9,61 mmol) en acetonitrilo (30 ml) se añadió 1,1'-tiocarbonildiimidazol (2,227 g, 12,5 mmol). La mezcla de reacción se agitó a 50 °C durante 18 horas. La reacción se enfrió hasta temperatura ambiente y el precipitado se filtró y se lavó con acetonitrilo (2 x 50 ml). El polvo amarillo se secó en un horno de vacío (40°C) durante 1 hora proporcionando N-(¹H-benzo[d]imidazol-2-il)-¹H-imidazol-1-carbotioamida (1,8 g, 7,4 mmol, 77 % de rendimiento) y luego se usó en la etapa siguiente sin purificación o caracterización posterior.

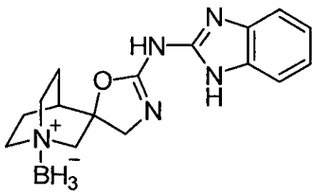
Etapa B: (3-((3-¹H-Benzo[d]imidazol-2-iltioureido)metil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato



A N-(¹H-benzo[d]imidazol-2-il)-¹H-imidazol-1-carbotioamida (1,07 g, 4,4 mmol) en N,N-dimetilformamida (20 ml) se añadió (3-(aminometil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (0,748 g, 4,4 mmol). La mezcla de reacción se agitó a 70 °C durante 4 horas. La reacción se concentró y purificó por cromatografía sobre gel de sílice (acetato de etilo del 60-100%/hexano). Las fracciones de producto se concentraron a vacío proporcionando (3-((3-¹H-benzo[d]imidazol-2-iltioureido)metil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (1,28 g, 3,71 mmol, 84 % de rendimiento) como un polvo blanco. RMN de ¹H (500 MHz, DMSO-d_6) δ ppm 11,41 (s, 1 H), 11,16 (s, 1 H),

7,43 (d, J=3,05 Hz, 3 H), 7,13 (ddd, J=9,46, 3,81, 3,51 Hz, 3 H), 5,36 (s, 1 H), 4,01-4,07 (m, 3 H), 3,79 (dd, J=13,28, 4,12 Hz, 1 H), 2,83-2,92 (m, 6 H), 2,71 (d, J=14,04 Hz, 2 H), 2,04-2,13 (m, 2 H), 1,89-1,94 (m, 3 H), 1,74 (td, J=9,46, 5,49 Hz, 2 H), 1,51-1,59 (m, 2 H), 1,38 (s, 2 H), 1,31 (s, 1 H). La LC/MS confirmó producto cuando se perdió el BH_3 en las condiciones de LC/MS: tiempo de retención 2,75 (M+1-BH_3 = 332,2).

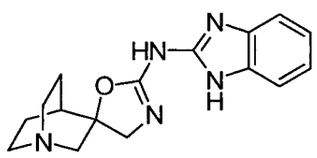
Etapa C: (2-(^{1}H-Benzo[d]imidazol-2-ilamino)-4H-1'-amoniospiro-[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato



A (3-((3-^{1}H-benzo[d]imidazol-2-iltioureido)metil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (1,0 g, 2,9 mmol) en N,N-dimetilformamida (20 ml) se añadió N,N'-diisopropilcarbodiimida (0,587 ml, 3,77 mmol). La mezcla de reacción se agitó a 70 °C durante 4 horas. La reacción se concentró y purificó por cromatografía sobre gel de sílice (acetato de etilo de 40-100%/hexano). Las fracciones de producto se concentraron a vacío proporcionando (2-(^{1}H-benzo[d]imidazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato (0,81 g, 2,6 mmol, 90 % de rendimiento) como un polvo blanco. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 7,29 (s, 1 H), 6,99 - 7,05 (m, 2 H), 3,90 (t, *J*=9,77 Hz, 1 H), 3,75 (d, *J*=10,38 Hz, 1 H), 3,26 - 3,35 (m, 1 H), 3,13 (dd, *J*=14,95, 1,53 Hz, 1 H), 2,98 - 3,06 (m, 1 H), 2,84 - 2,92 (m, 3 H), 2,22 (s, 1 H), 1,98 - 2,05 (m, 1 H), 1,72 - 1,82 (m, 3 H), 1,45 (s, 1 H). La LC/MS confirmó producto cuando se perdió el BH_3 en las

condiciones de LC/MS: tiempo de retención 2,29 (M+1-BH_3 = 298,2).

Etapa D: N-(1H-Benzo[d]imidazol-2-il)-4H-1'-azaspiro-[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



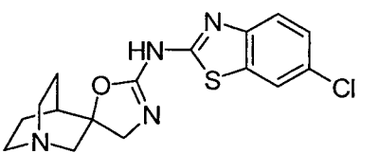
A (2-(1H-benzo[d]imidazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato (0,77 g, 2,5 mmol) en acetona (9 ml) se añadió HCl 3 M (6,2 ml, 18,6 mmol). La reacción se agitó a temperatura ambiente durante 4 horas. Se añadió acetato de etilo y la fase acuosa se recogió y neutralizó con hidróxido sódico 1N. El producto se extrajo con acetato de etilo (2 x 40 ml). Los orgánicos se reunieron, se secaron con sulfato de magnesio, se filtraron y concentraron a vacío proporcionando N-(1H-benzo[d]imidazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,5 g, 1,68 mmol, 68 % de rendimiento) como un polvo blanco. RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 11,45 (s, 1 H), 9,20 (s, 1 H), 7,32 (s, 1 H), 7,00 (dd, *J*=5,65, 2,90 Hz, 4 H), 3,91 (d, *J*=10,07 Hz, 2 H), 3,64 (d, *J*=10,07 Hz, 2 H), 2,98 - 3,05 (m, 4 H), 2,73 - 2,82 (m, 4 H), 2,67 (t, *J*=7,63 Hz, 4 H), 2,03 (d, *J*=2,75 Hz, 2 H), 1,85 - 1,92 (m, 2 H), 1,54 - 1,63 (m, 4 H), 1,44 - 1,51 (m, 2 H). MS (LC/MS) T. R. = 1,30; $[M+H]^+$ = 298,2.

Los enantiómeros se separaron usando una columna Chiralpak AS-H (30 x 250mm, 5μm) con una fase móvil constituida por 30% de metanol (0,1% de DEA) en CO_2 y control UV a 330 nm. Los picos separados se concentraron a vacío proporcionando polvos blancos. El primer pico que salió de la columna

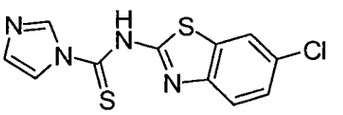
proporcionó 0,11 g, 0,36 mmol, 33,0 %. (8a; isómero R): P.F. 255 ºC (desc). RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 11,43 (s ancho, 1 H) 9,16 (s ancho, 1 H) 7,14 - 7,53 (m, 2 H) 6,82 - 7,09 (m, 2 H) 3,91 (d, *J*=9,77 Hz, 1 H) 3,64 (d, *J*=10,07 Hz, 1 H) 2,96 - 3,09 (m, 2 H) 2,71 - 2,87 (m, 2 H) 2,62 - 2,73 (m, 2 H) 2,01 - 2,08 (m, 1 H) 1,81 - 1,97 (m, 1 H) 1,54 - 1,66 (m, 2 H) 1,40 - 1,53 (m, 1 H). MS (LC/MS) T. R. = 1,26; $[M+H]^+$ = 298,2. El segundo pico proporcionó 0,11 g, 0,36 mmol, 33,0 %. (8b; isómero S): RMN de ^{1}H(500 MHz, DMSO-d_6) δ ppm 11,43 (s ancho, 1 H) 9,20 (s ancho, 1 H) 7,10 - 7,60 (m, 2 H) 6,83 - 7,11 (m, 2 H) 3,91 (d, *J*=9,77 Hz, 1 H) 3,64 (d, *J*=9,77 Hz, 1 H) 2,94 - 3,16 (m, 2 H) 2,71 - 2,86 (m, 2 H) 2,59 - 2,72 (m, 2 H) 1,97 - 2,09 (m, 1 H) 1,81 - 1,95 (m, 1 H) 1,53 - 1,71 (m, 2 H) 1,41 - 1,53 (m, 1 H). MS (LC/MS) T. R. = 1,28; $[M+H]^+$ = 298,2.

EJEMPLO 9

N-(6-Clorobenzo[d]tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



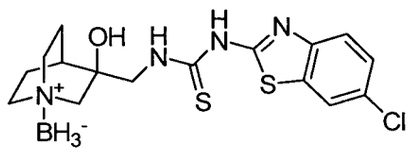
Etapa A: N-(6-Clorobenzo[d]tiazol-2-il)-^{1}H-imidazol-1-carbotioamida



A 6-clorobenzo[d]tiazol-2-amina (1,14 g, 6,17 mmol) en acetonitrilo (30 ml) se añadió 1,1'-tiocarbonildiimidazol (1,43 g, 8 mmol). La reacción se agitó a 50 ºC durante 18 horas. La reacción se enfrió hasta temperatura ambiente y el

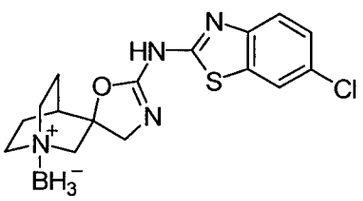
precipitado se filtró y se lavó con acetonitrilo (2 x 50 ml). El polvo amarillo se secó en un horno de vacío (40 °C) durante 1 hora proporcionando N-(6-clorobenzo[d]tiazol-2-il)- ^{1}H-imidazol-1-carbotioamida (1,16 g, 3,9 mmol, 64 % de rendimiento) y luego se usó en la etapa siguiente sin purificación o caracterización posterior.

Etapa B: (3-((3-(6-Clorobenzo[d]tiazol-2-il)tioureido)metil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato



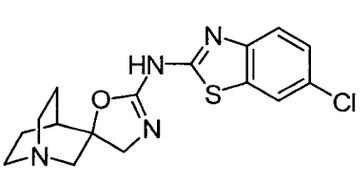
A N-(6-clorobenzo[d]tiazol-2-il)- ^{1}H-imidazol-1-carbotioamida (0,86 g, 2,9 mmol) en N,N-dimetilformamida (20 ml) se añadió (3-(aminometil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (0,5 g, 2,9 mmol). La reacción se agitó a 70 °C durante 4 horas. La reacción se concentró y purificó por cromatografía sobre gel de sílice (acetato de etilo del 60-100%/hexanos). Las fracciones de producto se concentraron a vacío proporcionando (3-((3-(6-clorobenzo[d]tiazol-2-il)tioureido)metil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (0,4 g, 1,01 mmol, 34,6 % de rendimiento) como un polvo blanco. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 11,92 (s ancho, 1 H) 9,89 (s ancho, 1 H) 8,08 (s ancho, 1 H) 7,62 (s ancho, 1 H) 7,40 - 7,50 (m, 1 H) 5,40 (s ancho, 1 H) 3,88 (d, *J*=10,20 Hz, 1 H) 3,76 (d, *J*=10,20 Hz, 1 H) 2,67 - 3,02 (m, 6 H) 2,08 (s ancho, 1 H) 1,80 - 1,95 (m, 2 H) 1,73 (s ancho, 1 H) 1,01 - 1,63 (m, 4 H). MS (LC/MS) T. R. = 3,87; $[M+H]^+$ = 395,1.

Etapa C: (2-(6-Clorobenzo[d]tiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato



A (3-((3-(6-clorobenzo[d]tiazol-2-il)tioureido)metil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (0,37 g, 0,93 mmol) en N,N-dimetilformamida (20 ml) se añadió N,N'-diisopropilcarbodiimida (0,19 ml, 1,2 mmol). La reacción se agitó a 70 °C durante 4 horas. La reacción se concentró y purificó por cromatografía sobre gel de sílice (acetato de etilo de 40-100%/hexano). Las fracciones de producto se concentraron a vacío proporcionando (2-(6-clorobenzo[d]tiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato (0,12 g, 0,33 mmol, 35,5 % de rendimiento) como un polvo blanco. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 9,10 (s ancho, 1 H) 7,95 (d, *J*=2,14 Hz, 1 H) 7,60 (d, *J*=8,55 Hz, 1 H) 7,36 (dd, *J*=8,55, 2,14 Hz, 1 H) 3,88 (d, *J*=10,38 Hz, 1 H) 3,76 (d, *J*=10,38 Hz, 1 H) 3,26 - 3,37 (m, 1 H) 3,17 (dd, *J*=14,95, 1,83 Hz, 1 H) 3,00 - 3,11 (m, 1 H) 2,80 - 2,97 (m, 3 H) 2,28 (s ancho, 1 H) 2,00 - 2,11 (m, 1 H) 1,69 - 1,88 (m, 3 H) 1,46 (s ancho, 3 H). LC/MS : tiempo de retención 2,94 (M+1-BH_3 = 349,1).

Etapa D: N-(6-Clorobenzo[d]tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



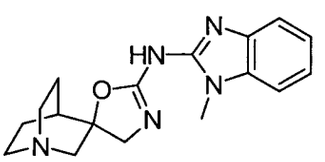
A (2-(6-clorobenzo[d]tiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato (0,1 g, 0,28 mmol) en acetona (9 ml) se añadió HCl 3 M (0,69 ml, 2,07 mmol). La reacción se agitó a temperatura ambiente durante 4 horas. Se añadió acetato de etilo y la fase acuosa se recogió y neutralizó con hidróxido sódico 1N. El producto se extrajo con acetato de etilo (2 x 40 ml). Los orgánicos se reunieron, se secaron con sulfato de magnesio, se filtraron y concentraron a vacío proporcionando N-(6-clorobenzo[d]tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,06 g, 0,17 mmol, 62,4 % de rendimiento) como un polvo blanco. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 9,03 (s ancho, 1 H) 7,93 (d, *J*=2,14 Hz, 1 H) 7,58 (d, *J*=8,55 Hz, 1 H) 7,35 (dd, *J*=8,55, 2,14 Hz, 1 H) 3,90 (d, *J*=10,07 Hz, 1 H) 3,65 (d, *J*=10,07 Hz, 1 H) 2,99 - 3,11 (m, 2 H) 2,73 - 2,89 (m, 2 H) 2,67 (t, *J*=7,63 Hz, 2 H) 2,08 (s ancho, 1 H) 1,82 - 1,99 (m, 1 H) 1,43 - 1,67 (m, 3 H). MS (LC/MS) T. R. = 2,07; $[M+H]^+$ = 349,1.

Los enantiómeros se separaron usando una columna Chiralpak AS-H (30 x 250mm, 5µm) con una fase móvil constituida por 30% de metanol (0,1% de DEA) en CO_2 y control UV a 220 nm. Los picos separados se concentraron a vacío proporcionando polvos blancos. El primer pico que salió de la columna proporcionó 0,034 g, 0,10 mmol, 36,2 %. (9a; isómero S): RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 9,02 (s ancho, 1 H) 7,93 (d, *J*=2,14 Hz, 1 H) 7,58 (d, *J*=8,55 Hz, 1 H) 7,35 (dd, *J*=8,55, 2,14 Hz, 1 H) 3,90 (d, *J*=10,07 Hz, 1 H) 3,65 (d, *J*=10,07 Hz, 1 H) 2,97 - 3,11 (m, 2 H) 2,73 - 2,89 (m, 2 H) 2,67 (t, *J*=7,48 Hz, 2 H) 2,08 (s ancho, 1 H) 1,93 (s ancho, 1 H) 1,43 - 1,69 (m, 3 H). MS (LC/MS) T. R. = 2,05; $[M+H]^+$ = 349,1. Rotación óptica = + 4,00°. El segundo pico proporcionó 0,037 g, 0,10 mmol, 39,4 %. (9b; isómero R): RMN de ^{1}H(500 MHz,

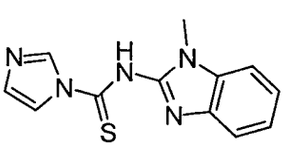
DMSO-d_6) δ ppm 9,02 (s ancho, 1 H) 7,93 (d, *J*=2,14 Hz, 1 H) 7,58 (d, *J*=8,55 Hz, 1 H) 7,35 (dd, *J*=8,55, 2,44 Hz, 1 H) 3,90 (d, *J*=10,07 Hz, 1 H) 3,65 (d, *J*=10,07 Hz, 1 H) 2,93 - 3,13 (m, 2 H) 2,72 - 2,91 (m, 2 H) 2,62 - 2,73 (m, 2 H) 2,08 (s ancho, 1 H) 1,93 (d, *J*=1,22 Hz, 1 H) 1,44 - 1,68 (m, 3 H). MS (LC/MS) T. R. = 2,04; $[M+H]^+$ = 349,1. Rotación óptica = -3,74°.

EJEMPLO 10

N-(1-Metil-^{1}H-benzo[d]imidazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

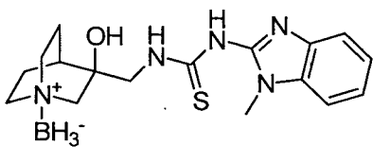


Etapa A: N-(1-Metil-^{1}H-benzo[d]imidazol-2-il)-^{1}H-imidazol-1-carbotioamida



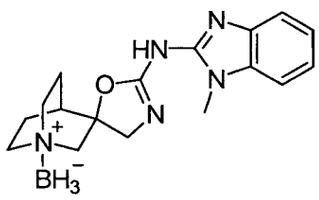
A 1-metil-^{1}H-benzo[d]imidazol-2-amina (1,28 g, 8,7 mmol) en acetonitrilo (30 ml) se añadió 1,1'-tiocarbonildiimidazol (2,015 g, 11,31 mmol). La reacción se agitó a 50 °C durante 18 horas. La reacción se enfrió hasta temperatura ambiente y el precipitado se filtró y se lavó con acetonitrilo (2 x 50 ml). El polvo amarillo se secó en un horno de vacío (40 °C) durante 1 hora proporcionando N-(1-metil-^{1}H-benzo[d]imidazol-2-il)-^{1}H-imidazol-1-carbotioamida (1,6 g, 6,22 mmol, 71,5 % de rendimiento) y luego se usó en la etapa siguiente sin purificación o caracterización posterior.

Etapa B: (3-Hidroxi-3-((3-(1-metil-^{1}H-benzo[d]imidazol-2-il)tioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato



A N-(1-metil-^{1}H-benzo[d]imidazol-2-il)-^{1}H-imidazol-1-carbotioamida (1,04 g, 4,04 mmol) en N,N-dimetilformamida (20 ml) se añadió (3-(aminometil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (0,687 g, 4,04 mmol). La reacción se agitó a 70 °C durante 4 horas. La reacción se concentró y purificó por cromatografía sobre gel de sílice (acetato de etilo del 60-100%/hexano). Las fracciones de producto se concentraron a vacío proporcionando (3-hidroxi-3-((3-(1-metil-^{1}H-benzo[d]imidazol-2-il)tioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (1,28 g, 3,56 mmol, 88 % de rendimiento) como un polvo blanco. La LC/MS confirmó producto cuando se perdió el BH_3 en las condiciones de LC/MS: tiempo de retención 3,01 ($M+1-BH_3$ = 346,2).

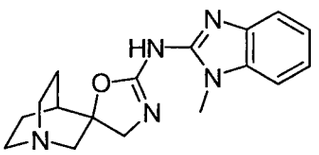
Etapa C: (2-(1-Metil-^{1}H-benzo[d]imidazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato



A (3-hidroxi-3-((3-(1-metil-^{1}H-benzo[d]imidazol-2-il)tioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (1,19 g, 3,31 mmol) en N,N-dimetilformamida (20 ml) se añadió N,N'-diisopropilcarbodiimida (1,55 ml, 9,9

mmol). La reacción se agitó a 70 °C durante 4 horas. La reacción se concentró y purificó por cromatografía sobre gel de sílice (acetato de etilo de 40-100%/hexano). Las fracciones de producto se concentraron a vacío proporcionando (2-(1-metil-^{1}H-benzo[d]imidazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato (0,94 g, 2,9 mmol, 87 % de rendimiento) como un polvo blanco. RMN de ^{1}H (400 MHz, DMSO-d_6) δ ppm 9,36 (s ancho, 1 H) 7,34 - 7,44 (m, 1 H) 7,26 - 7,34 (m, 1 H) 7,00 - 7,12 (m, 2 H) 3,90 (d, *J*=10,32 Hz, 1 H) 3,77 (d, *J*=10,32 Hz, 1 H) 3,57 (s, 3 H) 3,28 (dd, *J*=14,86, 2,27 Hz, 1 H) 3,13 (dd, *J*=14,86, 1,51 Hz, 1 H) 2,95 - 3,08 (m, 1 H) 2,75 - 2,95 (m, 3 H) 2,22 (s ancho, 1 H) 1,96 - 2,11 (m, 1 H) 1,67 - 1,89 (m, 3 H) 1,43 (s ancho, 3 H). LC/MS : tiempo de retención 2,37 (M+1-BH_3 = 312,2).

Etapa D: N-(1-Metil-^{1}H-benzo[d]imidazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



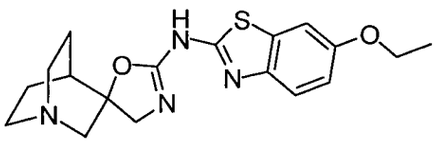
A (2-(1-metil-^{1}H-benzo[d]imidazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato (0,92 g, 2,8 mmol) en acetona (9 ml) se añadió HCl 3 M (7,1 ml, 21,2 mmol). La reacción se agitó a temperatura ambiente durante 4 horas. Se añadió acetato de etilo y la fase acuosa se recogió y neutralizó con hidróxido sódico 1N. El producto se extrajo con acetato de etilo (2 x 40 ml). Los orgánicos se reunieron, se secaron con sulfato de magnesio, se filtraron y se concentraron a vacío proporcionando N-(1-metil-^{1}H-

benzo[d]imidazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,84 g, 2,7 mmol, 95 % de rendimiento) como un polvo blanco. RMN de ^{1}H (400 MHz, DMSO-d_6) δ ppm 9,24 - 9,39 (m, 1 H) 7,33 - 7,42 (m, 1 H) 7,25 - 7,33 (m, 1 H) 6,99 - 7,10 (m, 2 H) 3,92 (d, *J*=10,07 Hz, 1 H) 3,66 (d, *J*=10,07 Hz, 1 H) 3,57 (s, 3 H) 2,97 - 3,08 (m, 2 H) 2,78 (t, *J*=7,81 Hz, 2 H) 2,67 (t, *J*=7,81 Hz, 2 H) 2,01 - 2,09 (m, 1 H) 1,80 - 1,96 (m, 1 H) 1,40 - 1,66 (m, 3 H). MS (LC/MS) T. R. = 1,49; $[M+H]^+$ = 312,2.

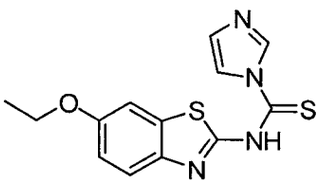
Los enantiómeros se separaron usando una columna Chiralcel OJ-H (30 x 250mm, 5μm) con una fase móvil constituida por 22% de metanol (0,1% de DEA) en CO_2 y control UV a 300 nm. Los picos separados se concentraron a vacío proporcionando polvos blancos. El primer pico que salió de la columna proporcionó 0,065 g, 0,205 mmol, 39,8 %. (10a, isómero R): RMN de ^{1}H(500 MHz, DMSO-d_6) δ ppm 9,31 (s ancho, 1 H) 7,35 - 7,45 (m, 1 H) 7,26 - 7,34 (m, 1 H) 7,00 - 7,15 (m, 2 H) 3,93 (d, *J*=10,10 Hz, 1 H) 3,67 (d, *J*=10,10 Hz, 1 H) 3,59 (s, 3 H) 2,93 - 3,13 (m, 2 H) 2,74 - 2,89 (m, 2 H) 2,61 - 2,74 (m, 2 H) 2,05 (s ancho, 1 H) 1,91 (s ancho, 1 H) 1,38 - 1,68 (m, 3 H). MS (LC/MS) T. R. = 1,37; $[M+H]^+$ = 312,2. Rotación óptica = - 16,02°. El segundo pico proporcionó 0,06 g, 0,19 mmol, 36,8 %. (10b; isómero S): RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 9,31 (s ancho, 1 H) 7,33 - 7,43 (m, 1 H) 7,25 - 7,33 (m, 1 H) 6,93 - 7,11 (m, 2 H) 3,93 (dd, *J*=9,92, 3,20 Hz, 1 H) 3,67 (dd, *J*=9,92, 3,20 Hz, 1 H) 3,58 (s, 3 H) 2,94 - 3,13 (m, 2 H) 2,74 - 2,85 (m, 2 H) 2,59 - 2,72 (m, 2 H) 2,04 (s ancho, 1 H) 1,90 (s ancho, 1 H) 1,37 - 1,70 (m, 3 H). MS (LC/MS) T. R. = 1,37; $[M+H]^+$ = 312,2. Rotación óptica = + 35,99°.

EJEMPLO 11

N-(6-Etoxibenzo[d]tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

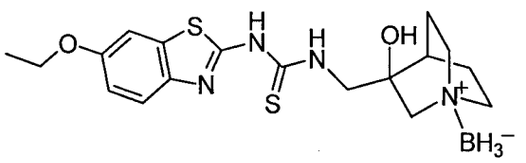


Etapa A: N-(6-Etoxibenzo[d]tiazol-2-il)- 1H-imidazol-1-carbotioamida



En un vial se colocó 6-etoxibenzo[d]tiazol-2-amina (1,5 g, 7,72 mmol) y di(^{1}H-imidazol-1-il)metanotiona (1,789 g, 10,04 mmol) en acetonitrilo (15 ml). La reacción se calentó hasta 80 °C durante la noche. La mezcla de reacción se filtró y el precipitado se recogió proporcionando 2,4 gramos (7,88 mmol, 102 %) de sólidos color óxido.

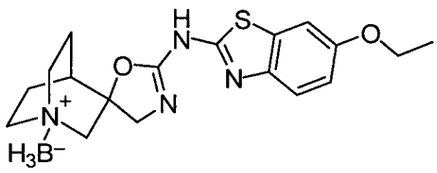
Etapa B: (3-((3-(6-Etoxibenzo[d]tiazol-2-il)tioureido)metil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato



En un vial se colocó N-(6-etoxibenzo[d]tiazol-2-il)- ^{1}H-imidazol-1-carbotioamida (2,4 g, 7,88 mmol) y (3-(aminometil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (1,341 g, 7,88 mmol) en N,N-dimetilformamida (8 ml). La reacción se calentó hasta 80 °C. Después de 2

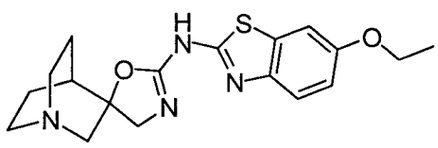
horas la reacción se vertió en agua y cloroformo y el orgánico se extrajo y se concentró hasta un aceite rojo. Este material se usó en la siguiente reacción sin purificación o caracterización posterior.

Etapa C: (2-(6-Etoxibenzo[d]tiazol-2-ilamino)-4H-1'-amoniospiro-[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato



Se colocó en un matraz (3-((3-(6-etoxibenzo[d]tiazol-2-il)tioureido)-metil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (3,2 g, 7,9 mmol) y N,N'-diisopropilcarbodiimida (4,3 ml, 27,6 mmol) en N,N-dimetilformamida (10 ml). La reacción se calentó hasta 70 °C durante 2 horas y luego se vertió en agua y cloroformo. El orgánico se recogió y se concentró hasta un residuo. El residuo se trituró con éter y el precipitado se recogió por filtración a vacío proporcionando 1,11 gramos (2,98 mmol, 37,8 %) de polvo gris.

Etapa D: N-(6-Etoxibenzo[d]tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



Se colocó en un vial (2-(6-etoxibenzo[d]tiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato (500 mg, 1,34 mmol) y HCl (8,06 ml, 24,17 mmol) en acetona (10 ml). La reacción se controló

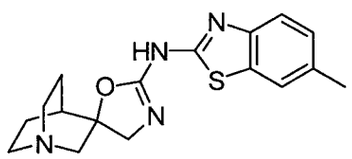
por HPLC. Después de 2 horas, la reacción se completó por LC/MS. La reacción se vertió en agua y cloroformo, y se separó la fase orgánica. La fase acuosa se neutralizó y se extrajo con cloroformo (2x). La segunda fracción de cloroformo se concentró hasta un residuo blanco. El sólido se trituró en éter y el precipitado se recogió proporcionando 314,4 mg (0,877 mmol, 65,3 %) del material deseado. RMN de ^{1}H (400 MHz, DMSO-d_6) δ ppm 8,89 (1 H, s ancho), 7,50 (1 H, d, *J*=8,81 Hz), 7,38 (1 H, d, *J*=2,52 Hz), 6,91 (1 H, dd, *J*=8,81, 2,52 Hz), 4,03 (2 H, c, *J*=7,05 Hz), 3,87 (1 H, d, *J*=10,07 Hz), 3,62 (1 H, d, *J*=10,07 Hz), 3,02 (2 H, s), 2,78 (2 H, t, *J*=7,81 Hz), 2,66 (2 H, t, *J*=7,68 Hz), 2,05 (1 H, s ancho), 1,91 (1 H, s ancho), 1,42 - 1,67 (3 H, m), 1,33 (3 H, t, *J*=7,05 Hz). MS (LC/MS) T. R. = 1,60; $[M+H]^+$ = 359,0.

Los enantiómeros se separaron usando una columna Chiralpak AS-H (30 x 250mm, 5μm) con una fase móvil constituida por 30% de metanol (0,1% de DEA) en CO_2 y control UV a 300 nm. Los picos separados se concentraron a vacío proporcionando polvos blancos. El primer pico que salió de la columna proporcionó 62,4 mg, 0,17 mmol, 31,2 %. (11a; isómero S): RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 8,87 (1 H, s ancho), 7,49 (1 H, d, *J*=8,55 Hz), 7,38 (1 H, d, *J*=2,44 Hz), 6,91 (1 H, dd, *J*=8,85, 2,44 Hz), 4,03 (2 H, c, *J*=7,02 Hz), 3,87 (1 H, d, *J*=10,07 Hz), 3,61 (1 H, d, *J*=10,07 Hz), 3,02 (2 H, s), 2,72 - 2,85 (2 H, m), 2,66 (2 H, t, *J*=7,63 Hz), 2,05 (1 H, s ancho), 1,91 (1 H, s ancho), 1,43 - 1,64 (3 H, m), 1,33 (3 H, t, *J*=7,02 Hz). MS (LC/MS) T. R. = 1,81; $[M+H]^+$ = 359,1. El segundo pico proporcionó 58,9 mg, 0,164 mmol, 29,5 %. (11b; isómero R): RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 8,86 (1 H, s ancho), 7,48 (1 H, d, *J*=8,85 Hz), 7,37 (1 H, d, *J*=2,44 Hz), 6,91 (1 H, d, *J*=2,75 Hz), 4,02 (2 H, c, *J*=7,02 Hz), 3,86 (1 H, d, *J*=9,77 Hz), 3,61 (1 H, d, *J*=9,77 Hz), 3,01 (2 H, s),

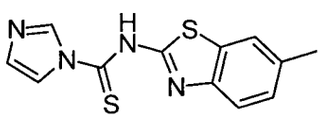
2,72 - 2,85 (2 H, m), 2,62 - 2,69 (2 H, m), 2,04 (1 H, d, *J*=2,44 Hz), 1,90 (1 H, d, *J*=4,27 Hz), 1,42 - 1,63 (3 H, m), 1,29 - 1,35 (3 H, m). MS (LC/MS) T. R. = 1,52; $[M+H]^+$ = 359,1.

EJEMPLO 12

N-(6-Metilbenzo[d]tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

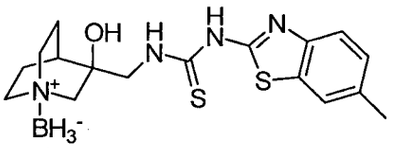


Etapa A: N-(6-Metilbenzo[d]tiazol-2-il)-^{1}H-imidazol-1-carbotioamida



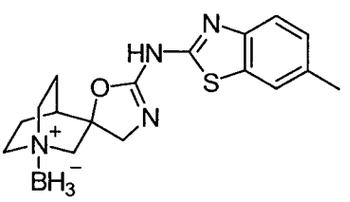
A 6-metilbenzo[d]tiazol-2-amina (1. g, 6,2 mmol) en acetonitrilo (30 ml) se añadió 1,1'-tiocarbonildiimidazol (1,44 g, 8,1 mmol). La reacción se agitó a 50 °C durante 18 horas. La reacción se enfrió hasta temperatura ambiente y el precipitado se filtró y se lavó con acetonitrilo (2 x 50 ml). El polvo amarillo se secó en un horno de vacío (40 °C) durante 1 hora proporcionando N-(6-metilbenzo[d]tiazol-2-il)-^{1}H-imidazol-1-carbotioamida (1,06 g, 3,86 mmol, 62 % de rendimiento) y luego se usó en la etapa siguiente sin purificación o caracterización posterior.

Etapa B: (3-Hidroxi-3-((3-(6-metilbenzo[d]tiazol-2-il)tioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato



A N-(6-metilbenzo[d]tiazol-2-il)- ^{1}H-imidazol-1-carbotioamida (0,96 g, 3,5 mmol) en N,N-dimetilformamida (20 ml) se añadió (3-(aminometil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (0,595 g, 3,5 mmol). La reacción se agitó a 70°C durante 4 horas. La mezcla de reacción se concentró y purificó por cromatografía sobre gel de sílice (acetato de etilo de 40-100%/hexanos). Las fracciones de producto se concentraron a vacío proporcionando (3-hidroxi-3-((3-(6-metilbenzo[d]tiazol-2-il)tioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (0,88 g, 2,338 mmol, 66,8 % de rendimiento) como un polvo blanco. MS (LC/MS) T. R. = 3,71; $[M+H]^+$ = 375,2.

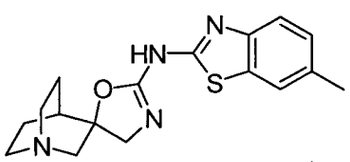
Etapa C: (2-(6-Metilbenzo[d]tiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato



A (3-hidroxi-3-((3-(6-metilbenzo[d]tiazol-2-il)tioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (0,86 g, 2,285 mmol) en N,N-dimetilformamida (20 ml) se añadió N,N'-diisopropilcarbodiimida (0,288 g, 2,285 mmol). La reacción se agitó a 70 °C durante 4 horas. La reacción se concentró y se añadió acetato de etilo. El precipitado se filtró y se lavó con más acetato de etilo. El polvo se secó en un horno de vacío (70°C) proporcionando (2-(6-metilbenzo[d]tiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-

biciclo[2.2.2]octano]-1'-il)trihidroborato (0,65 g, 1,899 mmol, 83 % de rendimiento) como un polvo blanco. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 9,03 (1 H, s ancho), 7,59 (1 H, s), 7,51 (1 H, d, *J*=8,24 Hz), 7,15 (1 H, d, *J*=8,24 Hz), 3,86 (1 H, d, *J*=10,38 Hz), 3,74 (1 H, d, *J*=10,38 Hz), 3,29 (1 H, dd, *J*=15,26, 1,83 Hz), 3,14 (1 H, d, *J*=15,26 Hz), 2,99 - 3,09 (1 H, m), 2,80 - 2,95 (3 H, m), 2,36 (3 H, s), 2,25 (1 H, s ancho), 2,03 (1 H, t, *J*=10,22 Hz), 1,70 - 1,85 (3 H, m). MS (LC/MS) T. R. = 2,78; $[M+H]^+$ = 343,2.

Etapa D: N-(6-Metilbenzo[d]tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



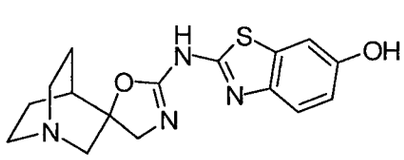
A (2-(6-metilbenzo[d]tiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato (0,24 g, 0,70 mmol) en acetona (9 ml) se añadió HCl 3 M (1,753 ml, 5,26 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 4 horas. Se añadió acetato de etilo y la fase acuosa se recogió y neutralizó con hidróxido sódico 1N. El producto se extrajo con acetato de etilo (2 x 40 ml). Los orgánicos se reunieron, se secaron con sulfato de magnesio, se filtraron y concentraron a vacío proporcionando N-(6-metilbenzo[d]tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,19 g, 0,58 mmol, 83 % de rendimiento) como un polvo blanco. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 8,96 (1 H, s ancho), 7,57 (1 H, s), 7,49 (1 H, d, *J*=8,24 Hz), 7,13 (1 H, d, *J*=8,24 Hz), 3,88 (1 H, d, *J*=10,07 Hz), 3,63 (1 H, d, *J*=9,77 Hz), 2,98 - 3,04 (2 H, m), 2,72 - 2,85 (2 H, m), 2,66 (2 H, t, *J*=7,63 Hz),

2,36 (3 H, s), 2,05 (1 H, d, *J*=2,14 Hz), 1,91 (1 H, s ancho), 1,53 - 1,64 (2 H, m), 1,42 - 1,53 (1 H, m). MS (LC/MS) T. R. = 1,79; $[M+H]^+$ = 329,2.

Los enantiómeros se separaron usando una columna Chiralcel OJ-H (4,6 x 25 cm, 5μm) con 30% de metanol (0,1% de DEA) en CO_2 y control UV a 300 nm. Los picos separados se concentraron a vacío proporcionando polvos blancos. El primer pico que salió de la columna proporcionó 0,11 g, 0,34 mmol, 55 %. (12a; isómero R): RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 8,95 (s, 1 H), 7,57 (s, 2 H), 7,48 (d, *J*=8,24 Hz, 2 H), 7,13 (d, *J*=8,24 Hz, 2 H), 3,89 (d, *J*=10,38 Hz, 2 H), 3,63 (d, *J*=10,38 Hz, 2 H), 2,99 - 3,06 (m, 4 H), 2,75 - 2,84 (m, 4 H), 2,67 (t, *J*=7,63 Hz, 4 H), 2,37 (s, 7 H), 2,06 (s, 2 H), 1,92 (s, 2 H), 1,55 - 1,64 (m, 4 H), 1,49 (dd, *J*=9,77, 2,44 Hz, 2 H). MS (LC/MS) T. R. = 1,80; $[M+H]^+$ = 329,2. Rotación óptica = -4,52. El segundo pico proporcionó 0,11 g, 0,34 mmol, 55 %. (12b; isómero S): RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 8,96 (s, 1 H), 7,58 (s, 1 H), 7,49 (d, *J*=8,24 Hz, 1 H), 7,14 (d, *J*=8,24 Hz, 1 H), 3,89 (d, *J*=10,07 Hz, 1 H), 3,63 (d, *J*=10,07 Hz, 1 H), 3,03 (d, *J*=2,44 Hz, 2 H), 2,75 - 2,84 (m, 2 H), 2,67 (t, *J*=7,78 Hz, 2 H), 2,37 (s, 3 H), 2,06 (s, 1 H), 1,92 (s, 1 H), 1,55 - 1,64 (m, 2 H), 1,49 (dd, *J*=9,77, 2,75 Hz, 1 H). MS (LC/MS) T. R. = 1,80; $[M+H]^+$ = 329,2. Rotación óptica= + 10,08.

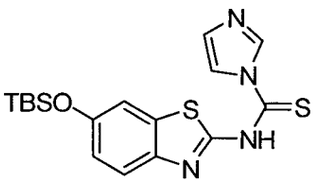
EJEMPLO 13

2-(4H-1'-Azaspiro[oxazol-5,3'-biciclo[2.2.2]octano]-2-ilamino)benzo[d]tiazol-6-ol



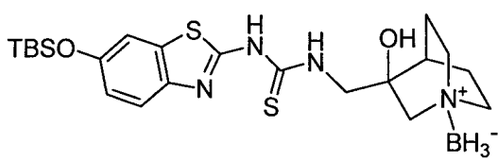
Etapa A: N-(6-(terc-Butildimetilsililoxi)benzo[d]tiazol-2-il)-1H-imidazol-1-

carbotioamida



A 6-(terc-butildimetilsililoxi)benzo[d]tiazol-2-amina (preparado como se describe en el documento WO 2007/086800 p,102) (3,1 g, 11,05 mmol) en acetonitrilo (30 ml) se añadió tiocarbonilo diimidazol (2,56 g, 14,37 mmol). La reacción se calentó hasta 70°C durante la noche. La reacción se enfrió hasta temperatura ambiente y el precipitado se filtró y se lavó con acetonitrilo proporcionando un sólido amarillo. El producto, N-(6-(terc-butildimetilsililoxi)benzo[d]tiazol-2-il)-1H-imidazol-1-carbotioamida (3,85 g, 9,86 mmol, 89 % de rendimiento), se llevó directamente a la etapa siguiente sin purificación posterior. MS (LC/MS) T. R. = 2,56; $[M+H]^+$ = 388,9.

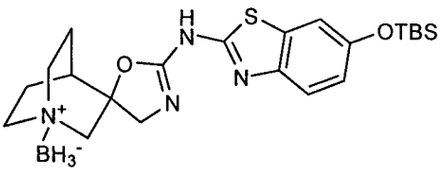
Etapa B: (3-((3-(6-(terc-Butildimetilsililoxi)benzo[d]tiazol-2-il)tioureido)metil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato



A N-(6-(terc-butildimetilsililoxi)benzo[d]tiazol-2-il)-1H-imidazol-1-carbotioamida (3,85 g, 9,86 mmol) en N,N-dimetilformamida (40 ml) se añadió (3-(aminometil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (1,68 g, 9,86 mmol). La reacción se calentó a 80 °C durante 2 horas. La reacción se enfrió y luego se vertió en una mezcla de cloroformo y agua. La fase orgánica se recogió y se concentró a vacío proporcionando (3-((3-(6-(terc-

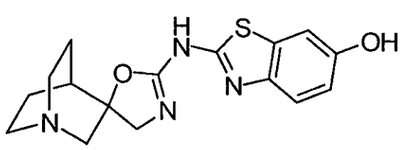
butildimetilsililoxi)benzo[d]tiazol-2-il)tioureido)metil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (6,2 g) como un aceite amarillo.

Etapa C: (2-(6-(terc-Butildimetilsililoxi)benzo[d]tiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato



A (3-((3-(6-(terc-butildimetilsililoxi)benzo[d]tiazol-2-il)tioureido)metil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (4,9 g, 9,9 mmol) en N,N-dimetilformamida (10 ml) se añadió 1,3-diisopropilcarbodiimida (5,4 ml, 34,5 mmol). La reacción se calentó hasta 80 °C y se controló por LC/MS. La reacción se enfrió y luego se vertió en una mezcla de cloroformo y agua. La fase orgánica se recogió y se concentró a vacío. El residuo que quedó se trituró en éter. El precipitado se recogió proporcionando (2-(6-(terc-butildimetilsililoxi)benzo[d]tiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato (3,28 g, 7,15 mmol, 72,6 % de rendimiento). MS (LC/MS) T. R. = 3,60; $[M+H-BH_3]^+$ = 445,2.

Etapa D: 2-(4H-1'-Azaspiro[oxazol-5,3'-biciclo[2.2.2]octano]-2-ilamino)benzo[d]tiazol-6-ol



A (2-(6-(terc-butildimetilsililoxi)benzo[d]tiazol-2-ilamino)-4H-1'-

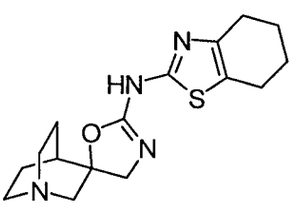
amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato (3,2 g, 6,98 mmol) en acetona (10 ml) se añadió HCl (8,14 ml, 24,43 mmol). La reacción se agitó a temperatura ambiente durante 3 horas. La mezcla se vertió en agua y se neutralizó con bicarbonato sódico saturado. La fase acuosa se extrajo entonces con cloroformo. La fase orgánica se recogió y se concentró a vacío. El residuo que quedó se trituró en éter proporcionando 2-(4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octano]-2-ilamino)benzo[d]tiazol-6-ol racémico (958 mg, 2,90 mmol, 41,5 % de rendimiento) como un polvo blanco. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 9,36 (1 H, s ancho), 8,85 (1 H, s ancho), 7,41 (1 H, d, *J*=8,85 Hz), 7,12 (1 H, d, *J*=2,44 Hz), 6,78 (1 H, dd, *J*=8,85, 2,44 Hz), 3,86 (1 H, d, *J*=10,07 Hz), 3,61 (1 H, d, *J*=10,07 Hz), 2,96 - 3,06 (2 H, m), 2,71 - 2,85 (2 H, m), 2,66 (2 H, t, *J*=7,78 Hz), 2,04 (1 H, s ancho), 1,90 (1 H, s ancho), 1,43 - 1,64 (3 H, m). MS (LC/MS) T. R. = 1,03; $[M+H]^+$ = 331,29.

Los enantiómeros se separaron usando una columna Chiralpak AD-H (30 x 250mm, 5μm) con una fase móvil constituida por 30% de metanol (0,1% de DEA) en CO_2. La longitud de onda se fijó a 300 nM. Los picos separados se concentraron a vacío proporcionando polvos blancos. El primer pico que salió de la columna fue (S)-2-(4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octano]-2-ilamino)benzo[d]tiazol-6-ol (395,2 mg, 1,19 mmol, 41,4 % de rendimiento). (13a, isómero S): RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 9,36 (1 H, s ancho), 8,84 (1 H, s ancho), 7,41 (1 H, d, *J*=8,55 Hz), 7,12 (1 H, d, *J*=2,44 Hz), 6,78 (1 H, dd, *J*=8,55, 2,44 Hz), 3,86 (1 H, d, *J*=9,77 Hz), 3,61 (1 H, d, *J*=10,07 Hz), 2,96 - 3,05 (2 H, m), 2,72 - 2,84 (2 H, m), 2,65 (2 H, t, *J*=7,63 Hz), 2,04 (1 H, s ancho), 1,90 (1 H, s ancho), 1,52 - 1,64 (2 H, m), 1,43 - 1,52 (1 H, m). MS (LC/MS) T. R. = 1,30; $[M+H]^+$ = 331,4. El segundo pico fue (R)-2-(4H-1'-azaspiro[oxazol-

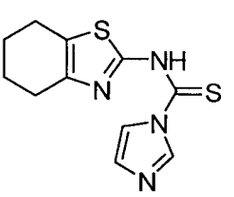
5,3'-biciclo[2.2.2]octano]-2-ilamino)benzo[d]tiazol-6-ol (375 mg, 1,14 mmol, 39,3 % de rendimiento). (13b, isómero R): RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 7,40 (1 H, d, *J*=8,55 Hz), 7,11 (1 H, d, *J*=2,44 Hz), 6,77 (1 H, dd, *J*=8,55, 2,44 Hz), 3,86 (1 H, d, *J*=10,07 Hz), 3,60 (1 H, d, *J*=10,07 Hz), 3,01 (2 H, s), 2,73 - 2,84 (2 H, m), 2,65 (2 H, t, *J*=7,78 Hz), 2,04 (1 H, s ancho), 1,90 (1 H, s ancho), 1,54 - 1,62 (2 H, m), 1,43 - 1,52 (1 H, m). MS (LC/MS) T. R. = 1,43; $[M+H]^+$ = 331,4.

EJEMPLO 14

N-(4,5,6,7-Tetrahidrobenzo[d]tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



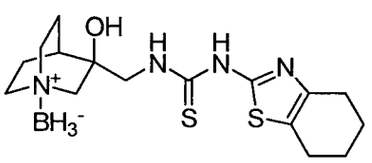
Etapa A: N-(4,5,6,7-Tetrahidrobenzo[d]tiazol-2-il)-1H-imidazol-1-carbotioamida



A 4,5,6,7-tetrahidrobenzo[d]tiazol-2-amina (0,5 g, 3,24 mmol) en acetonitrilo (20 ml) se añadió di(1H-imidazol-1-il)metanotiona (0,58 g, 3,24 mmol). La reacción se agitó a 50 °C durante 4 horas. La reacción se enfrió y se concentró proporcionando producto bruto. El material bruto se purificó por

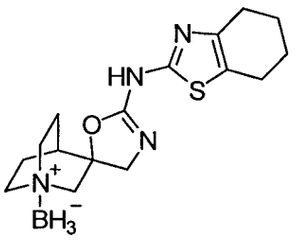
cromatografía ultrarrápida (acetato de etilo al 50-100%-hexano) proporcionando N-(4,5,6,7-tetrahidrobenzo[d]tiazol-2-il)-1H-imidazol-1-carbotioamida (0,60 g, 2,27 mmol, 70,0 % de rendimiento) como un polvo blanco.

Etapa B: (3-Hidroxi-3-((3-(4,5,6,7-tetrahidrobenzo[d]tiazol-2-il)tioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato



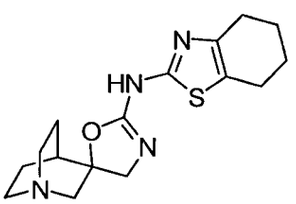
A N-(4,5,6,7-tetrahidrobenzo[d]tiazol-2-il)-1H-imidazol-1-carbotioamida (0,54 g, 2 mmol) en N,N-dimetilformamida (20 ml) se añadió (3-(aminometil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (0,35 g, 2 mmol). La reacción se agitó a 50 °C durante 3 horas. La reacción se enfrió y se concentró proporcionando producto bruto. El material bruto se purificó por cromatografía ultrarrápida (acetato de etilo al 50-100%-hexano) proporcionando las primeras manchas/fracciones (TLC) como producto. Las fracciones se reunieron y concentraron proporcionando (3-hidroxi-3-((3-(4,5,6,7-tetrahidrobenzo[d]tiazol-2-il)tioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (0,51 g, 1,39 mmol, 68,2 % de rendimiento) como un polvo blanco. RMN de ^{1}H (500 MHz, *DMSO-D6*) δ ppm 11,46 (s, 1 H), 5,26 (s, 1 H), 3,89 (dd, *J*=13,58, 5,34 Hz, 1 H), 3,68 (dd, *J*=13,73, 4,88 Hz, 1 H), 2,55 - 2,94 (m, 8 H), 2,06 (dd, *J*=9,31, 3,20 Hz, 1 H), 1,66 - 1,90 (m, 6 H), 1,21 - 1,59 (m, 4 H); $[M+H]^+$ = 365,1.

Etapa C: (2-(4,5,6,7-Tetrahidrobenzo[d]tiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato



A (3-hidroxi-3-((3-(4,5,6,7-tetrahidrobenzo[d]tiazol-2-il)tioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (0,5 g, 1,37 mmol) en N,N-dimetilformamida (20 ml) se añadió N,N-diisopropilcarbodiimida (0,74 ml, 4,78 mmol). La reacción se agitó a 70°C durante 4 horas. La reacción se concentró proporcionando un residuo bruto. El material bruto se purificó por cromatografía ultrarrápida (acetato de etilo al 50-100%-hexanos) proporcionando las segundas manchas/fracciones (TLC) como producto. Las fracciones se reunieron y concentraron proporcionando (2-(4,5,6,7-tetrahidrobenzo[d]tiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato (0,38 g, 1,14 mmol, 84 % de rendimiento) como un polvo blanco. RMN de ^{1}H (500 MHz, *DMSO-D6*) δ ppm 8,26 - 8,86 (m, 1 H), 3,78 (d, *J*=9,46 Hz, 1 H), 3,66 (d, *J*=9,77 Hz, 1 H), 3,19 - 3,30 (m, *J*=14,95, 2,14 Hz, 1 H), 2,96 - 3,12 (m, 2 H), 2,78 - 2,94 (m, 3 H), 2,54 - 2,65 (m, 4 H), 2,19 (s, 1 H), 2,00 (s, 1 H), 1,66 - 1,85 (m, 7 H), 1,43 (m, 3 H). MS (LC/MS) T. R. = 2,50; $[M+H-BH_3]^+$ = 319,1.

Etapa D: N-(4,5,6,7-Tetrahidrobenzo[d]tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



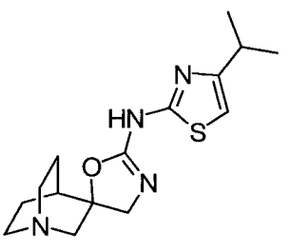
A (2-(4,5,6,7-tetrahidrobenzo[d]tiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato (0,36 g, 1,08 mmol) en acetona (9 ml) se añadió HCl 3M (0,36 ml, 1,08 mmol). La reacción se agitó a temperatura ambiente durante 4 horas. La reacción se completó por TLC (mancha inferior). Se añadió acetato de etilo y se separó entonces la fase acuosa. La fase acuosa se neutralizó con hidróxido sódico 1N. El producto se extrajo con acetato de etilo (2 x 40 ml). Los orgánicos se reunieron, se secaron con sulfato de magnesio, se filtraron y se concentraron a vacío proporcionando N-(4,5,6,7-tetrahidrobenzo[d]tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina racémica (0,28 g, 0,84 mmol, 78 % de rendimiento) como un polvo blanco. RMN de ^{1}H (500 MHz, *DMSO-D6*) δ ppm 8,30 - 8,75 (s ancho, 1 H), 3,79 (d, *J*=9,44 Hz , 1 H), 3,55 (d, *J*=9,76 Hz , 1 H), 2,90 - 3,03 (m, 2 H), 2,54 - 2,84 (m, 8 H), 2,00 (s, 1 H), 1,81 - 1,93 (m, 1 H), 1,75 (d, *J*=2,44 Hz, 4 H), 1,36 - 1,67 (m, 3 H). MS (LC/MS) T. R. = 1,39; $[M+H]^+$ = 319,1.

Los enantiómeros se separaron usando una columna Chiralpak AD-H (30 x 250mm, 5µm) con una fase móvil constituida por 23% de metanol (0,1% de DEA) en CO_2. La longitud de onda se fijó a 300 nM. Los picos separados se concentraron a vacío proporcionando polvos blancos. El primer pico que salió de la columna fue (S)-N-(4,5,6,7-tetrahidrobenzo[d]tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,1 g, 0,29 mmol, 36,8 % de rendimiento). (14a, isómero S): RMN de ^{1}H (500 MHz, *DMSO-D6*) δ ppm 8,29 - 8,89 (s ancho, 1 H), 3,80 (d, *J*=9,46 Hz, 1 H), 3,54 (d, *J*=9,77 Hz, 1 H), 2,94 - 3,04 (m, 2 H), 2,55 - 2,85 (m, 8 H), 2,00 (s, 1 H), 1,85 - 1,94 (m, 1 H), 1,70 - 1,81 (m, *J*=2,43 Hz , 4 H), 1,39 - 1,65 (m, 3 H). MS (LC/MS) T. R. = 1,54; $[M+H]^+$ = 319,1. El segundo pico fue (R)-N-(4,5,6,7-tetrahidrobenzo[d]tiazol-2-

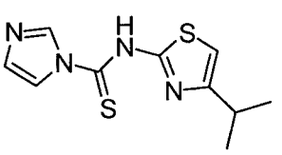
il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,11 g, 0,30 mmol, 38,2 % de rendimiento). (14b, isómero R): RMN de ^{1}H (500 MHz, *DMSO-D6*) δ ppm 8,24 - 8,96 (s ancho, 1 H), 3,79 (d, *J*=9,46 Hz, 1 H), 3,52 (d, *J*=9,76 Hz, 1 H), 2,95 - 3,08 (m, 2 H), 2,55 - 2,80 (m, 8 H), 2,00 (s, 1 H), 1,85 - 1,90 (m, 1 H), 1,70 - 1,79 (m, *J*=2,42 Hz , 4 H), 1,39 - 1,63 (m, 3 H); $[M+H]^+$ = 319,1.

EJEMPLO 15

N-(4-Isopropiltiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

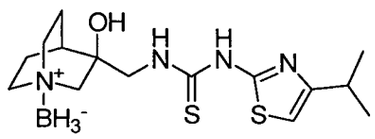


Etapa A: N-(4-Isopropiltiazol-2-il)-1H-imidazol-1-carbotioamida



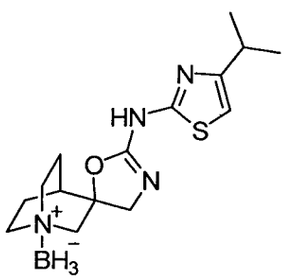
A 4-isopropiltiazol-2-amina (1,04 g, 7,31 mmol) en acetonitrilo (30 ml) se añadió 1,1-tiocarbonildiimidazol (1,7 g, 9,5 mmol). La reacción se agitó a 50 ºC durante 18 horas. La reacción se enfrió hasta temperatura ambiente y el precipitado se filtró y se lavó con acetonitrilo (2 x 50 ml). El polvo amarillo se secó en un horno de vacío (40ºC) durante 2 horas. El producto, N-(4-isopropiltiazol-2-il)-1H-imidazol-1-carbotioamida (1,02 g, 4,04 mmol, 55,3 % de rendimiento), se llevó directamente a la etapa siguiente sin purificación posterior.

Etapa B: (3-Hidroxi-3-((3-(4-isopropiltiazol-2-il)tioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato



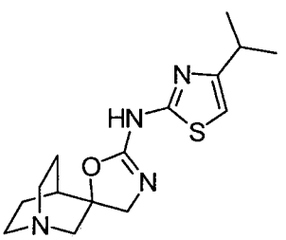
A N-(4-isopropiltiazol-2-il)-1H-imidazol-1-carbotioamida (0,57 g, 2,26 mmol) en N,N-dimetilformamida (20 ml) se añadió (3-(aminometil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (0,38 g, 2,26 mmol). La reacción se agitó a 70°C durante 24 horas. La reacción se enfrió y se concentró proporcionando producto bruto. El material bruto se purificó por cromatografía ultrarrápida (acetato de etilo al 50-100%-hexano) proporcionando (3-hidroxi-3-((3-(4-isopropiltiazol-2-il)tioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (0,56 g, 1,58 mmol, 70,0 % de rendimiento) como un polvo blanco. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 11,62 (s, 1 H), 6,70 (s, 1 H), 5,31 (s, 1 H), 3,58 - 3,96 (m, 2 H), 2,63 - 3,11 (m, 7 H), 2,00 - 2,22 (m, 1 H), 1,65 - 1,97 (m, 3 H), 1,16 - 1,61 (m, 10 H). MS (LC/MS) T. R. = 3,43; $[M+H]^+$ = 353,2.

Etapa C: (2-(5-Isopropiltiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato



A (3-hidroxi-3-((3-(5-isopropiltiazol-2-il)tioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (0,54 g, 1,52 mmol) en N,N-dimetilformamida (20 ml) se añadió N,N'-diisopropilcarbodiimida (0,83 ml, 5,33 mmol). La reacción se agitó a 50 °C durante 24 horas. La reacción se concentró proporcionando un residuo bruto. El material bruto se purificó por cromatografía ultrarrápida (acetato de etilo al 50-100%-hexanos) proporcionando las segundas manchas/fracciones (TLC) como producto. Las fracciones se reunieron y concentraron proporcionando (2-(5-isopropiltiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato (0,39 g, 1,22 mmol, 80 % de rendimiento) como un polvo blanco. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 6,55 (s, 1 H), 3,75 (m, 2 H), 3,20 - 3,31 (m, 1 H), 2,96 - 3,15 (m, 2 H), 2,77 - 2,97 (m, 4 H), 2,22 (s, 1 H), 2,01 (s, 1 H), 1,68 - 1,90 (m, 3 H), 1,43 (s, 3 H), 1,21 (d, *J*=7,02 Hz, 6 H). MS (LC/MS) T. R. = 2,36; $[M+H-BH_3]^+$ = 307,2.

Etapa D: N-(4-Isopropiltiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



A (2-(4-isopropiltiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato (0,42 g, 1,31 mmol) en acetona (9 ml) se añadió HCl 3M (0,44 ml, 1,31 mmol). La reacción se agitó a temperatura ambiente durante 4 horas. La reacción se completó por TLC (mancha inferior).

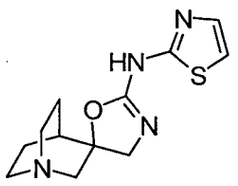
Se añadió acetato de etilo y se separó entonces la fase acuosa. La fase acuosa se neutralizó con hidróxido sódico 1N. El producto se extrajo con acetato de etilo (2 x 40 ml). Los orgánicos se reunieron, se secaron con sulfato de magnesio, se filtraron y se concentraron a vacío proporcionando N-(4-isopropiltiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina racémica (0,34 g, 1,05 mmol, 80 % de rendimiento) como un polvo blanco. RMN de ^{1}H (500 MHz, *DMSO-D6*) δ ppm 8,20 - 8,91 (m, 1 H), 6,52 (s, 1 H), 3,83 (d, *J*=9,46 Hz, 1 H), 3,57 (d, *J*=9,46 Hz, 1 H), 2,99 (s, 2 H), 2,58 - 2,92 (m, 5 H), 2,02 (s, 1 H), 1,82 - 1,96 (m, 1 H), 1,38 - 1,66 (m, 3 H), 1,20 (d, *J*=7,02 Hz, 6 H). MS (LC/MS) T. R. = 1,27; $[M+H]^+$ = 307,1.

Los enantiómeros se separaron usando una columna Chiralcel OJ-H (30 x 250mm, 5μm) con una fase móvil constituida por 23% de metanol (0,1% de DEA) en CO_2. La longitud de onda se fijó a 300 nM. Los picos separados se concentraron a vacío proporcionando polvos blancos. El primer pico que salió de la columna fue (S)-N-(4-isopropiltiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,01 g, 0,03 mmol, 2,95 % de rendimiento). (15a, isómero S): RMN de ^{1}H (500 MHz, *DMSO-D6*) δ ppm 8,35 - 8,95 (m, 1 H), 6,52 (s, 1 H), 3,82 (d, *J*=9,41 Hz , 1 H), 3,57 (d, *J*=9,46 Hz, 1 H), 2,99 (s, 2 H), 2,60 - 2,88 (m, 5 H), 2,02 (s, 2 H), 1,82 - 1,96 (m, 1 H), 1,38 - 1,65 (m, 3 H), 1,20 (d, *J*=6,71 Hz, 6 H). MS (LC/MS) T. R. = 1,38; $[M+H]^+$ = 307,1. El segundo pico fue (R)-N-(4-isopropiltiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,02 g, 0,05 mmol, 4,83 % de rendimiento). (15b, isómero R): RMN de ^{1}H (500 MHz, *DMSO-D6*) δ ppm 8,35 - 8,91 (m, 1 H), 6,52 (s, 1 H), 3,82 (d, *J*=9,44 Hz , 1 H), 3,57 (d, *J*=9,46 Hz, 1 H), 2,99 (s, 2 H), 2,60 - 2,90 (m, 5 H), 2,02 (s, 2 H), 1,82 - 1,96 (m, 1 H), 1,38 - 1,62 (m, 3 H), 1,20 (d, *J*=6,78 Hz, 6 H).

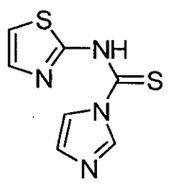
MS (LC/MS) T. R. = 1,49; $[M+H]^+$ = 307,3.

EJEMPLO 16

N-(Tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

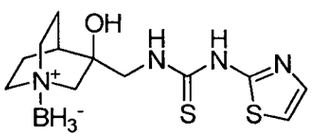


Etapa A: N-(Tiazol-2-il)-1H-imidazol-1-carbotioamida



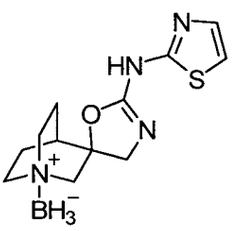
A tiazol-2-amina (2,12 g, 21,17 mmol) en acetonitrilo (30 ml) y tetrahidrofurano (5 ml) se añadió di(1H-imidazol-1-il)metanotiona (4,90 g, 27,5 mmol). La reacción se agitó a 60 °C durante 5 horas. La reacción se enfrió hasta temperatura ambiente y el precipitado se filtró y se lavó con acetonitrilo frío (2 x 15 ml) proporcionando un polvo naranja-pardo. El producto, N-(tiazol-2-il)-1H-imidazol-1-carbotioamida (3,70 g, 17,60 mmol, 83 % de rendimiento), se llevó directamente a la etapa siguiente sin caracterización posterior.

Etapa B: (3-Hidroxi-3-((3-tiazol-2-iltioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato



A N-(tiazol-2-il)-1H-imidazol-1-carbotioamida (1,7 g, 8 mmol) en N,N-dimetilformamida (30 ml) se añadió (3-(aminometil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (1,37 g, 8 mmol). La reacción se agitó a 50 °C durante 4 horas. La reacción se enfrió y se concentró proporcionando producto bruto. El material bruto se purificó por cromatografía ultrarrápida (acetato de etilo al 50-100%-hexano) proporcionando las primeras manchas/fracciones (TLC) como producto. Las fracciones se reunieron y concentraron proporcionando (3-hidroxi-3-((3-tiazol-2-iltioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (1,5 g, 4,80 mmol, 59,8 % de rendimiento) como un polvo blanco. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 11,64 (s, 1 H), 7,42 (d, *J*=3,36 Hz, 1 H), 7,14 (m, 1 H), 5,32 (s, 1 H), 3,78 (dd, 2 H), 2,59 - 3,02 (m, 6 H), 1,99 - 2,18 (m, 1 H), 1,79 - 1,92 (m, 2 H), 1,64 - 1,80 (m, 1 H), 1,19 - 1,65 (m, 4 H). MS (LC/MS) T. R. = 2,73; $[M+H]^+$ = 311,1.

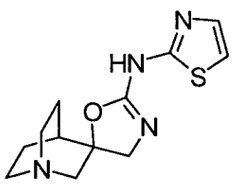
Etapa C: (2-(Tiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato



A (3-hidroxi-3-((3-tiazol-2-iltioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (1,2 g, 3,84 mmol) en N,N-dimetilformamida (20 ml) se añadió N,N'-diisopropilcarbodiimida (2,09 ml, 13,45 mmol). La reacción se agitó a 50 °C durante 24 horas. La reacción se concentró proporcionando un residuo bruto. El material bruto se purificó por cromatografía ultrarrápida (acetato de

etilo al 50-100%-hexano) proporcionando las primeras manchas/fracciones (TLC) como producto. Las fracciones se reunieron y concentraron proporcionando (2-(tiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato (0,84 g, 3,02 mmol, 79 % de rendimiento) como un polvo blanco. RMN de ^{1}H (500 MHz, *DMSO-D6*) δ ppm 8,37 - 9,14 (m, 1 H), 7,32 (d, *J*=3,66 Hz, 1 H), 7,04 (d, *J*=3,66 Hz, 2 H), 3,79 (d, *J*=10,07 Hz, 1 H), 3,67 (d, *J*=10,07 Hz, 1 H), 3,20 - 3,29 (m, *J*=14,95, 2,14 Hz, 1 H), 2,97 - 3,15 (m, 2 H), 2,78 - 2,94 (m, 3 H), 2,22 (s, 1 H), 1,95 - 2,08 (m, 1 H), 1,66 - 1,85 (m, 3 H), 1,43 (s, 3 H). MS (LC/MS) T. R. = 1,57; $[M+H-BH_3]^+$ = 265,1.

Etapa D: N-(Tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



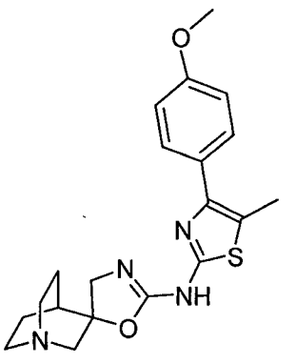
A (2-(tiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato (0,57 g, 2,05 mmol) en acetona (9 ml) se añadió HCl 3M (0,68 ml, 2,05 mmol). La reacción se agitó a temperatura ambiente durante 4 horas. La reacción se completó por TLC (mancha inferior). Se añadió acetato de etilo y se separó entonces la fase acuosa. La fase acuosa se neutralizó con hidróxido sódico 1N. El producto se extrajo con acetato de etilo (2 x 40 ml). Los orgánicos se reunieron, se secaron con sulfato de magnesio, se filtraron y se concentraron a vacío proporcionando N-(tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina racémica (0,4 g, 1,44 mmol, 70,2 % de rendimiento) como un polvo blanco. RMN de ^{1}H (400 MHz,

DMSO-d_6) δ ppm 8,64 (s, 1 H), 7,24 (d, *J*=3,74 Hz, 2 H), 7,01 (d, *J*=3,75 Hz, 2 H), 3,78 (d, *J*=9,80 Hz, 2 H), 3,53 (d, *J*=9,80 Hz, 2 H), 2,97 - 3,05 (m, 4 H), 2,74 - 2,86 (m, 4 H), 2,65 (t, *J*=7,84 Hz, 4 H), 2,01 (s, 2 H), 1,88 (s, 2 H), 1,53 - 1,64 (m, 4 H), 1,45 - 1,56 (m, 2 H). MS (LC/MS) T. R. = 0,28; $[M+H]^+$ = 265,1.

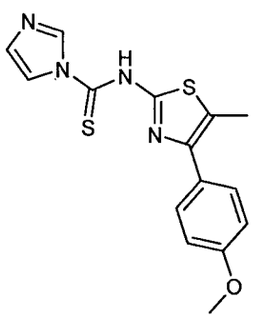
Los enantiómeros se separaron usando una columna Chiralcel OJ-H (30 x 250mm, 5μm) con una fase móvil constituida por 23% de metanol (0,1% de DEA) en CO_2. La longitud de onda se fijó a 300 nM. Los picos separados se concentraron a vacío proporcionando polvos blancos. El primer pico que salió de la columna fue (S)-N-(tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,12 g, 0,43 mmol, 18,80 % de rendimiento). (16a, isómero S): RMN de ^{1}H (400 MHz, DMSO-d_6) δ ppm 8,64 (s, 1 H), 7,26 (d, *J*=3,75 Hz, 2 H), 7,00 (d, *J*=3,77 Hz, 2 H), 3,78 (d, *J*=9,81 Hz, 2 H), 3,54 (d, *J*=9,82 Hz, 2 H), 2,95 - 3,10 (m, 4 H), 2,75 - 2,82 (m, 4 H), 2,65 (t, *J*=7,80 Hz, 4 H), 2,01 (s, 2 H), 1,88 (s, 2 H), 1,53 - 1,60 (m, 4 H), 1,42 - 1,51 (m, 2 H). MS (LC/MS) T. R. = 0,32; $[M+H]^+$ = 265,1. El segundo pico fue (R)-N-(tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,15 g, 0,52 mmol, 22,96 % de rendimiento). (16b, isómero R): RMN de ^{1}H (400 MHz, DMSO-d_6) δ ppm 8,64 (s, 1 H), 7,25 (d, *J*=3,74 Hz, 2 H), 7,00 (d, *J*=3,76 Hz, 2 H), 3,78 (d, *J*=9,80 Hz, 2 H), 3,53 (d, *J*=9,80 Hz, 2 H), 2,95 - 3,08 (m, 4 H), 2,75 - 2,84 (m, 4 H), 2,65 (t, *J*=7,80 Hz, 4 H), 2,01 (s, 2 H), 1,88 (s, 2 H), 1,54 - 1,62 (m, 4 H), 1,43 - 1,53 (m, 2 H). MS (LC/MS) T. R. = 0,28; $[M+H]^+$ = 265,3.

Ejemplo 17

N-(4-(4-Metoxifenil)-5-metiltiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

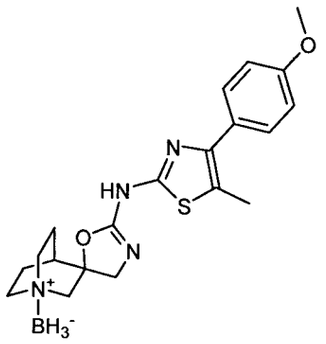


Etapa A: N-(4-(4-Metoxifenil)-5-metiltiazol-2-il)-1H-imidazol-1-carbotioamida



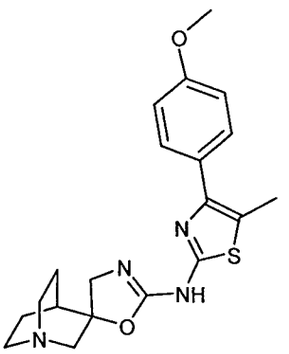
A 4-(4-metoxifenil)-5-metiltiazol-2-amina (0,98 g, 4,45 mmol) en acetonitrilo (25 ml) se añadió di(1H-imidazol-1-il)metanotiona (1,03 g, 5,78 mmol). La reacción se agitó a 50 °C durante 3 horas. La reacción se enfrió hasta temperatura ambiente y se filtró el precipitado. El polvo se lavó con acetonitrilo (2 x 10 ml) y se secó proporcionando N-(4-(4-metoxifenil)-5-metiltiazol-2-il)-1H-imidazol-1-carbotioamida racémica (1,28 g, 3,87 mmol, 87 % de rendimiento) como un polvo amarillo. El producto se llevó directamente a la etapa siguiente.

Etapa B: (2-(4-(4-Metoxifenil)-5-metiltiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato



A N-(4-(4-metoxifenil)-5-metiltiazol-2-il)-1H-imidazol-1-carboxamida (0,44 g, 1,39 mmol) en N,N-dimetilformamida (25 ml) se añadió (3-(aminometil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (0,24 g, 1,39 mmol). La reacción se agitó a 70 °C durante 2 horas. N,N'-Se añadió diisopropilcarbodiimida (0,65 ml, 4,16 mmol) y la reacción se calentó hasta 75 °C durante 2 horas. La reacción se enfrió y se concentró proporcionando el producto bruto. El material bruto se purificó por cromatografía en columna (acetato de etilo del 60-100%/hexanos) proporcionando (2-(4-(4-metoxifenil)-5-metiltiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato (0,41 g, 1,029 mmol, 74,2 % de rendimiento) como un polvo amarillo. RMN de ^{1}H (500 MHz, *DMSO-D6*) δ ppm 7,59 (d, *J*=7,63 Hz, 2 H), 6,98 (d, *J*=8,55 Hz, 2 H), 3,80 (s, 4 H), 3,67 (s, 1 H), 3,24 - 3,31 (m, 1 H), 3,13 (s, 1 H), 3,03 (s, 1 H), 2,83 - 2,92 (m, 3 H), 2,39 (s, 3 H), 2,23 (s, 1 H), 2,07 (s, 1 H), 1,73 - 1,82 (m, 2 H), 1,44 (s, 1 H). MS (LC/MS) T. R. = 2,88; $[M+H]^+$ = 399,34.

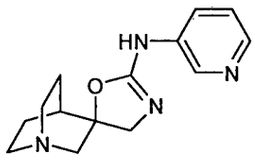
Etapa C: N-(4-(4-Metoxifenil)-5-metiltiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



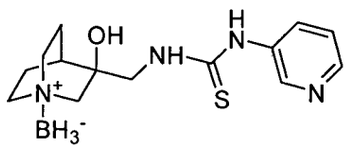
A (3-hidroxi-3-((3-(4-(4-metoxifenil)-5-metiltiazol-2-il)tioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (0,08 g, 0,19 mmol) en acetona (9 ml) se añadió 2M HCl (0,09 ml, 0,19 mmol). La reacción se agitó a temperatura ambiente durante 1 hora. La reacción se completó por TLC (mancha inferior). Se añadió acetato de etilo y la fase acuosa se recogió y neutralizó con hidróxido sódico 1N. El producto se extrajo con acetato de etilo (2 x 40 ml). Los orgánicos se reunieron, se secaron con sulfato de magnesio, se filtraron y se concentraron a vacío proporcionando N-(4-(4-metoxifenil)-5-metiltiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina racémica (0,05 g, 0,12 mmol, 66,8 % de rendimiento) como un polvo blanco. RMN de ^{1}H (500 MHz, *DMSO-D6*) δ ppm 7,58 (d, *J*=8,24 Hz, 2 H), 6,98 (d, *J*=8,55 Hz, 2 H), 3,83 (d, *J*=9,16 Hz, 1 H), 3,80 (s, 3 H), 3,56 (d, *J*=9,46 Hz, 1 H), 3,00 (s, 2 H), 2,74 - 2,83 (m, 2 H), 2,66 (t, *J*=7,63 Hz, 2 H), 2,38 (s, 3 H), 2,03 (s, 1 H), 1,91 (s, 1 H), 1,54 - 1,62 (m, 2 H), 1,48 (d, *J*=7,02 Hz, 1 H). MS (LC/MS) T. R. = 2,04; $[M+H]^+$ = 385,28.

EJEMPLO 18

(E)-N-(1'-Azaspiro[oxazolidin-5,3'-biciclo[2.2.2]octano]-2-iliden)piridin-3-amina



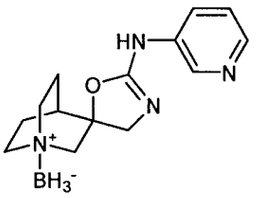
Etapa A: (3-Hidroxi-3-((3-piridin-3-iltioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato



A una suspensión agitada de (3-(aminometil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (247 mg, 1,45 mmol) en tetrahidrofurano (3 ml) se añadió una solución de 3-isotiocianatopiridina (298 mg, 2,19 mmol) en tetrahidrofurano (1,5 ml) y la mezcla de reacción se agitó a temperatura ambiente durante la noche. La mezcla de reacción se evaporó a vacío y el residuo (sólido céreo blanco) se purificó por cromatografía en columna (3% de metanol/acetato de etilo) proporcionando (3-hidroxi-3-((3-piridin-3-iltioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (294,6 mg, 0,96 mmol, 66,2 % de rendimiento) como una espuma blanca. RMN de ^{1}H (500 MHz, *MeOD-d$_4$*) δ ppm 8,56 - 8,70 (m, 1 H), 8,24 - 8,36 (m, 1 H), 8,08 - 8,16 (m, 1 H), 7,32 - 7,48 (m, 1 H), 4,02 - 4,18 (m, 1 H), 3,67 - 3,77 (m, 1 H), 3,53 - 3,62 (m, 1 H), 2,88 - 3,11 (m, 3 H), 2,70 - 2,88 (m, 1 H), 2,15 - 2,29 (m, 1 H), 1,92 - 2,12 (m, 2 H), 1,73 - 1,89 (m, 1 H), 1,54 - 1,69 (m, 2 H). MS (LC/MS) T. R. = 1,00; [MH^+-BH_3] = 293,10.

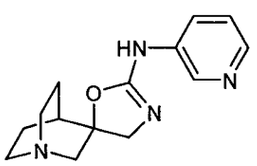
Etapa B: (E)-(2-(Piridin-3-ilimino)-1'-amoniospiro[oxazolidin-5,3'-

biciclo[2.2.2]octano]-1'-il)trihidroborato



A una solución de (3-hidroxi-3-((3-piridin-3-iltioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (294,6 mg, 0,96 mmol) en N,N-dimetilformamida (5 ml) se añadió una solución de N,N'-metanodiilidendipropan-2-amina (121 mg, 0,96 mmol) en N,N-dimetilformamida (1 ml) y la mezcla de reacción se dejó reposar a temperatura ambiente durante 7 días. Se añadieron otros 133 mg de N,N'-metanodiilidendipropan-2-amina en 0,5 ml de N,N-dimetilformamida y la reacción se dejó continuar durante otros 7 días. La reacción se purificó por cromatografía en columna (5-10% de metanol/acetato de etilo) proporcionando (E)-(2-(piridin-3-ilimino)-1'-amoniospiro[oxazolidin-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato (134,3 mg, 0,49 mmol, 51,3 % de rendimiento). RMN de ^{1}H (500 MHz, *MeOD*) δ ppm 8,34 - 8,60 (m, 1 H), 8,16 (d, *J*=4,27 Hz, 1 H), 7,59 - 7,96 (m, 1 H), 7,35 (dd, *J*=8,24, 4,88 Hz, 1 H), 3,89 (s ancho, 1 H), 3,65 (d, *J*=9,46 Hz, 1 H), 3,16 - 3,23 (m, 1 H), 3,04 - 3,16 (m, 1 H), 2,85 - 3,04 (m, 2 H), 2,23 (s ancho, 1 H), 1,74 - 1,97 (m, 4 H), 1,36 - 1,70 (m, 2 H). MS (LC/MS) T. R. = 0,65; $[M+H-BH_3]^+$ = 259,21.

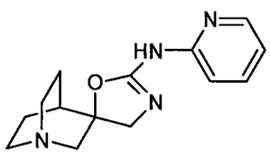
Etapa C: (E)-N-(1'-Azaspiro[oxazolidin-5,3'-biciclo[2.2.2]octano]-2-iliden)piridin-3-amina



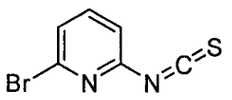
A una suspensión de (E)-(2-(piridin-3-ilimino)-1'-amoniospiro[oxazolidin-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato (127 mg, 0,47 mmol) en acetona (5 ml) se añadió ácido clorhídrico 3M (2 ml, 6,00 mmol) y la mezcla se dejó reposar a temperatura ambiente durante 2 horas. Se añadió esta entonces a un embudo de separación que contenía agua y cloroformo. Se separaron las fases, luego se basificó la fase acuosa con solución de carbonato sódico y la mezcla se volvió a extraer con cloroformo. Finalmente, la fase acuosa se lavó con acetato de etilo. Los orgánicos se reunieron, se secaron con sulfato de magnesio, se filtraron y se concentraron a vacío. El residuo se purificó por cromatografía en columna (1% de hidróxido amónico / 9% de metanol / 90% diclorometano) proporcionando (E)-N-(1'-azaspiro[oxazolidin-5,3'-biciclo[2.2.2]octano]-2-iliden)piridin-3-amina racémica (19 mg, 0,074 mmol, 15,8 % de rendimiento) como un sólido blanco. RMN de ^{1}H (500 MHz, *MeOD-d$_4$*) δ ppm 8,39 (s ancho, 1 H), 8,14 (d, *J*=4,27 Hz, 1 H), 7,72 (s ancho, 1 H), 7,34 (dd, *J*=8,24, 4,88 Hz, 1 H), 3,89 (d, *J*=9,77 Hz, 1 H), 3,57 (d, *J*=10,38 Hz, 1 H), 3,14 - 3,27 (m, 1 H), 3,00 - 3,13 (m, 1 H), 2,70 - 3,00 (m, 4 H), 1,97 - 2,22 (m, 2 H), 1,54 - 1,84 (m, 3 H). MS (LC/MS) T. R. = 0,26; $[M+H]^+$ = 259,16.

EJEMPLO 19

N-(Piridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

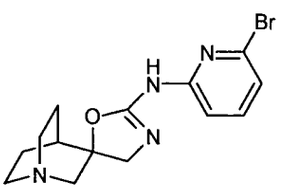


Etapa A: 2-Bromo-6-isotiocianatopiridina



Se combinó una mezcla de 6-bromopiridin-2-amina (253 mg, 1,46 mmol), cloroformo (2 ml), bicarbonato sódico (850 mg, 10,12 mmol) y agua (3 ml), y a esta se añadió una solución de tiofosgeno (190 mg, 1,65 mmol) en cloroformo (1 ml). La mezcla de reacción se agitó a temperatura ambiente durante 4 horas. La mezcla de reacción se transfirió a un embudo de separación y se repartió entre acetato de etilo y agua. La fase orgánica se lavó con salmuera, se secó sobre sulfato de magnesio, se filtró y el disolvente se evaporó dando un sólido amarillo. El sólido se purificó por cromatografía en columna (5% de acetato de etilo/hexanos) proporcionando 2-bromo-6-isotiocianatopiridina (281 mg, 1,31 mmol, 89 % de rendimiento) como un sólido blanco. RMN de ^{1}H (500 MHz, *CDCl$_3$*) δ ppm 7,50 - 7,62 (m, 1 H), 7,34 - 7,43 (m, 1 H), 6,91 - 7,11 (m, 1 H). MS (LC/MS) T. R. = 1,92; $[M+H]^+$ = 216,86.

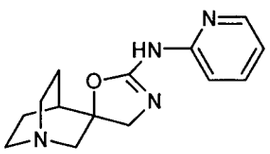
Etapa B: N-(6-Bromopiridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



A una solución de 2-bromo-6-isotiocianatopiridina (281 mg, 1,31 mmol) en N,N-dimetilformamida (8 ml) y base de Hunig (0,6 ml, 3,44 mmol) se añadió diclorhidrato de (+/-) 3-(aminometil)quinuclidin-3-ol (300 mg, 1,31 mmol) y la mezcla resultante se calentó hasta 75 °C durante 2,5 horas. MS (LC/MS) T. R.

= 1,04; $[M+H]^+$ = 373,01. A esta mezcla de reacción se añadió di-isopropil-carbodiimida (523 mg, 4,14 mmol) y se continuó el calentamiento a 75 °C durante 2,25 horas. Se dejó enfriar la mezcla hasta temperatura ambiente durante el fin de semana. La mezcla de reacción se concentró a vacío. El material se purificó por cromatografía en columna y luego HPLC preparativa proporcionando N-(6-bromopiridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (291,5 mg, 0,86 mmol, 66,2 % de rendimiento) como un sólido amarillo (que contenía impureza de 2-amino-6-bromopiridina). MS (LC/MS) T. R. = 0,65; $[M+H]^+$ = 337,0.

Etapa C: N-(Piridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

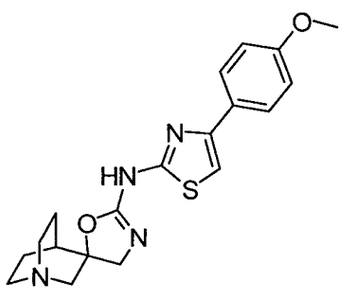


Se sometió a hidrogenación N-(6-bromopiridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (291 mg, 0,86 mmol) en metanol (20 ml) sobre paladio al 10% en carbón (23 mg) en el aparato de Parr durante 2 horas. El catalizador se separó por filtración y el filtrado se concentró a vacío. El residuo se purificó por cromatografía en columna (0,7% de hidróxido amónico / 6,3% de metanol / 93% cloroformo) dando N-(piridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina racémica (41,3 mg, 0,16 mmol, 18,6% de rendimiento). RMN de ^{1}H (500 MHz, *MeOD*) δ ppm 8,13 - 8,33 (m, 1 H), 7,57 - 7,72 (m, 1 H), 6,83 - 7,04 (m, 2 H), 3,97 (d, *J*=10,07 Hz, 1 H), 3,66 (d, *J*=10,07 Hz, 1 H), 3,18 - 3,27 (m, 1 H), 3,03 - 3,14 (m, 1 H), 2,94 (t, *J*=7,63 Hz, 2 H), 2,70 - 2,90 (m, 2 H), 2,06 - 2,24 (m, 2 H), 1,57 - 1,87 (m, 3 H).

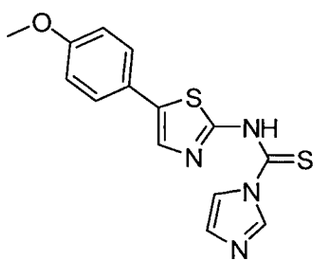
MS (LC/MS) T. R. = 1,76; $[M+H]^+$ = 259,25.

EJEMPLO 20

N-(4-(4-Metoxifenil)tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



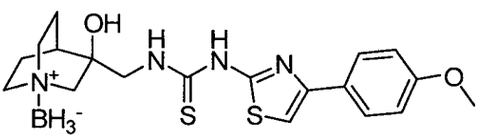
Etapa A: N-(5-(4-Metoxifenil)tiazol-2-il)-1H-imidazol-1-carbotioamida



A 5-(4-metoxifenil)tiazol-2-amina (1,07 g, 5,19 mmol) en acetonitrilo (30 ml) y tetrahidrofurano (5 ml) se añadió di(1H-imidazol-1-il)metanotiona (1,20 g, 6,74 mmol). La reacción se agitó a 60 °C durante 18 horas. La reacción se enfrió hasta temperatura ambiente y se filtró el precipitado. El polvo se lavó con acetonitrilo frío (2 x 15 ml) y se secó proporcionando N-(5-(4-metoxifenil)tiazol-2-il)-1H-imidazol-1-carbotioamida (0,59 g, 1,86 mmol, 35,9 % de rendimiento) como un polvo naranja-pardo. El producto se llevó directamente a la etapa

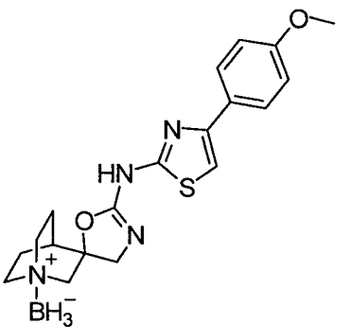
siguiente sin caracterización posterior.

Etapa B: (3-Hidroxi-3-((3-(4-(4-metoxifenil)tiazol-2-il)tioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato



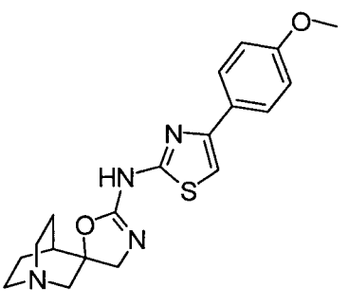
A N-(4-(4-metoxifenil)tiazol-2-il)-1H-imidazol-1-carbotioamida (0,57 g, 1,82 mmol) en N,N-dimetilformamida (20 ml) se añadió (3-(aminometil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (0,31 g, 1,82 mmol). La reacción se agitó a 60 °C durante 4 horas. La reacción se enfrió y se concentró proporcionando producto bruto. El material bruto se purificó por cromatografía ultrarrápida (acetato de etilo del 60-100%-hexano) proporcionando las primeras manchas/fracciones (TLC) como producto. Las fracciones se reunieron y concentraron a vacío proporcionando (3-hidroxi-3-((3-(4-(4-metoxifenil)tiazol-2-il)tioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (0,6 g, 1,43 mmol, 79 % de rendimiento) como un polvo blanco. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 11,74 (s, 1 H), 7,91 (d, *J*=8,55 Hz, 2 H), 7,43 (s, 1 H), 6,97 (d, *J*=8,85 Hz, 2 H), 5,50 (s, 1 H), 3,62 - 3,98 (m, 5 H), 2,70 - 3,10 (m, 6 H), 2,13 (s, 1 H), 1,94 (s, 1 H), 1,66 - 1,91 (m, 2 H), 1,11 - 1,62 (m, 4 H). MS (LC/MS) T. R. = 3,54; $[M+H]^+$ = 417,1.

Etapa C: (2-(4-(4-Metoxifenil)tiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato



A (3-hidroxi-3-((3-(4-(4-metoxifenil)tiazol-2-il)tioureido)metil)-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (0,59 g, 1,41 mmol) en N,N-dimetilformamida (20 ml) se añadió N,N'-diisopropilcarbodiimida (0,66 ml, 4,23 mmol). La reacción se agitó a 70 °C durante 24 horas. El disolvente se eliminó a vacío y el residuo se purificó por cromatografía ultrarrápida (acetato de etilo al 50-100%-hexanos), recogiendo el primer componente como producto, *proporcionando* (2-(4-(4-metoxifenil)tiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato (0,45 g, 1,17 mmol, 83 % de rendimiento) como un polvo blanco. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 8,65 (s, 1 H), 7,89 (d, *J*=7,32 Hz, 2 H), 7,15 - 7,43 (m, 1 H), 6,95 (d, *J*=8,85 Hz, 2 H), 3,64 - 3,93 (m, 5 H), 3,23 - 3,31 (m, *J*=1,53 Hz, 1 H), 3,09 - 3,21 (m, 1 H), 2,99 - 3,09 (m, 1 H), 2,79 - 2,97 (m, 3 H), 2,25 (s, 1 H), 1,96 - 2,16 (m, 1 H), 1,68 - 1,91 (m, 3 H), 1,45 (s, 3 H). MS (LC/MS) T. R. = 2,80; $[M+H-BH_3]^+$ = 371,1.

Etapa D: N-(4-(4-Metoxifenil)tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



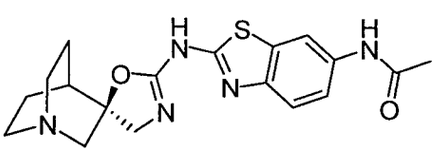
A (2-(4-(4-metoxifenil)tiazol-2-ilamino)-4H-1'-amoniospiro[oxazol-5,3'-biciclo[2.2.2]octano]-1'-il)trihidroborato (0,41 g, 1,07 mmol) en acetona (9 ml) se añadió HCl 3M (0,36 ml, 1,07 mmol). La reacción se agitó a temperatura ambiente durante 4 horas. La reacción se completó por TLC (mancha inferior). Se añadió acetato de etilo y se separó entonces la fase acuosa. La fase acuosa se neutralizó con hidróxido sódico 1N. El producto se extrajo con acetato de etilo (2 x 40 ml). Los orgánicos se reunieron, se secaron con sulfato de magnesio, se filtraron y se concentraron a vacío proporcionando N-(4-(4-metoxifenil)tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina racémica (0,3 g, 0,77 mmol, 72,1 % de rendimiento) como un polvo blanco. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 8,56 (s, 1 H), 7,77 - 8,00 (m, *J*=8,55 Hz, 2 H), 7,27 (s, 1 H), 6,80 - 7,08 (m, 2 H), 3,87 (d, *J*=9,77 Hz, 1 H), 3,79 (s, 3 H), 3,61 (d, *J*=9,77 Hz, 1 H), 3,02 (s, 3 H), 2,60 - 2,92 (m, 4 H), 2,06 (s, 2 H), 1,82 - 2,00 (m, 1 H), 1,39 - 1,70 (m, 3 H). MS (LC/MS) T. R. = 1,95; $[M+H]^+$ = 371,2.

Los enantiómeros se separaron usando una columna Chiralpak AD-H (30 x 250mm, 5μm) con una fase móvil constituida por 30% de metanol (0,1% de DEA) en CO_2. La longitud de onda se fijó a 220 nM. Los picos separados se concentraron a vacío proporcionando polvos blancos. El primer pico que salió de la columna fue (S)-N-(4-(4-metoxifenil)tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-

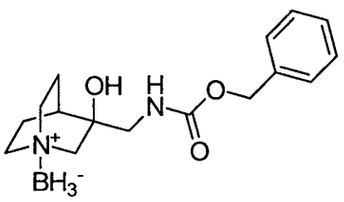
biciclo[2.2.2]octan]-2-amina (0,035 g, 0,09 mmol, 22,87 % de rendimiento). RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 8,56 (1 H, s ancho), 7,86 (2 H, d, *J*=8,55 Hz), 7,25 (1 H, s), 6,93 - 6,96 (2 H, m), 3,86 (1 H, d, *J*=9,77 Hz), 3,78 (3 H, s), 3,60 (1 H, d, *J*=9,46 Hz), 3,01 (2 H, s), 2,72 - 2,84 (2 H, m), 2,62 - 2,71 (2 H, m), 2,05 (1 H, s ancho), 1,91 (1 H, s ancho), 1,55 - 1,64 (2 H, m), 1,44 - 1,52 (1 H, m). MS (LC/MS) T. R. = 2,03; $[M+H]^+$ = 371,3. El segundo pico fue (R)-N-(4-(4-metoxifenil)tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,055 g, 0,15 mmol, 35,9 % de rendimiento). (21b, isómero R): RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 8,58 (1 H, s ancho), 7,87 (2 H, d, *J*=8,55 Hz), 7,26 (1 H, s), 6,92 - 6,97 (2 H, m), 3,86 (1 H, d, *J*=9,77 Hz), 3,78 (3 H, s), 3,60 (1 H, d, *J*=9,77 Hz), 3,01 (2 H, s), 2,73 - 2,85 (2 H, m), 2,63 - 2,71 (2 H, m), 2,05 (1 H, s ancho), 1,91 (1 H, s ancho), 1,54 - 1,64 (2 H, m), 1,43 - 1,53 (1 H, m). MS (LC/MS) T. R. = 2,03; $[M+H]^+$ = 371,3.

EJEMPLO 21

(R)-N-(2-(4H-1'-Azaspiro[oxazol-5,3'-biciclo[2.2.2]octano]-2-ilamino)benzo[d]tiazol-6-il)acetamida



Etapa A: (3-((Benciloxicarbonilamino)metil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato

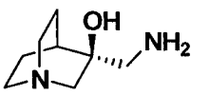


A (3-(aminometil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (10 g, 47,0 mmol) en diclorometano (150 ml) se añadió carbonato sódico (200 ml, 200 mmol) y cloroformiato de bencilo (9,5 ml, 66,5 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 40 minutos. Se añadieron diclorometano y agua y se separó entonces la fase acuosa y se extrajo de nuevo con diclorometano (2x). Las fases orgánicas se reunieron, se secaron sobre sulfato sódico, se filtraron y concentraron. El residuo se purificó por cromatografía ultrarrápida (acetato de etilo al 12-100%-hexanos). Las fracciones de producto se reunieron y concentraron proporcionando (3-((benciloxicarbonilamino)metil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato racémico (3 g, 9,86 mmol, 20,96 % de rendimiento) como un aceite transparente. RMN de ^{1}H (400 MHz, $CDCl_3$) δ ppm 7,30 - 7,43 (5 H, m), 5,27 (1 H, s ancho), 5,12 (2 H, s), 3,36 (2 H, d, *J*=6,04 Hz), 2,76 - 3,21 (6 H, m), 2,21 (1 H, s ancho), 1,97 (1 H, s ancho), 1,71 - 1,86 (2 H, m).

Los enantiómeros se separaron usando una columna Chiralpak OJ-H (5 x 25) con una fase móvil constituida por 20% acetonitrilo/metanol (1:1) en CO_2. La longitud de onda se fijó a 210 nM. El primer pico que salió de la columna fue (R)-(3-(aminometil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (37,67 g, 123 mmol) como un aceite incoloro. Rotación óptica: +28,2, c=2,9 en cloroformo. El segundo pico en salir de la columna fue (S)-(3-((benciloxicarbonilamino)metil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (46,82 g, 153 mmol) como un aceite ámbar claro. Rotación

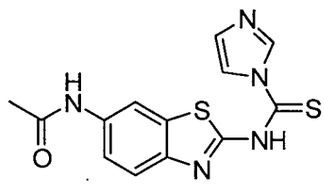
óptica: -27,4, c=2,5 en cloroformo.

Etapa B: (S)-3-(Aminometil)quinuclidin-3-ol, 2 HCl



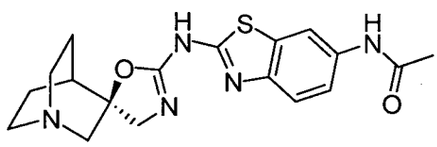
Una solución de (S)-(3-((benciloxicarbonilamino)metil)-3-hidroxi-1-amoniobiciclo[2.2.2]octan-1-il)trihidroborato (20,5 g, 67 mmol) en acetona (120 ml) se enfrió en un baño de hielo. Se añadió HCl acuoso 3M (120 ml, 360 mmol) durante 2 minutos. Se observó burbujeo intenso. Después de 10 minutos, se retiró el baño de hielo frío y se dejó calentar la mezcla hasta temperatura ambiente. Después de 20 minutos, se diluyó con metanol (800 ml) y cubrió con nitrógeno. Se añadió paladio sobre carbón (2 g, 1,88 mmol) y la reacción se cubrió con nitrógeno y se equipó con un balón de hidrógeno. La mezcla de reacción se agitó a temperatura ambiente durante la noche. Se cubrió entonces con nitrógeno y se filtró a través de una almohadilla de Celite usando metanol. El disolvente se evaporó proporcionando un sólido amarillo crudo. Los sólidos se disolvieron en agua (25 ml), luego se añadió etanol (400 ml). Se formaron inmediatamente cristales blancos. Se recogieron por filtración y se lavaron con etanol, seguido por éter. Se obtuvo un sólido cristalino blanco, (S)-3-(aminometil)quinuclidin-3-ol, 2 HCl (10,7 g, 46,7 mmol, 69,3 % de rendimiento). RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 10,93 (1 H, s ancho), 8,24 (3 H, s ancho), 6,02 (1 H, s), 3,26 (1 H, d, *J*=13,43 Hz), 2,99 - 3,22 (5 H, m), 2,10 - 2,19 (2 H, m), 1,81 - 1,90 (1 H, m), 1,72 - 1,81 (1 H, m), 1,60 - 1,72 (1 H, m). Rotación óptica: $[\alpha]^{20}_D$ = -50,9° (c=6,4, agua).

Etapa C: N-(2-(1H-Imidazol-1-carbotioamido)benzo[d]tiazol-6-il)acetamida



A N-(2-aminobenzo[d]tiazol-6-il)acetamida (4 g, 19,3 mmol) en acetonitrilo (100 ml) se añadió di(1H-imidazol-1-il)metanotiona (3,44 g, 19,30 mmol). Se dejó agitar la reacción a 80 °C durante la noche. La reacción se enfrió hasta temperatura ambiente y se filtró el precipitado. El producto, N-(2-(1H-imidazol-1-carbotioamido)benzo[d]tiazol-6-il)acetamida (3,6 g, 11,34 mmol, 58,8 % de rendimiento), se llevó directamente a la etapa siguiente sin purificación posterior.

Etapa D: (R)-N-(2-(4H-1'-Azaspiro[oxazol-5,3'-biciclo[2.2.2]octano]-2-ilamino)benzo[d]tiazol-6-il)acetamida

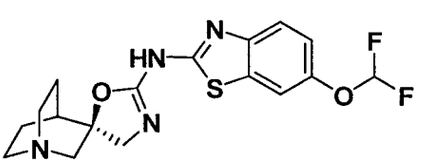


A N-(2-(1H-imidazol-1-carbotioamido)benzo[d]tiazol-6-il)acetamida (300 mg, 0,95 mmol) en N,N-dimetilformamida (10 ml) se añadió (S)-3-(aminometil)quinuclidin-3-ol, 2 HCl (238 mg, 1 mmol) y trietilamina (0,39 ml, 2,84 mmol). La reacción se calentó hasta 80 °C durante 3 horas. Se añadió entonces a la mezcla de reacción N,N'-diisopropilcarbodiimida (0,59 ml, 3,78 mmol). La mezcla se calentó a 80 °C durante otras 2 horas. La reacción se enfrió, luego se añadieron cloroformo y agua a la mezcla. La fase orgánica se concentró a vacío proporcionando producto bruto. El material bruto se purificó

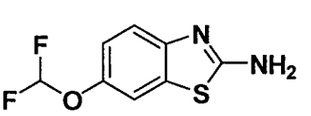
por cromatografía ultrarrápida (2-20% [hidróxido amónico al 10% /metanol-cloroformo). Las fracciones de producto se trituraron entonces con éter proporcionando (R)-N-(2-(4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octano]-2-ilamino)benzo[d]tiazol-6-il)acetamida (144,5 mg, 0,39 mmol, 41,2% de rendimiento) como un sólido blanco. RMN de ^{1}H (300 MHz, DMSO-d_6) δ ppm 9,98 (1 H, s), 8,93 (1 H, s ancho), 8,12 (1 H, d, *J*=1,83 Hz), 7,52 (1 H, d, *J*=8,42 Hz), 7,38 (1 H, dd, *J*=8,60, 2,01 Hz), 3,88 (1 H, d, *J*=9,88 Hz), 3,62 (1 H, d, *J*=9,88 Hz), 3,02 (2 H, s), 2,74 - 2,85 (2 H, m), 2,66 (2 H, t, *J*=7,68 Hz), 2,05 (4 H, s), 1,91 (1 H, s ancho), 1,41 - 1,64 (3 H, m). MS (LC/MS) T. R. = 1,55; $[M+H]^+$ = 372,2.

EJEMPLO 22

(R)-N-(6-(Difluorometoxi)benzo[d]tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



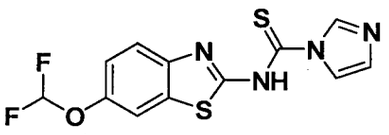
Etapa A: 6-(Difluorometoxi)benzo[d]tiazol-2-amina



A 4-(difluorometoxi)anilina (9,55 g, 60 mmol) en ácido acético (90 ml) se añadió tiocianato potásico (KSCN) (12,41 ml, 240 mmol). La mezcla se agitó durante 20 minutos (KSCN disuelto en solución). A esta mezcla se añadió bromo (3,08 ml, 60,0 mmol) en ácido acético (40 ml) gota a gota durante 20

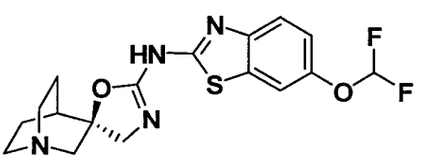
minutos. La reacción se agitó a temperatura ambiente durante la noche. Se vertió en una mezcla de 800 ml de hielo-agua y 200 ml de hidróxido amónico saturado. El producto se extrajo con acetato de etilo (5x). Los orgánicos se reunieron, se lavaron con salmuera, se secaron sobre sulfato sódico, se filtraron y concentraron a vacío proporcionando 6-(difluorometoxi)benzo[d]tiazol-2-amina (12,6 g, 52,4 mmol, 87 % de rendimiento) como un sólido amarillo.

Etapa B: N-(6-(Difluorometoxi)benzo[d]tiazol-2-il)-1H-imidazol-1-carbotioamida



A 6-(difluorometoxi)benzo[d]tiazol-2-amina (0,5 g, 2,3 mmol) en acetonitrilo (15 ml) se añadió 1,1'-tiocarbonildiimidazol (0,49 g, 2,8 mmol). La reacción se agitó a 70 °C durante la noche. La reacción se enfrió hasta temperatura ambiente y se filtró el precipitado proporcionando N-(6-(difluorometoxi)benzo[d]tiazol-2-il)-1H-imidazol-1-carbotioamida (500 mg, 1,53 mmol, 66,3 % de rendimiento) como un sólido amarillo.

Etapa C: (R)-N-(6-(Difluorometoxi)benzo[d]tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

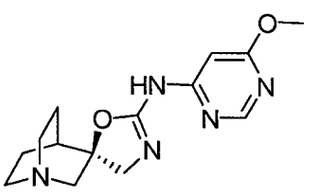


A una solución de N-(6-(difluorometoxi)benzo[d]tiazol-2-il)-1H-imidazol-1-carbotioamida (285 mg, 0,87 mmol) en N,N-dimetilformamida (5 ml) se añadió

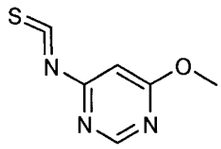
(S)-3-(aminometil)quinuclidin-3-ol, 2 HCl (200 mg, 0,87 mmol) y trietilamina (0,4 ml, 2,87 mmol). La reacción se calentó hasta 70 °C durante 2 horas. Se añadió entonces N,N'-diisopropilcarbodiimida (0,4 ml, 2,57 mmol) a la mezcla de reacción. La mezcla se calentó a 70 °C durante otros 3 horas. Se enfrió y luego se vertió en tolueno/hidróxido sódico 0,3M. El producto se extrajo con tolueno (4x) y cloroformo (3x). Los orgánicos se reunieron, se lavaron con agua (3x), se secaron sobre sulfato sódico, se filtraron y concentraron a vacío proporcionando producto bruto. El material bruto se purificó por cromatografía ultrarrápida (2-20% [10% de hidróxido amónico/metanol]-cloroformo) proporcionando (R)-N-(6-(difluorometoxi)benzo[d]tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (186,2mg, 0,49 mmol, 55,5 % de rendimiento) como un polvo blanco. P.F. 223-5 °C. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 8,99 (1 H, s ancho), 7,69 (1 H, d, *J*=2,75 Hz), 7,61 (1 H, d, *J*=8,55 Hz), 7,02 - 7,34 (2 H, m), 3,89 (1 H, d, *J*=10,07 Hz), 3,64 (1 H, d, *J*=9,77 Hz), 3,03 (2 H, d, *J*=2,44 Hz), 2,73 - 2,86 (2 H, m), 2,62 - 2,70 (2 H, m), 2,07 (1 H, s ancho), 1,92 (1 H, s ancho), 1,54 - 1,65 (2 H, m), 1,44 - 1,53 (1 H, m). MS (LC/MS) T. R. = 1,43; $[M+H]^+$ = 381,1.

EJEMPLO 23

(R)-N-(6-Metoxipirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

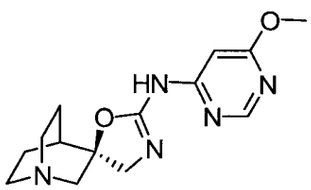


Etapa A: 4-Isotiocianato-6-metoxipirimidina



A una solución naranja brillante de 1,1'-tiocarbonildipiridin-2(1H)-ona (1,86 g, 7,99 mmol) en diclorometano a temperatura ambiente se añadió 6-metoxipirimidin-4-amina (1 g, 8 mmol). La solución naranja se agitó a temperatura ambiente durante 18 horas. La LC/MS mostró el producto deseado como uno de los picos mayoritarios. La solución naranja intenso se concentró y el residuo restante se filtró. El filtrado se purificó por cromatografía sobre gel de sílice (acetato de etilo del 10-50%/hexanos) proporcionando 4-isotiocianato-6-metoxipirimidina (0,72 g, 4,3 mmol, 54 % de rendimiento) como un aceite amarillo. RMN de ^{1}H (400 MHz, DMSO-d_6) δ ppm 8,49 (1 H, d, J=5,79 Hz), 6,95 (1 H, d, J=5,79 Hz), 3,92 (3 H, s). MS (LC/MS) T. R. = 3,15; $[M+H]^+$ = 168,1.

Etapa B: (R)-N-(6-Metoxipirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

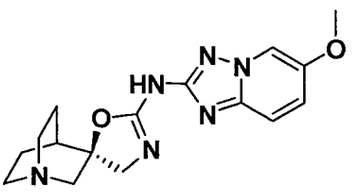


A diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (de la Etapa B del Ejemplo 21) (0,34 g, 1,49 mmol) en N,N-dimetilformamida (15 ml) se añadió Cs_2CO_3 (1,22 g, 3,74 mmol) y 4-isotiocianato-6-metoxipirimidina (0,25 g, 1,5 mmol). La suspensión se agitó a temperatura ambiente durante 30 minutos. Se añadió entonces N,N'-diisopropilcarbodiimida (0,7 ml, 4,5 mmol) y la mezcla se

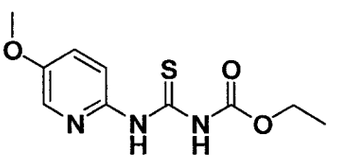
agitó a temperatura ambiente durante 18 horas. La mezcla se concentró y se purificó por cromatografía sobre gel de sílice (5-15 % [metanol:hidróxido amónico 9:1]/cloroformo) proporcionando (R)-N-(6-metoxipirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,21 g, 0,72 mmol, 48,2% de rendimiento) como un sólido blanco. P.F. 186-8 °C. RMN de ^{1}H (400 MHz, MeOD) δ ppm 8,40 (1 H, s), 6,17 (1 H, s ancho), 3,92 - 4,04 (1 H, m), 3,89 (3 H, s), 3,68 (1 H, d, *J*=10,32 Hz), 3,12 - 3,23 (1 H, m), 2,98 - 3,12 (1 H, m), 2,67 - 2,97 (4 H, m), 2,11 (2 H, s ancho), 1,48 - 1,82 (3 H, m). MS (LC/MS) T. R. = 0,82; $[M+H]^+$ = 290,3.

EJEMPLO 24

(R)-N-(6-Metoxi-[1,2,4]triazolo[1,5-a]piridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



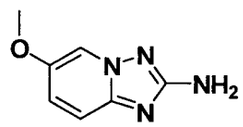
Etapa A: 5-Metoxipiridin-2-amina etoxicarbonil tiourea



A 5-metoxipiridin-2-amina (5g, 40 mmol) en dioxano (40 ml) se añadió isotiocianato de etoxicarbonilo (5,23 ml, 44,3 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche. La mezcla se concentró a vacío proporcionando 5-metoxipiridin-2-amina etoxicarbonil tiourea (10,28 g, 40,3

mmol, 100 % de rendimiento). RMN de ^{1}H (300 MHz, DMSO-d_6) δ ppm 12,03 (1 H, s ancho), 11,37 (1 H, s ancho), 8,53 (1 H, s ancho), 8,11 (1 H, d, *J*=2,93 Hz), 7,50 (1 H, dd, *J*=8,97, 3,11 Hz), 4,22 (2 H, c, *J*=7,07 Hz), 3,84 (3 H, s), 1,26 (3 H, t, *J*=7,14 Hz). MS (LC/MS) T. R. = 2,40; $[M+H]^+$ = 256,1.

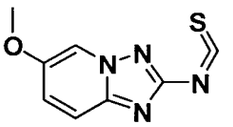
Etapa B: 6-Metoxi-[1,2,4]triazolo[1,5-a]piridin-2-amina



A 5-metoxipiridin-2-amina etoxicarbonil tiourea (10,21 g, 40 mmol) en etanol (57 ml) y metanol (57 ml) se añadió clorhidrato de hidroxilamina (14 g, 200 mmol) y base de Hunig (21 ml, 120 mmol). La mezcla se agitó a temperatura ambiente durante 2 horas, y luego se calentó a 60 °C durante 4 horas. La reacción se enfrió hasta temperatura ambiente y se filtró para separar los sólidos. Se concentró a vacío y luego se suspendió en cloroformo. Se separaron los sólidos por filtración proporcionando 6-metoxi-[1,2,4]triazolo[1,5-a]piridin-2-amina (6,05 g, 33,2 mmol, 83 % de rendimiento). RMN de ^{1}H (300 MHz, DMSO-d_6) δ ppm 8,30 (1 H, d, *J*=1,83 Hz), 7,24 - 7,32 (1 H, m), 7,16 - 7,23 (1 H, m), 5,82 (2 H, s ancho), 3,78 (3 H, s). MS (LC/MS) T. R. = 0,53; $[M+H]^+$ = 165,2.

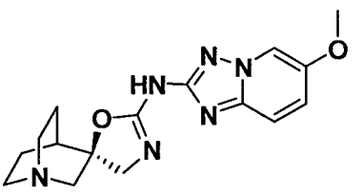
Se purificaron dos gramos 6-metoxi-[1,2,4]triazolo[1,5-a]piridin-2-amina por cromatografía ultrarrápida (2-20% [10% de hidróxido amónico/metanol]/cloroformo) proporcionando 6-metoxi-[1,2,4]triazolo[1,5-a]piridin-2-amina (1,35 g, 8,22 mmol, 67,5 % de rendimiento). RMN de ^{1}H (300 MHz, DMSO-d_6) δ ppm 8,29 (1 H, d, *J*=2,20 Hz), 7,24 - 7,30 (1 H, m), 7,15 - 7,22 (1 H, m), 5,79 (2 H, s), 3,78 (3 H, s).

Etapa C: 2-Isotiocianato-6-metoxi-[1,2,4]triazolo[1,5-a]piridina



A 6-metoxi-[1,2,4]triazolo[1,5-a]piridin-2-amina (0,3 g, 1,8 mmol) en diclorometano (15 ml) se añadió 1,1'-tiocarbonildi-2(1H)-piridona (0,51 g, 2,2 mmol). La reacción se agitó a temperatura ambiente durante la noche, se concentró a vacío y se purificó por cromatografía ultrarrápida proporcionando 2-isotiocianato-6-metoxi-[1,2,4]triazolo[1,5-a]piridina (166 mg, 0,8 mmol, 44 % de rendimiento) como un sólido blanco. RMN de ^{1}H (300 MHz, $CDCl_3$) δ ppm 8,03 (1 H, d, *J*=2,20 Hz), 7,54 (1 H, d, *J*=9,88 Hz), 7,34 (1 H, dd, *J*=9,51, 2,56 Hz), 3,88 (3 H, s).

Etapa D: (R)-N-(6-Metoxi-[1,2,4]triazolo[1,5-a]piridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

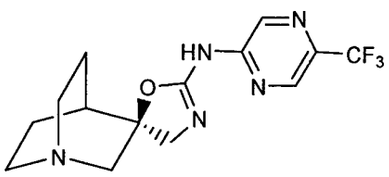


A 2-isotiocianato-6-metoxi-[1,2,4]triazolo[1,5-a]piridina (160 mg, 0,78 mmol) en N,N-dimetilformamida (5ml) se añadió (S)-3-(aminometil)quinuclidin-3-ol, 2 HCl (178 mg, 0,78 mmol) y trietilamina (0,32 ml, 2,33 mmol). La reacción se agitó a 70 °C durante 1 hora. Se añadió entonces N,N'-diisopropilcarbodiimida (0,36 ml, 2,33 mmol) a la mezcla de reacción. La mezcla se calentó a 70 °C durante 4 horas, luego se enfrió y se vertió en bicarbonato sódico acuoso/cloroformo. El producto se extrajo (3x) con

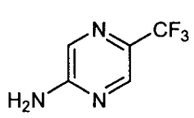
cloroformo. Los orgánicos reunidos se lavaron con agua (3x), se secaron sobre sulfato sódico, se filtraron y se concentraron a vacío, luego se purificó por cromatografía ultrarrápida (2-20% [10% de hidróxido amónico:metanol]/cloroformo) proporcionando (R)-N-(6-metoxi-[1,2,4]triazolo[1,5-a]piridin-2-il)-4H-1'-azaspiro-[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (114,5 mg, 0,33 mmol, 42 % de rendimiento) como un polvo blanco. RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 8,51 (1 H, s ancho), 8,08 (1 H, d, *J*=2,44 Hz), 7,35 (1 H, d, *J*=9,77 Hz), 7,18 (1 H, dd, *J*=9,46, 2,44 Hz), 3,92 (1 H, d, *J*=8,85 Hz), 3,84 (3 H, s), 3,58 (1 H, d, *J*=8,85 Hz), 3,36 - 3,41 (1 H, m), 2,72 - 3,05 (4 H, m), 2,18 - 2,26 (1 H, m, *J*=13,26, 9,98, 3,66, 3,49, 3,49 Hz), 2,13 (1 H, s ancho), 1,79 (1 H, s ancho), 1,67 - 1,76 (1 H, m, *J*=13,96, 9,84, 4,27, 4,27 Hz), 1,45 - 1,63 (2 H, m). MS (LC/MS) T. R. = 0,86; $[M+H]^+$ = 329,2.

EJEMPLO 25

(R)-N-(5-(Trifluorometil)pirazin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



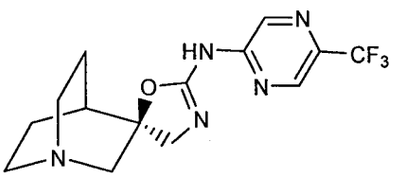
Etapa A: 5-(Trifluorometil)pirazin-2-amina



A una solución enfriada en baño de hielo de 5,6-diaminopirimidin-4-ol (18 g, 143 mmol) en hidróxido sódico 3M (180 ml, 540 mmol), se añadió 3,3-

dibromo-1,1,1-trifluoropropan-2-ona (25,2 g, 93 mmol). La reacción se agitó durante 3 días a temperatura ambiente. Los sólidos se filtraron, se disolvieron en ácido sulfúrico al 60% (140 ml) y se agitaron a 135 °C durante 8 h. La reacción se enfrió, se vertió sobre hielo y se dejó asentar durante 16 horas. La solución se neutralizó hasta pH 8 con hidróxido amónico concentrado y se extrajo con acetato de etilo (5 X 100 ml), se secó sobre sulfato sódico, se filtró y se concentró. El residuo sólido se recristalizó en benceno/hexano proporcionando 5-(trifluorometil)pirazin-2-amina (2,28 g, 14 mmol, 15 % de rendimiento). RMN de ^{1}H (400 MHz, *CDCl$_3$*) δ ppm 8,32 (1 H, s), 7,99 (1 H, d, *J*=1,26 Hz), 5,02 (2 H, s ancho). MS (LC/MS) T. R. = 1,56; $[M+H]^+$ = 164,03.

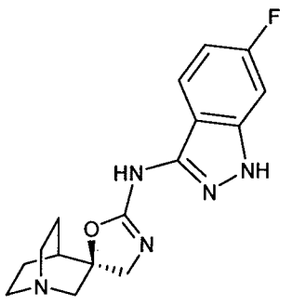
Etapa B: (R)-N-(5-(Trifluorometil)pirazin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



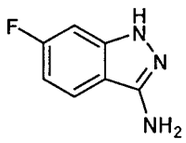
(R)-N-(5-(trifluorometil)pirazin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina se preparó siguiendo los procedimientos generales del Ejemplo **23, Etapas A-B** y usando 5-(trifluorometil)pirazin-2-amina **(de la Etapa A anterior)** como material de partida. RMN de ^{1}H (400 MHz, *CDCl$_3$*) δ ppm 9,08 (1 H, s ancho), 8,35 (1 H, s), 8,32 (1 H, s), 3,95 (1 H, d, *J*=9,57 Hz), 3,61 (1 H, d, *J*=9,57 Hz), 3,30 (1 H, dd, *J*=14,86, 1,76 Hz), 2,65 - 2,99 (5 H, m), 2,05 - 2,16 (2 H, m), 1,64 - 1,74 (1 H, m), 1,42 - 1,57 (2 H, m). MS (LC/MS) T. R. = 1,06; $[M+H]^+$ = 328,30.

Ejemplo 26

(R)-N-(6-Fluoro-1H-indazol-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



Etapa A: 6-Fluoro-1H-indazol-3-amina



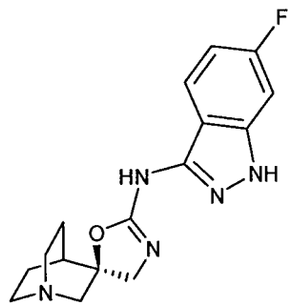
A 2,4-difluorobenzonitrilo (1,21 g, 8,70 mmol) se añadió hidrazina monohidratada (8,46 ml, 174 mmol). La mezcla se calentó hasta reflujo durante 5 horas y luego se vertió en hielo. La solución se extrajo con acetato de etilo, se secó sobre sulfato de magnesio, se filtró y se concentró. El residuo se purificó por cromatografía en columna (acetato de etilo del 25-100%/hexano) proporcionando 6-fluoro-1H-indazol-3-amina (0,5 g, 3,3 mmol, 38 % de rendimiento) como polvo amarillo claro. RMN de ^{1}H (500 MHz, *DMSO-D6*) δ ppm 11,42 (s, 1 H), 7,70 (dd, *J*=8,55, 5,49 Hz, 1 H), 6,97 (dd, *J*=10,07, 1,83 Hz, 1 H), 6,72 - 6,79 (m, 1 H), 5,40 (s, 2 H). MS (LC/MS) T. R. = 0,61; $[M+H]^+$ = 152,11.

Etapa B: 6-Fluoro-3-isotiocianato-1H-indazol



A 6-fluoro-1H-indazol-3-amina (0,32 g, 2,1 mmol) en diclorometano (15 ml) se añadió 1,1'-tiocarbonildipiridin-2(1H)-ona (0,53 g, 2,30 mmol). La reacción se agitó a 50 °C durante 3 horas. La reacción se enfrió hasta temperatura ambiente y el producto bruto se purificó por cromatografía en columna (acetato de etilo al 25%/hexanos) proporcionando 6-fluoro-3-isotiocianato-1H-indazol (0,30 g, 1,53 mmol, 73,0 % de rendimiento) como un polvo amarillo claro. RMN de ^{1}H (500 MHz, *DMSO-D6*) δ ppm 13,39 (s, 1 H), 7,78 (dd, *J*=8,85, 4,88 Hz, 1 H), 7,41 (dd, *J*=9,31, 1,68 Hz, 1 H), 7,14 (td, *J*=9,16, 1,83 Hz, 1 H). MS (LC/MS) T. R. = 3,69; $[M+H]^+$ = 194,07.

Etapa C: (R)-N-(6-Fluoro-1H-indazol-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

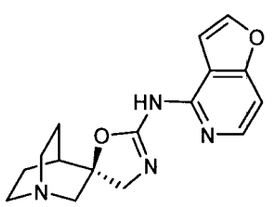


A 6-fluoro-3-isotiocianato-1H-indazol (0,20 g, 1,04 mmol) en DMF (15 ml) se añadió trietilamina (0,43 ml, 3,11 mmol) y diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (0,26 g, 1,14 mmol) a temperatura ambiente. La reacción se agitó a 70 °C durante 2 horas. La reacción se enfrió hasta

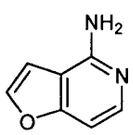
temperatura ambiente y se trató con N,N'-diisopropilcarbodiimida (0,48 ml, 3,11 mmol). La reacción se calentó entonces hasta 70 °C durante 2 horas. La reacción se enfrió hasta temperatura ambiente y se concentró. El producto bruto se purificó por cromatografía en columna (85% cloroformo, 14% de metanol, 1% de hidróxido amónico) proporcionando (R)-N-(6-fluoro-1H-indazol-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,22 g, 0,66 mmol, 64 % de rendimiento) como un polvo blanco. RMN de ^{1}H (500 MHz, *DMSO-D6*) δ ppm 12,16 (s, 1 H), 8,00 (s, 1 H), 7,59 - 7,67 (m, 1 H), 7,09 (dd, *J*=9,77, 2,14 Hz, 1 H), 6,81 - 6,88 (m, 1 H), 3,81 (d, *J*=9,16 Hz, 1 H), 3,56 (d, *J*=8,85 Hz, 1 H), 3,00 (s, 2 H), 2,78 (s, 2 H), 2,67 (t, *J*=7,32 Hz, 2 H), 2,01 (d, *J*=2,44 Hz, 1 H), 1,92 (s, 1 H), 1,59 (d, *J*=5,80 Hz, 2 H), 1,46 (s, 1 H). MS (LC/MS) T. R. = 1,44; $[M+H]^+$ = 316,16.

EJEMPLO 27

(R)-N-(Furo[3,2-c]piridin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



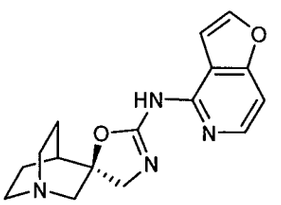
Etapa A: Furo[3,2-c]piridin-4-amina



A 4-clorofuro[3,2-c]piridina (1 g, 6,5 mmol) en tolueno en nitrógeno se añadió BINAP racémico (0,243 g, 0,4 mmol) , $Pd_2(dba)_3$ (0,12 g, 0,13 mmol) y

terc-butóxido sódico (0,88 g, 9,1 mmol). Se añadió benzofenonaimina (1,3 ml, 7,81 mmol) y la mezcla se calentó hasta 80 ºC durante 3 h y se enfrió hasta temperatura ambiente. La mezcla de reacción se diluyó con éter, se filtró a través de Celite, y se lavó con éter. El filtrado se concentró y el residuo naranja intenso se suspendió en metanol (90 ml) y se trató con hidroxilamina (1,2 ml, 19,5 mmol). La mezcla se agitó a temperatura ambiente durante 18 horas y se concentró. El residuo se purificó por cromatografía en columna (acetato de etilo del 95-100 %/hexanos) proporcionando furo[3,2-c]piridin-4-amina (776 mg, 5,79 mmol, 89 % de rendimiento) como un sólido naranja intenso. MS (LC/MS) T. R. = 0,51; $[M+H]^+$ = 135,02.

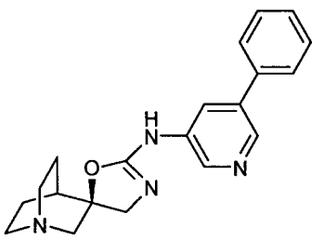
Etapa B: (R)-N-(Furo[3,2-c]piridin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



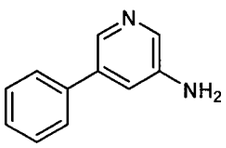
(R)-N-(Furo[3,2-c]piridin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina se preparó siguiendo los procedimientos generales del Ejemplo **23, Etapas A-B** usando furo[3,2-c]piridin-4-amina **(Etapa A anterior)** como material de partida. RMN de ^{1}H (400 MHz, *MeOD*) δ ppm 8,08 (1 H, d, *J*=5,79 Hz), 7,69 (1 H, d, *J*=2,01 Hz), 6,99 - 7,13 (2 H, m), 4,00 (1 H, d, *J*=10,07 Hz), 3,69 (1 H, d, *J*=10,07 Hz), 3,19 - 3,26 (1 H, m), 3,05 - 3,13 (1 H, m), 2,93 (2 H, t, *J*=7,43 Hz), 2,73 - 2,87 (2 H, m), 2,08 - 2,24 (2 H, m), 1,52 - 1,82 (3 H, m). MS (LC/MS) T. R. = 0,68; $[M+H]^+$ = 299,19.

EJEMPLO 28

(R)-N-(5-Fenilpiridin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

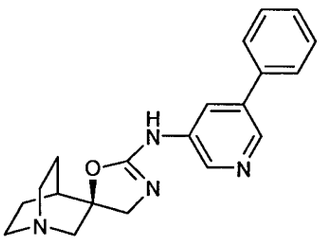


Etapa A: 5-Fenilpiridin-3-amina



Se calentó durante 4 horas en un baño de aceite a 90ºC una mezcla de 5-bromopiridin-3-amina (248 mg, 1,43 mmol), $Pd(PPh_3)_4$ (50,4 mg, 0,04 mmol), tolueno (3 ml), carbonato sódico (2 M, 3 ml, 6 mmol) y ácido fenilborónico (195 mg, 1,60 mmol) disuelto en etanol (3 ml) y se dejó enfriar hasta temperatura ambiente durante 16 horas. La mezcla de reacción se transfirió a un embudo de separación y se repartió entre acetato de etilo y agua. La fase acuosa se lavó una vez más con acetato de etilo, y las fases orgánicas reunidas se lavaron con salmuera y se secaron sobre sulfato de magnesio, se filtraron y concentraron a vacío. El residuo se purificó por cromatografía en columna (80% acetato de etilo/hexanos) proporcionando 5-fenilpiridin-3-amina (31,9 mg, 0,19 mmol, 13 % de rendimiento) como un sólido blanco. RMN de ^1H (500 MHz, *$CDCl_3$*) δ ppm 8,17 - 8,42 (m, 1 H), 8,02 - 8,20 (m, 1 H), 7,32 - 7,62 (m, 4 H), 7,25 (s, 1 H), 7,06 - 7,20 (m, 1 H). MS (LC/MS) T. R. = 0,91; $[M+H]^+$ = 171,09.

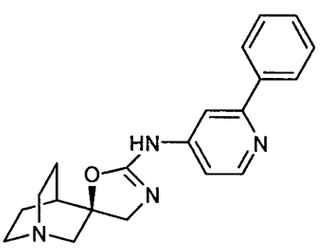
Etapa B: (R)-N-(5-Fenilpiridin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



(R)-N-(5-Fenilpiridin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina se preparó siguiendo los procedimientos generales del Ejemplo **23, Etapas A-B** usando 5-fenilpiridin-3-amina **(de la Etapa A anterior)** como material de partida. RMN de ^{1}H (500 MHz, *MeOD-d$_4$*) δ ppm 8,40 (s ancho, 2 H), 7,66 (d, *J*=7,32 Hz, 2 H), 7,46 - 7,56 (m, 3 H), 7,43 (d, *J*=7,32 Hz, 1 H), 3,79 - 4,02 (m, 1 H), 3,51 - 3,68 (m, 1 H), 3,22 (d, *J*=14,95 Hz, 1 H), 3,02 - 3,15 (m, 1 H), 2,72 - 2,99 (m, 3 H), 2,14 (s ancho, 2 H), 1,76 (dd, *J*=9,31, 4,12 Hz, 3 H), 1,12 - 1,35 (m, 1 H). MS (LC/MS) T. R. = 0,90; $[M+H]^+$ = 335,17.

EJEMPLO 29

(R)-N-(2-Fenilpiridin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

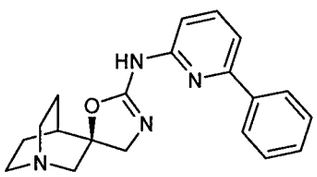


(R)-N-(2-Fenilpiridin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina se preparó a partir de 2-bromopiridin-4-amina siguiendo los

procedimientos generales del **Ejemplo 28, Etapas A-B.** RMN de ^{1}H (500 MHz, *MeOD*) δ ppm 8,38 (d, *J*=5,49 Hz, 1 H), 7,88 (d, *J*=7,93 Hz, 2 H), 7,71 - 7,84 (m, 1 H), 7,48 (d, *J*=7,63 Hz, 3 H), 7,19 - 7,36 (m, 1 H), 3,94 - 4,09 (m, 1 H), 3,61 - 3,79 (m, 1 H), 3,17 - 3,27 (m, 1 H), 3,00 - 3,14 (m, 1 H), 2,74 - 3,00 (m, 4 H), 2,05 - 2,23 (m, 2 H), 1,55 - 1,86 (m, 3 H). MS (LC/MS) T. R. = 0,86; $[M+H]^+$ = 335,23.

EJEMPLO 30

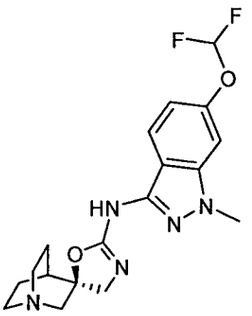
(R)-N-(6-Fenilpiridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



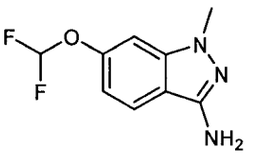
(R)-N-(6-Fenilpiridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina se preparó a partir de 6-bromopiridin-2-amina siguiendo los procedimientos generales del **Ejemplo 28, Etapas A-B**. RMN de ^{1}H (500 MHz, *MeOD-d$_4$*) δ ppm 7,91 (d, *J*=7,63 Hz, 2 H), 7,71 (t, *J*=7,78 Hz, 1 H), 7,32 - 7,55 (m, 5 H), 4,04 (d, *J*=10,07 Hz, 1 H), 3,72 (d, *J*=9,77 Hz, 1 H), 3,23 (d, *J*=1,22 Hz, 1 H), 3,12 (s, 1 H), 2,95 (s, 2 H), 2,84 (s, 2 H), 2,16 (s ancho, 2 H), 1,58 - 1,85 (m, 3 H). MS (LC/MS) T. R. = 0,75; $[M+H]^+$ = 335,23.

Ejemplo 31

(R)-N-(6-(Difluorometoxi)-1-metil-1H-indazol-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

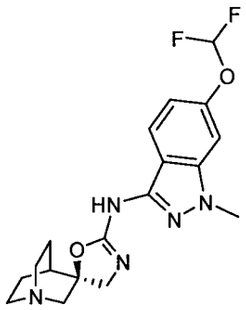


Etapa A: 6-(Difluorometoxi)-1-metil-1H-indazol-3-amina



A 4-(difluorometoxi)-2-fluorobenzonitrilo (1 g, 5,3 mmol) se añadió metilhidrazina (4,92 g, 107 mmol). La mezcla se calentó hasta 50 °C durante 5 horas y luego se enfrió hasta temperatura ambiente. El producto bruto se purificó por cromatografía en columna (acetato de etilo de 40-100%/hexanos) proporcionando 6-(difluorometoxi)-1-metil-1H-indazol-3-amina (0,5 g, 2,35 mmol, 44 % de rendimiento) como un polvo blanco. RMN de ^{1}H (500 MHz, *DMSO-d*$_6$) δ ppm 7,70 (d, *J*=8,55 Hz, 1 H), 7,14 (s, 1 H), 6,73 (d, *J*=8,55 Hz, 1 H), 5,49 (s, 1 H), 3,70 (s, 3 H).

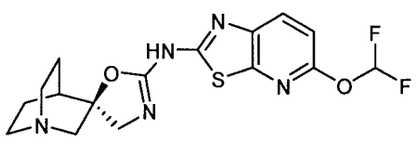
Etapa B: (R)-N-(6-(Difluorometoxi)-1-metil-1H-indazol-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



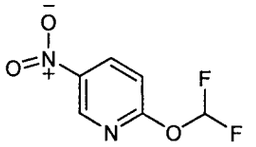
(R)-N-(6-(difluorometoxi)-1-metil-1H-indazol-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina se preparó siguiendo los procedimientos generales del Ejemplo **23, Etapas A-B** usando 6-(difluorometoxi)-1-metil-1H-indazol-3-amina **(Etapa A)** como material de partida. RMN de ^{1}H (500 MHz, *DMSO-d*$_6$) δ ppm 7,64 (d, *J*=8,55 Hz, 1 H), 7,28 (d, *J*=5,19 Hz, 1 H), 6,83 (dd, *J*=8,55, 1,83 Hz, 1 H), 3,88 (s, 3 H), 3,77 - 3,84 (m, 1 H), 3,51 - 3,64 (m, 1 H), 3,00 (s, 2 H), 2,72 - 2,84 (m, 2 H), 2,67 (t, *J*=7,48 Hz, 2 H), 2,02 (s ancho, 1 H), 1,85 - 1,98 (m, 1 H), 1,59 (d, *J*=5,80 Hz, 2 H), 1,36 - 1,53 (m, 1 H), 1,09 (d, *J*=6,41 Hz, 1 H). MS (LC/MS) T. R. = 1,04; $[M+H]^+$ = 378,19.

EJEMPLO 32

(R)-N-(5-(Difluorometoxi)tiazolo[5,4-b]piridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

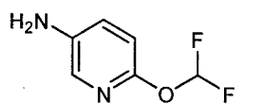


Etapa A: 2-(Difluorometoxi)-5-nitropiridina



A 2-hidroxi-5-nitropiridina (7 g, 50 mmol) en acetonitrilo (500 ml) se añadió sulfato sódico (1,5 g, 10,6 mmol) y ácido 2,2-difluoro-2-(fluorosulfonil)acético (6,2 ml, 60 mmol) y la reacción se dejó agitar a temperatura ambiente durante 16 horas. La reacción se inactivó con bicarbonato sódico acuoso saturado y el acetonitrilo se eliminó a vacío. El componente acuoso restante se extrajo con acetato de etilo, se lavó con salmuera, se secó sobre sulfato sódico, se filtró y se concentró a vacío. El sólido oleoso pardo claro se trituró con éter/hexanos, se filtró y el filtrado se concentró proporcionando 2-(difluorometoxi)-5-nitropiridina (4,7 g, 24,7 mmol, 49 % de rendimiento) como un aceite amarillo. RMN de ^{1}H (400 MHz, *DMSO-d_6*) δ ppm 9,14 (d, *J*=2,76 Hz, 1 H), 8,68 (dd, *J*=9,03, 2,76 Hz, 1 H), 7,98 (s, 0,5 H), 7,62 (s, 0,5 H), 7,34 (d, *J*=9,03 Hz, 1 H).

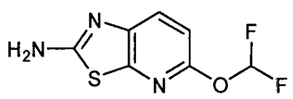
Etapa B: 6-(Difluorometoxi)piridin-3-amina



A 2-(difluorometoxi)-5-nitropiridina (4,7 g, 24,7 mmol) en metanol desgasificado (100 ml) se añadió paladio al 10% sobre carbón (500 mg, 0,47 mmol) y la reacción se sometió a hidrogenación a presión atmosférica durante 1 hora. A esta se añadió ácido acético (2,83 ml, 49,4 mmol) y la reacción se filtró a través de Celite y se concentró a vacío *proporcionando* 6-

(difluorometoxi)piridin-3-amina (6,33 g, 25,9 mmol, 105 % de rendimiento) como un líquido verde aceituna. RMN de ^{1}H (400 MHz, *MeOD-d$_4$*) δ ppm 7,60 (d, *J*=2,76 Hz, 1 H), 7,37 (s, 0,5 H), 7,15 (dd, *J*=8,66, 2,89 Hz, 1 H), 7,00 (s, 0,5 H), 6,71 (d, *J*=8,78 Hz, 1 H).

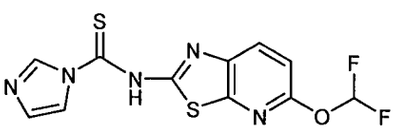
Etapa C: 5-(Difluorometoxi)tiazolo[5,4-b]piridin-2-amina



A acético ácido (10 ml) enfriado en un baño de hielo se añadió tiocianato potásico (3,18 g, 32,8 mmol) y 6-(difluorometoxi)piridin-3-amina (1 g, 4,1 mmol). La reacción se enfrió en un baño de hielo-sal hasta que la temperatura de reacción alcanzó <0°C. Se añadió una solución de bromo (0,65 ml, 12,7 mmol) en ácido acético (3 ml) gota a gota durante 2 horas a una velocidad que mantenía la temperatura de reacción <0°C. Esto dio una mezcla muy densa. Después de completar la adición, se dejó agitar la mezcla y se dejó calentar lentamente hasta temperatura ambiente. Después de agitar durante la noche, se añadió agua (5 ml) y la mezcla se calentó hasta 85°C en un baño de aceite. Esta mezcla se filtró entonces mientras estaba todavía caliente. La torta del filtro amarilla se devolvió al matraz de reacción y se añadieron otros 5 ml de ácido acético. La mezcla de calentó de nuevo hasta 85°C, y luego se filtró mientras estaba todavía caliente. Los filtrados reunidos se enfriaron en un baño de hielo y se neutralizó hasta pH 8 con hidróxido amónico concentrado. Se formó un precipitado amarillo que se recogió por filtración. Este material bruto se purificó por cromatografía en columna (acetato de etilo al 12-100%/hexanos) proporcionando 5-(difluorometoxi)tiazolo[5,4-b]piridin-2-amina (321 mg, 1,48

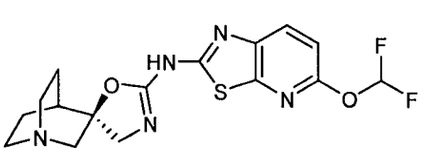
mmol, 36,1 % de rendimiento) como un sólido amarillo. RMN de ^{1}H (400 MHz, *DMSO-d$_6$*) δ ppm 7,64 - 7,81 (m, 2 H), 6,92 (d, *J*=8,53 Hz, 1 H). MS (LC/MS) T. R. = 1,66; $[M+H]^+$ = 218,10.

Etapa D: N-(5-(Difluorometoxi)tiazolo[5,4-b]piridin-2-il)-1H-imidazol-1-carbotioamida



Se disolvieron 5-(difluorometoxi)tiazolo[5,4-b]piridin-2-amina (310 mg, 1,43 mmol) y di(1H-imidazol-1-il)metanotiona (311 mg, 1,75 mmol) en acetonitrilo (5 ml) y se calentó hasta 70 °C en un vial sellado durante 10 horas. El vial se almacenó entonces en el congelador durante 16 horas. Se recogieron los sólidos por filtración y se lavó con acetonitrilo proporcionando N-(5-(difluorometoxi)tiazolo[5,4-b]piridin-2-il)-1H-imidazol-1-carbotioamida (296 mg, 0,72 mmol, 51 % de rendimiento). RMN de ^{1}H (400 MHz, *DMSO-d$_6$*) δ ppm 8,77 (d, *J*=4,77 Hz, 1 H), 8,06 (d, *J*=8,53 Hz, 1 H), 8,01 (s, 1 H), 7,72 (s, 1 H), 7,54 (s, 1 H), 6,94 - 7,13 (m, 1 H).

Etapa E: (R)-N-(5-(Difluorometoxi)tiazolo[5,4-b]piridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



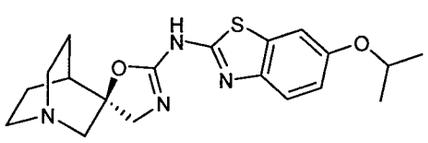
A N-(5-(difluorometoxi)tiazolo[5,4-b]piridin-2-il)-1H-imidazol-1-carbotioamida (296 mg, 0,72 mmol) en N,N-dimetilformamida (4 ml) en un vial

sellado se añadió (S)-3-(aminometil)quinuclidin-3-ol, 2 HCl (175 mg, 0,76 mmol) y trietilamina (0,3 ml, 2,2 mmol) y la mezcla se calentó hasta 70 °C durante la noche.

A esta se añadió N,N'-diisopropilcarbodiimida (350 µl, 2,25 mmol) y la reacción se calentó hasta 70 ºC durante 6 horas. Se enfrió hasta temperatura ambiente y se vertió en agua/cloroformo, se extrajo con más cloroformo y se concentró a vacío. El residuo se suspendió entonces en tolueno y se lavó con agua para eliminar la N,N-dimetilformamida residual. El residuo se purificó por cromatografía en columna (2%-20% (10% de hidróxido amónico/metanol)/cloroformo) proporcionando (R)-N-(5-(difluorometoxi)tiazolo[5,4-b]piridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (104 mg, 0,27 mmol, 37 % de rendimiento) como un sólido color crema pálido. RMN de ^{1}H (400 MHz, *DMSO-d*$_6$) δ ppm 7,99 (d, *J*=8,78 Hz, 1 H), 7,68 (s, 1 H), 7,03 (d, *J*=8,53 Hz, 1 H), 3,87 (d, *J*=10,04 Hz, 1 H), 3,62 (d, *J*=10,04 Hz, 1 H), 3,03 (d, *J*=5,02 Hz, 2 H), 2,80 (d, *J*=9,03 Hz, 2 H), 2,65 (t, *J*=7,65 Hz, 2 H), 2,08 (s ancho, 1 H), 1,83 - 1,99 (m, 1 H), 1,43 - 1,68 (m, 3 H). MS (LC/MS) T. R. = 1,73; $[M+H]^+$ = 382,20.

EJEMPLO 33

(R)-N-(6-Isopropoxibenzo[d]tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

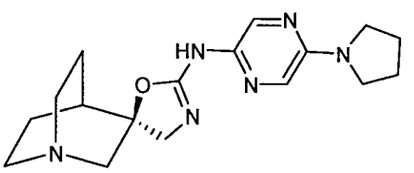


(R)-N-(6-Isopropoxibenzo[d]tiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina se preparó a partir de 4-isopropoxianilina siguiendo

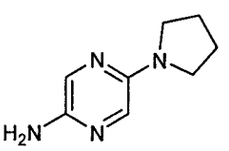
los procedimientos generales del **Ejemplo 32, Etapas C-E**. RMN de ^{1}H (400 MHz, *DMSO-d*$_6$) δ ppm 7,49 (d, *J*=8,78 Hz, 1 H), 7,38 (d, *J*=2,51 Hz, 1 H), 6,90 (dd, *J*=8,78, 2,51 Hz, 1 H), 4,50 - 4,68 (m, 1 H), 3,87 (d, *J*=10,04 Hz, 1 H), 3,62 (d, *J*=9,79 Hz, 1 H), 2,79 (d, *J*=9,03 Hz, 2 H), 2,66 (t, *J*=7,78 Hz, 2 H), 2,06 (s ancho, 1 H), 1,85 - 1,96 (m, 1 H), 1,42 - 1,67 (m, 3 H), 1,17 - 1,34 (m, 6 H), 0,96 - 1,19 (m, 2 H).

EJEMPLO 34

(R)-N-(5-(Pirrolidin-1-il)pirazin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



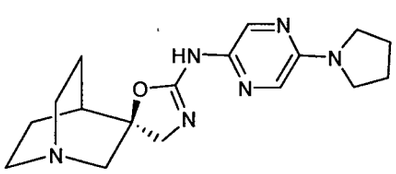
Etapa A: 5-(Pirrolidin-1-il)pirazin-2-amina



Se trató en microondas a 180ºC 200 W durante 2 horas una mezcla de 5-bromopirazin-2-amina (1,2 g, 6,9 mmol) y pirrolidina (4 ml, 48 mmol). La reacción se diluyó en 125 ml de acetato de etilo y se extrajo con agua (3 x 50 ml) y salmuera (50 ml). Se secó sobre sulfato sódico, se filtró y se concentró. El producto bruto se purificó por cromatografía en columna (0 de 3% de metanol/cloruro de metileno) proporcionando 5-(pirrolidin-1-il)pirazin-2-amina (495 mg, 3. mmol, 43,7 % de rendimiento). RMN de ^{1}H (400 MHz, *DMSO-d*$_6$) δ

ppm 7,52 (1 H, d, *J*=1,51 Hz), 7,36 (1 H, d, *J*=1,76 Hz), 5,21 (2 H, s), 3,24 - 3,29 (4 H, m), 1,90 (4 H, ddd, *J*=6,48, 3,53, 3,34 Hz). MS (LC/MS) T. R. = 0,52; $[M+H]^+$ = 165,29.

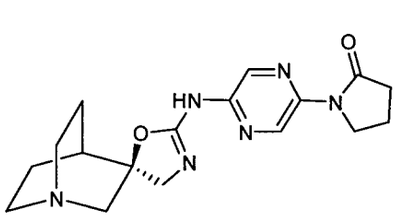
Etapa B: (R)-N-(5-(Pirrolidin-1-il)pirazin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



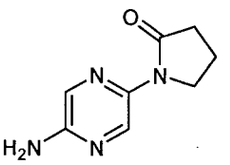
(R)-N-(5-(Pirrolidin-1-il)pirazin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina se preparó a partir de 5-(pirrolidin-1-il)pirazin-2-amina siguiendo los procedimientos generales del **Ejemplo 23, Etapas A-B.** RMN de ^1H (500 MHz, *$CDCl_3$*) δ ppm 8,51 (1 H, s ancho), 8,02 (1 H, s), 7,44 (1 H, d, *J*=0,92 Hz), 3,84 (1 H, d, *J*=9,16 Hz), 3,51 (1 H, d, *J*=8,85 Hz), 3,39 - 3,45 (4 H, m), 3,31 (1 H, dd, *J*=14,80, 1,07 Hz), 2,69 - 3,04 (5 H, m), 2,15 - 2,25 (1 H, m), 2,09 (1 H, s ancho), 1,98 - 2,02 (4 H + HOD, m), 1,64 - 1,74 (1 H, m), 1,42 - 1,61 (2 H, m). MS (LC/MS) T. R. = 0,76; $[M+H]^+$ = 329,40.

EJEMPLO 35

(R)-1-(5-(4H-1'-Azaspiro[oxazol-5,3'-biciclo[2.2.2]octano]-2-ilamino)pirazin-2-il)pirrolidin-2-ona

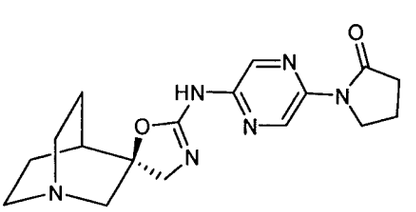


Etapa A: 1-(5-Aminopirazin-2-il)pirrolidin-2-ona



Una mezcla de 5-bromopirazin-2-amina (5 g, 29 mmol), pirrolidin-2-ona (11 ml, 144 mmol), yoduro de cobre (I) (1,1 g, 5,75 mmol), carbonato potásico (7,94 g, 57,5 mmol), y (1R,2R)-ciclohexano-1,2-diamina (1,38 ml, 11,49 mmol) se llevó a reflujo en nitrógeno en dioxano (100 ml) durante 18 h. Después de enfriar, se añadieron a la reacción 200 ml de acetato de etilo y 20 ml de metanol. Este material se filtró a través de celite, se concentró y se absorbió sobre sulfato sódico para la purificación por cromatografía en columna (0-5% de metanol/cloruro de metileno). El producto purificado se recristalizó en éter/acetato de etilo proporcionando 1-(5-aminopirazin-2-il)pirrolidin-2-ona (1,57 g, 8,81 mmol, 30,7 % de rendimiento). RMN de ^{1}H (400 MHz, *DMSO-d$_6$*) δ ppm 8,74 (1 H, d, *J*=1,51 Hz), 7,69 (1 H, d, *J*=1,51 Hz), 6,20 (2 H, s), 3,84 (2 H, t, *J*=7,05 Hz), 2,49 (2 H, t, *J*=7,93 Hz), 2,04 (2 H, dc, *J*=7,68, 7,51 Hz). MS (LC/MS) T. R. = 0,48; $[M+H]^+$ = 179,27.

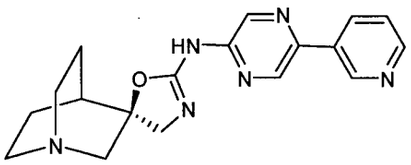
Etapa B: (R)-1-(5-(4H-1'-Azaspiro[oxazol-5,3'-biciclo[2.2.2]octano]-2-ilamino)pirazin-2-il)pirrolidin-2-ona



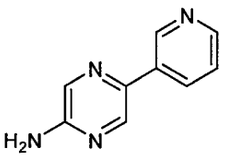
(R)-1-(5-(4H-1'-Azaspiro[oxazol-5,3'-biciclo[2.2.2]octano]-2-ilamino)pirazin-2-il)pirrolidin-2-ona se preparó a partir de 1-(5-aminopirazin-2-il)pirrolidin-2-ona siguiendo los procedimientos generales del **Ejemplo 23, Etapas A-B.** RMN de ^{1}H (500 MHz, *CDCl$_3$*) δ ppm 9,20 (1 H, d, *J*=1,22 Hz), 8,91 (1 H, s ancho), 8,13 (1 H, s), 4,02 (2 H, t, *J*=7,02 Hz), 3,92 (1 H, d, *J*=9,46 Hz), 3,58 (1 H, d, *J*=9,16 Hz), 3,33 (1 H, dd, *J*=14,95, 1,53 Hz), 2,71 - 3,01 (5 H, m), 2,63 (2 H, t, *J*=8,09 Hz), 2,08 - 2,23 (4 H, m), 1,66 - 1,76 (1 H, m), 1,42 - 1,61 (2 H, m). MS (LC/MS) T. R. = 0,67; $[M+H]^+$ = 343,30.

EJEMPLO 36

(R)-N-(5-(Piridin-3-il)pirazin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



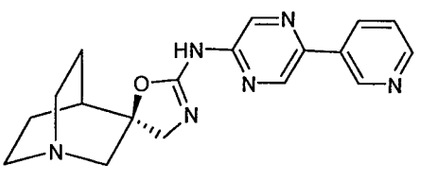
Etapa A: 5-(Piridin-3-il)pirazin-2-amina



Se añadieron ácido piridin-3-ilborónico (307 mg, 2,50 mmol), 5-bromopirazin-2-amina (391 mg, 2,25 mmol) y diclorobis(trifenilfosfina)-paladio(II) (88 mg, 0,13 mmol) a dioxano desgasificado (12 ml) y la mezcla se agitó durante 30 min. A continuación se añadieron carbonato sódico (795 mg, 7,50 mmol) y agua desgasificada (8 ml) y la reacción se calentó en un vial de

reacción cerrado a 100 °C durante 8 h. La reacción se dejó reposar a temperatura ambiente durante el fin de semana. Se diluyó en acetato de etilo (100 ml) y se extrajo con salmuera (3 x 25 ml). Las fases orgánicas se secaron sobre sulfato sódico y se concentraron a vacío. El producto bruto se purificó por cromatografía en columna (0 a 5% de metanol/acetato de etilo) proporcionando 5-(piridin-3-il)pirazin-2-amina (235 mg, 1,37 mmol, 54,6 % de rendimiento). RMN de ^{1}H (400 MHz, *Acetona*) δ ppm 9,13 (1 H, d, *J*=1,51 Hz), 8,54 (1 H, d, *J*=1,26 Hz), 8,50 (1 H, dd, *J*=4,78, 1,51 Hz), 8,22 - 8,28 (1 H, m), 8,07 (1 H, d, *J*=1,26 Hz), 7,39 (1 H, ddd, *J*=7,87, 4,72, 0,76 Hz), 6,05 (2 H, s ancho). MS (LC/MS) T. R. = 0,58; $[M+H]^+$ = 173,20.

Etapa B: (R)-N-(5-(Piridin-3-il)pirazin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

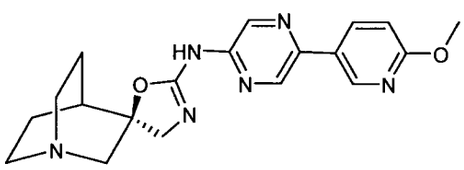


(R)-N-(5-(Piridin-3-il)pirazin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina se preparó a partir de 5-(piridin-3-il)pirazin-2-amina siguiendo los procedimientos generales del **Ejemplo 23, Etapas A-B.** RMN de ^{1}H (400 MHz, *$CDCl_3$*) δ ppm 9,12 (1 H, dd, *J*=2,27, 0,76 Hz), 9,08 (1 H, s ancho), 8,59 (1 H, dd, *J*=4,78, 1,76 Hz), 8,55 (1 H, d, *J*=1,51 Hz), 8,45 (1 H, d, *J*=1,26 Hz), 8,25 (1 H, dt, *J*=7,99, 1,92 Hz), 7,38 (1 H, ddd, *J*=8,06, 4,78, 0,76 Hz), 3,97 (1 H, d, *J*=9,57 Hz), 3,63 (1 H, d, *J*=9,32 Hz), 3,36 (1 H, dd, *J*=14,86, 1,76 Hz), 2,69 - 3,06 (5 H, m), 2,14 - 2,24 (1 H, m), 2,12 (1 H, s ancho), 1,66 - 1,77 (1 H, m, *J*=13,94, 9,66, 4,31, 4,31 Hz), 1,44 - 1,62 (2 H, m). MS (LC/MS) T.

R. = 0,65; $[M+H]^+$ = 337,30.

Ejemplo 37

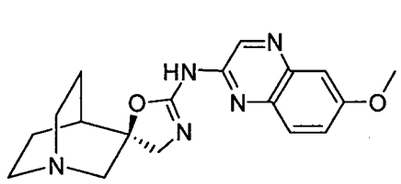
(R)-N-(5-(6-Metoxipiridin-3-il)pirazin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



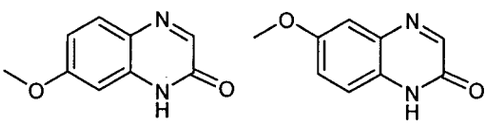
(R)-N-(5-(6-Metoxipiridin-3-il)pirazin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina se preparó a partir de 5-bromopirazin-2-amina siguiendo los procedimientos generales del **Ejemplo 36, Etapas A-B.** RMN de ^{1}H (400 MHz, *$CDCl_3$*) δ ppm 9,04 (1 H, s ancho), 8,66 (1 H, d, *J*=2,01 Hz), 8,46 (1 H, d, *J*=1,51 Hz), 8,41 (1 H, d, *J*=1,01 Hz), 8,15 (1 H, dd, *J*=8,81, 2,52 Hz), 6,82 (1 H, d, *J*=8,31 Hz), 3,97 (3 H, s), 3,95 (1 H, d, *J*=9,57 Hz), 3,61 (1 H, d, *J*=9,32 Hz), 3,35 (1 H, dd, *J*=14,86, 1,51 Hz), 2,68 - 3,07 (5 H, m), 2,14 - 2,24 (1 H, m, *J*=13,27, 9,93, 3,53, 3,38, 3,38 Hz), 2,11 (1 H, s ancho), 1,67 - 1,77 (1 H, m), 1,45 - 1,61 (2 H, m). MS (LC/MS) T. R. = 0,81; $[M+H]^+$ = 367,40.

EJEMPLO 38

(R)-N-(6-Metoxiquinoxalin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

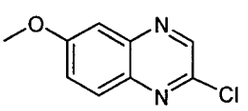


Etapa A: 7-Metoxiquinoxalin-2(1H)-ona y 6-metoxiquinoxalin-2(1H)-ona



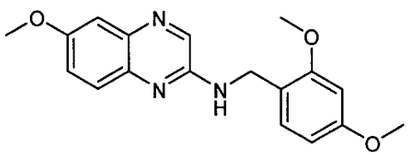
Una solución al 50% de 2-oxoacetato de etilo (18,47 ml, 93 mmol) en tolueno se añadió a una solución de 4-metoxibenceno-1,2-diamina (10,73 g, 78 mmol) en etanol (100 ml) a temperatura ambiente y la reacción se llevó a reflujo durante 2 h. La reacción se concentró a vacío y cristalizó en etanol proporcionando una mezcla de 6-metoxiquinoxalin-2(1H)-ona y 7-metoxiquinoxalin-2(1H)-ona (5,73 g, 32,50 mmol, 42 % de rendimiento). MS (LC/MS) T. R. = 0,68; $[M+H]^+$ = 177,10.

Etapa B: 2-Cloro-6-metoxiquinoxalina



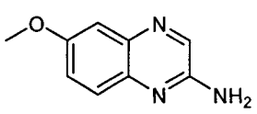
Una mezcla de 6-metoxiquinoxalin-2(1H)-ona y 7-metoxiquinoxalin-2(1H)-ona (5,67 g, 32,20 mmol) se llevó a reflujo en oxicloruro de fósforo (120 ml) durante 1 h. La reacción se concentró y inactivó mediante adición de hielo, luego se basificó con carbonato sódico, y se extrajo con acetato de etilo (3 x 200 ml). Las fases orgánicas se reunieron y concentraron a vacío. El producto bruto se absorbió sobre sulfato sódico y se purificó por cromatografía en columna (0 a 5% de acetato de etilo/hexanos) proporcionando 2-cloro-6-metoxiquinoxalina (2,21 g, 11,36 mmol, 35% de rendimiento). RMN de ^{1}H (400 MHz, *CDCl$_3$*) δ ppm 8,69 (s, 1 H), 7,88 (d, *J*=9,32 Hz, 1 H), 7,43 (dd, *J*=9,32, 2,77 Hz, 1 H), 7,37 (d, *J*=2,77 Hz, 1 H), 3,95 (s, 3 H).

Etapa C: N-(2,4-Dimetoxibencil)-6-metoxiquinoxalin-2-amina



Se trataron en microondas 2-cloro-6-metoxiquinoxalina (0,93 g, 4,77 mmol) y (2,4-dimetoxifenil)metanamina (2,2 ml, 14,64 mmol) en dimetilsulfóxido (5 ml) durante 30 min a 150 °C. La reacción se diluyó en acetato de etilo (250 ml) y se extrajo con salmuera (3 x 100 ml). El producto bruto se purificó por cromatografía en columna (20 a 80% de acetato de etilo/hexanos) proporcionando N-(2,4-dimetoxibencil)-6-metoxiquinoxalin-2-amina (1,46 g, 87% de rendimiento). RMN de ^{1}H (400 MHz, *CDCl$_3$*) δ ppm 8,13 (1 H, s), 7,59 - 7,63 (1 H, m), 7,30 (1 H, d, *J*=8,31 Hz), 7,21 - 7,24 (2 H, m), 6,47 (1 H, d, *J*=2,27 Hz), 6,42 (1 H, dd, *J*=8,31, 2,27 Hz), 5,10 (1 H, t, *J*=5,92 Hz), 4,61 (2 H, d, *J*=5,79 Hz), 3,88 (3 H, s), 3,84 (3 H, s), 3,78 (3 H, s). MS (LC/MS) T. R. = 1,95; $[M+H]^+$ = 326,23.

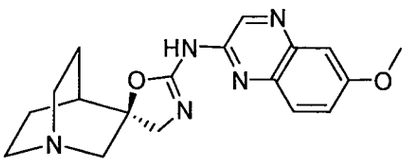
Etapa D: 6-Metoxiquinoxalin-2-amina



Se agitó N-(2,4-dimetoxibencil)-6-metoxiquinoxalin-2-amina (2,8 g, 8,61 mmol) en TFA (10 ml, 130 mmol) y diclorometano (10 ml) a temperatura ambiente durante 30 min. Los disolventes se eliminaron a vacío. Se añadió al residuo rojo hidrógenocarbonato sódico acuoso (200 ml), que luego precipitó en un sólido amarillo. La mezcla se extrajo de forma extensiva con diclorometano. La fase orgánica se secó sobre sulfato sódico, se filtró y se concentró a vacío

proporcionando 6-metoxiquinoxalin-2-amina (1,50 g, 8,56 mmol, 99 % de rendimiento). RMN de ^{1}H (400 MHz, *CDCl$_3$*) δ ppm 8,27 (1 H, s), 7,54 - 7,58 (1 H, m), 7,25 - 7,29 (2 H, m), 4,71 (2 H, s ancho), 3,90 (3 H, s). MS (LC/MS) T. R. = 0,86; $[M+H]^+$ = 176,23.

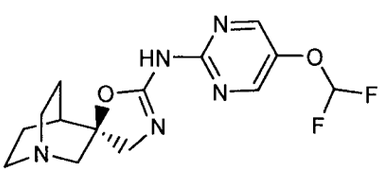
Etapa E: (R)-N-(6-Metoxiquinoxalin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



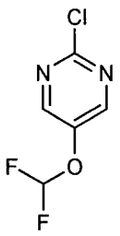
(R)-N-(6-Metoxiquinoxalin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina se preparó a partir de 6-metoxiquinoxalin-2-amina siguiendo los procedimientos generales del **Ejemplo 23, Etapas A-B**. RMN de ^{1}H (400 MHz, *CDCl$_3$*) δ ppm 9,61 (1 H, s ancho), 8,57 (1 H, s), 7,62 (1 H, d, *J*=9,06 Hz), 7,23 - 7,32 (2 H, m), 4,01 (1 H, d, *J*=9,32 Hz), 3,90 (3 H, s), 3,66 (1 H, d, *J*=9,32 Hz), 3,37 (1 H, dd, *J*=14,86, 1,51 Hz), 2,68 - 3,08 (5 H, m), 2,15 - 2,25 (1 H, m), 2,10 - 2,14 (1 H, m), 1,67 - 1,77 (1 H, m), 1,42 - 1,63 (2 H, m). MS (LC/MS) T. R. = 0,81; $[M+H]^+$ = 340,30.

EJEMPLO 39

(R)-N-(5-(Difluorometoxi)pirimidin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

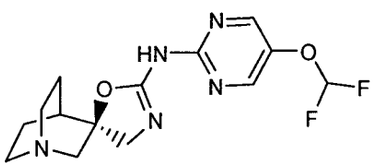


Etapa A: 2-Cloro-5-(Difluorometoxi)pirimidina



Se calentaron hasta 90ºC durante 24 horas 2-cloropirimidin-5-ol (1 g, 7,66 mmol) y 2-cloro-2,2-difluoroacetato sódico (3,50 g, 22,98 mmol) en N,N-dimetilformamida (20 ml) y agua (0,2 ml) y se concentró a vacío. El residuo se purificó por cromatografía en columna (5-30% de acetato de etilo/hexanos) proporcionando 2-cloro-5-(difluorometoxi)pirimidina (549 mg, 3,04 mmol, 39,7 % de rendimiento) como un aceite amarillo pálido. MS (LC/MS) T. R. = 1,32; $[M+H]^+$ = 181,14.

Etapa B: (R)-N-(5-(Difluorometoxi)pirimidin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

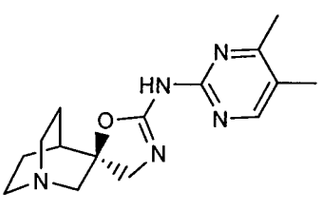


(R)-N-(5-(Difluorometoxi)pirimidin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina se preparó a partir de 2-cloro-5-(difluorometoxi)pirimidina siguiendo los procedimientos generales del **Ejemplo 23, Etapas A-B**. RMN de ^{1}H (400 MHz, *MeO-d$_4$*) δ ppm 8,46 (2 H, s), 6,85 (1 H, t), 4,02 (1 H, d, *J*=10,07 Hz), 3,73 (1 H, d, *J*=10,32 Hz), 3,28 (1 H, d, *J*=1,01

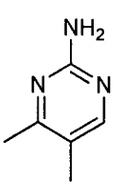
Hz), 3,16 (1 H, d), 2,81 - 3,05 (4 H, m), 2,08 - 2,25 (2 H, m), 1,46 - 1,89 (3 H, m). MS (LC/MS) T. R. = 0,53; $[M+H]^+$ = 326,30.

EJEMPLO 40

(R)-N-(4,5-Dimetilpirimidin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

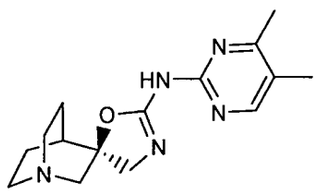


Etapa A: 4,5-Dimetilpirimidin-2-amina



Una solución de 4-cloro-5,6-dimetilpirimidin-2-amina (0,35 g, 2,22 mmol) en amoníaco 2M en metanol (100 ml) se cubrió con nitrógeno y se añadió paladio sobre carbón (0,035 g, 0,33 mmol), se cubrió con nitrógeno y la reacción se sometió a hidrogenación a 1 atm, temperatura ambiente durante 18 h. La mezcla de reacción se cubrió con nitrógeno y se filtró a través de celite y la almohadilla de celite se lavó con metanol. El filtrado se evaporó hasta sequedad a vacío proporcionando 4,5-dimetilpirimidin-2-amina (0,35 g, 2,56 mmol, 90 % de rendimiento) que se usó sin purificación posterior. RMN de ^1H (400 MHz, *DMSO-d_6*) δ ppm 7,89 (1 H, s), 6,19 (2 H, s), 2,18 (3 H, s), 1,99 (3 H, s). MS (LC/MS) T. R. = 0,56; $[M+H]^+$ = 124,20.

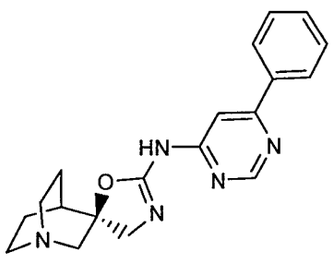
Etapa B: (R)-N-(4,5-Dimetilpirimidin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



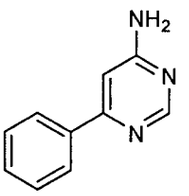
(R)-N-(4,5-Dimetilpirimidin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina se preparó a partir de 4,5-dimetilpirimidin-2-amina siguiendo los procedimientos generales del **Ejemplo 23, Etapas A-B**. RMN de ^{1}H (400 MHz, *MeOD-d$_4$*) δ ppm 8,22 (1 H, s), 4,01 (1 H, d, *J*=10,07 Hz), 3,73 (1 H, d, *J*=10,32 Hz), 3,40 (1 H, d), 3,25 (1 H, d), 2,91 - 3,12 (4 H, m), 2,41 (3 H, s), 2,09 - 2,28 (5 H, m), 1,62 - 1,97 (3 H, m). MS (LC/MS) T. R. = 0,47; $[M+H]^+$ = 288,31.

EJEMPLO 41

(R)-N-(6-Fenilpirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

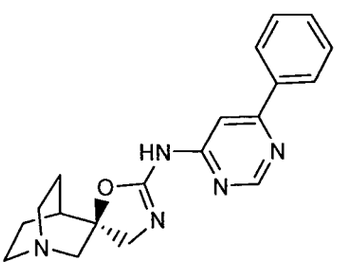


Etapa A: 6-Fenilpirimidin-4-amina



Se suspendió una mezcla de 6-cloropirimidin-4-amina (0,32 g, 2,5 mmol), ácido fenilbórico (0,38 g, 3,13 mmol), carbonato sódico acuoso saturado (0,80 g, 7,50 mmol) y cloruro de bis(trifenilfosfina)paladio(II) (0,035 g, 0,05 mmol) en una mezcla de dimetoxietano (15 ml)/etanol (2 ml)/agua (2 ml). La mezcla se calentó en el microondas a 125 °C durante 20 min y luego se concentró a vacío. El residuo se purificó por cromatografía en columna (acetato de etilo del 10-60%/hexanos) proporcionando 6-fenilpirimidin-4-amina (167 mg, 0,98 mmol, 39 % de rendimiento) como un sólido blanquecino. MS (LC/MS) T. R. = 0,99; $[M+H]^+$ = 172,23.

Etapa B: (R)-N-(6-Fenilpirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

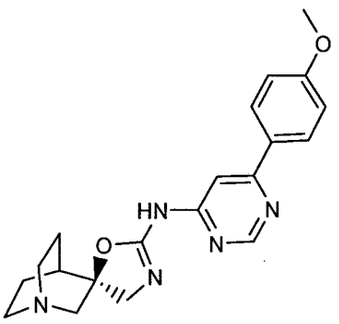


(R)-N-(6-Fenilpirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina se preparó a partir de 6-fenilpirimidin-4-amina siguiendo los procedimientos generales del **Ejemplo 23, Etapas A-B**. RMN de ^{1}H (400 MHz, *MeOD-d$_4$*) δ ppm 9,54 (1 H, d, *J*=1,01 Hz), 8,75 - 8,86 (2 H, m),

8,18 - 8,28 (3 H, m), 8,00 (1 H, s ancho), 4,70 (1 H, d, *J*=10,32 Hz), 4,43 (1 H, d, *J*=10,58 Hz), 3,72 - 3,88 (2 H, m), 3,41 - 3,63 (4 H, m), 2,63 - 2,87 (2 H, m), 2,18 - 2,48 (3 H, m). MS (LC/MS) T. R. = 1,36; $[M+H]^+$ = 336,24.

EJEMPLO 42

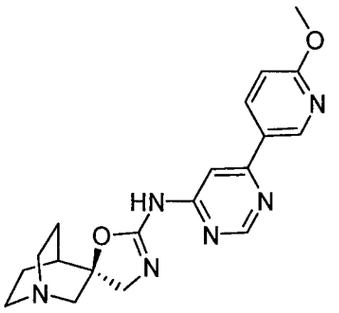
(R)-N-(6-(4-Metoxifenil)pirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



(R)-N-(6-(4-Metoxifenil)pirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina se preparó a partir de 6-cloropirimidin-4-amina siguiendo los procedimientos generales del **Ejemplo 41, Etapas A-B**. RMN de ^{1}H (400 MHz, *MeOD-d$_4$*) δ ppm 8,72 (1 H, d, *J*=1,26 Hz), 7,90 - 8,00 (2 H, m), 7,16 (1 H, s ancho), 6,96 - 7,05 (2 H, m), 4,04 (1 H, d, *J*=10,07 Hz), 3,84 (3 H, s), 3,73 (1 H, d, *J*=10,07 Hz), 3,22 (1 H, d), 3,09 (1 H, d), 2,73 - 2,98 (4 H, m), 2,02 - 2,21 (2 H, m), 1,51 - 1,85 (3 H, m). MS (LC/MS) T. R. = 1,44; $[M+H]^+$ = 366,28.

Ejemplo 43

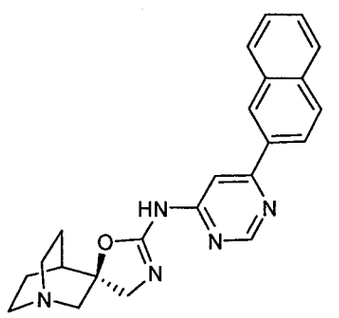
(R)-N-(6-(6-Metoxipiridin-3-il)pirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



(R)-N-(6-(6-Metoxipiridin-3-il)pirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina se preparó a partir de 6-cloropirimidin-4-amina siguiendo los procedimientos generales del **Ejemplo 41, Etapas A-B**. RMN de ^{1}H (400 MHz, *MeOD-d$_4$*) δ ppm 8,79 (2 H, dd, *J*=19,01, 1,89 Hz), 8,27 (1 H, dd, *J*=8,56, 2,52 Hz), 7,18 (1 H, s ancho), 6,89 (1 H, d, *J*=8,81 Hz), 4,05 (1 H, d, *J*=10,32 Hz), 3,96 (3 H, s), 3,74 (1 H, d, *J*=10,32 Hz), 3,23 (1 H, d), 3,10 (1 H, d), 2,73 - 2,99 (4 H, m), 2,02 - 2,21 (2 H, m), 1,53 - 1,84 (3 H, m). MS (LC/MS) T. R. = 1,34; $[M+H]^+$ = 367,25.

EJEMPLO 44

(R)-N-(6-(Naftalen-2-il)pirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

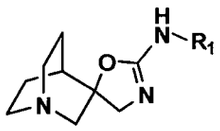


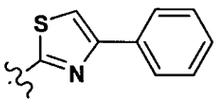
(R)-N-(6-(Naftalen-2-il)pirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina se preparó a partir de 6-cloropirimidin-4-amina

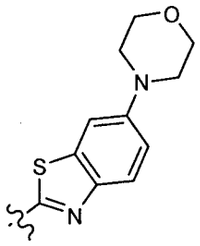
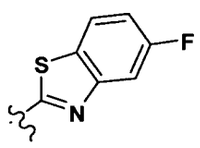
siguiendo los procedimientos generales del **Ejemplo 41, Etapas A-B**. RMN de ^{1}H (400 MHz, *MeOD-d$_4$*) δ ppm 8,83 (1 H, s), 8,56 (1 H, s), 7,83 - 8,13 (4 H, m), 7,49 - 7,58 (2 H, m), 7,37 (1 H, s ancho), 4,06 (1 H, d, *J*=10,32 Hz), 3,76 (1 H, d, *J*=10,32 Hz), 3,23 (1 H, s), 3,12 (1 H, d), 2,75 - 3,00 (4 H, m), 2,02 - 2,24 (2 H, m), 1,56 - 1,84 (3 H, m). MS (LC/MS) T. R. = 1,93; $[M+H]^+$ = 386,31.

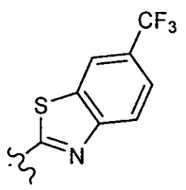
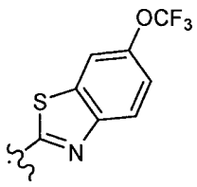
Los compuestos de la Tabla 2 se sintetizaron de acuerdo con el procedimiento del Ejemplo 1 usando el isotiocianato o amina disponible comercialmente apropiado. Los intermedios que contienen amida se obtuvieron por los procedimientos descritos en el Ejemplo 3.

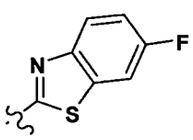
Tabla 2.

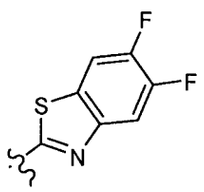
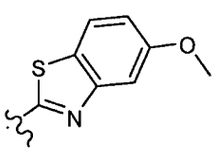


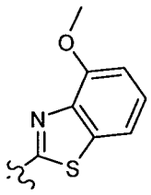
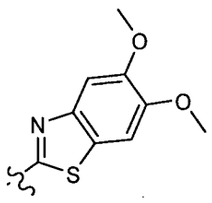
Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
45		1,48	341,3	RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 8,60 (1 H, s ancho), 7,94 (2 H, d, *J*=7,63 Hz), 7,43 (1 H, s), 7,39 (2 H, t, *J*=7,78 Hz), 7,28 (1 H, t, *J*=7,32 Hz), 3,86 (1 H, d, *J*=9,77 Hz), 3,60 (1 H, d, *J*=9,77 Hz), 2,98 - 3,06 (2 H, m), 2,71 - 2,85 (2 H, m), 2,66 (2 H, t, *J*=7,78 Hz), 2,05 (1 H, s ancho), 1,91 (1 H, s ancho), 1,53 - 1,64 (2 H, m), 1,48 (1 H, td, *J*=9,99, 7,78 Hz)

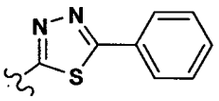
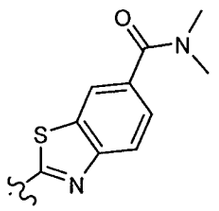
Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
46		1,41	400,4	RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 8,86 (1 H, s ancho), 7,47 (1 H, d, *J*=8,85 Hz), 7,33 (1 H, d, *J*=2,44 Hz), 7,01 (1 H, dd, *J*=8,85, 2,75 Hz), 3,87 (1 H, d, *J*=10,07 Hz), 3,71 - 3,77 (4 H, m), 3,61 (1 H, d, *J*=9,77 Hz), 3,06 - 3,12 (4 H, m), 3,01 (2 H, s), 2,72 - 2,86 (2 H, m), 2,66 (2 H, t, *J*=7,63 Hz), 2,05 (1 H, s ancho), 1,91 (1 H, s ancho), 1,53 - 1,64 (2 H, m), 1,43 - 1,52 (1 H, m)
47		1,31	333,3	RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 9,03 (1 H, s ancho), 7,80 (1 H, dd, *J*=8,70, 5,65 Hz), 7,37 (1 H, dd, *J*=10,38, 2,44 Hz), 7,04 (1 H, td, *J*=9,08, 2,59 Hz), 3,89 (1 H, d, *J*=10,07 Hz), 3,64 (1 H, d, *J*=10,07 Hz), 3,03 (2 H, d, *J*=2,75 Hz), 2,74 - 2,85 (2 H, m), 2,62 - 2,70 (2 H, m), 2,07 (1 H, d, *J*=2,44 Hz), 1,90 (1 H, d, *J*=8,85 Hz), 1,54 - 1,64 (2 H, m), 1,43 - 1,53 (1 H, m)

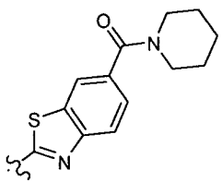
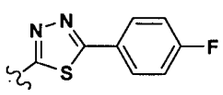
Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
48		2,07	383,3	RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 8,00 (1 H, s), 7,41 - 7,54 (2 H, m), 3,89 (1 H, d, *J*=11,29 Hz), 3,57 (1 H, d, *J*=11,60 Hz), 2,96 - 3,03 (1 H, m), 2,88 - 2,93 (1 H, m), 2,73 - 2,81 (2 H, m), 2,64 (2 H, dd, *J*=8,85, 5,19 Hz), 1,93 (2 H, s ancho), 1,56 (2 H, s ancho), 1,38 - 1,50 (1 H, m)
49		2,15	399,4	RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 9,03 (1 H, s ancho), 7,91 (1 H, s ancho), 7,65 (1 H, d, *J*=8,85 Hz), 7,30 (1 H, d, *J*=7,63 Hz), 3,89 (1 H, d, *J*=10,07 Hz), 3,64 (1 H, d, *J*=10,07 Hz), 2,97 - 3,09 (2 H, m), 2,80 (2 H, d, *J*=8,55 Hz), 2,66 (2 H, t, *J*=7,48 Hz), 2,08 (1 H, s ancho), 1,93 (1 H, s ancho), 1,54 - 1,66 (2 H, m), 1,44 - 1,54 (1 H, m)

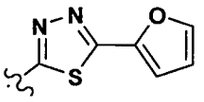
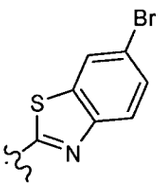
Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
50		1,89	333,1	RMN de ^1H (500 MHz, MeOD) δ ppm 7,51 - 7,58 (1 H, m), 7,17 - 7,25 (1 H, m), 7,08 - 7,16 (1 H, m), 4,04 - 4,13 (1 H, m), 3,72 - 3,82 (1 H, m), 3,30 (1 H, s ancho), 3,17 (1 H, d, *J*=14,95 Hz), 3,01 (2 H, t, *J*=7,48 Hz), 2,80 - 2,92 (2 H, m), 2,12 - 2,27 (2 H, m), 1,66 - 1,88 (3 H, m)
51		1,24	333,4	RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 8,95 (1 H, s ancho), 7,66 - 7,77 (1 H, m), 7,52 - 7,63 (1 H, m), 7,08 - 7,24 (1 H, m), 3,88 (1 H, d, *J*=9,77 Hz), 3,63 (1 H, d, *J*=9,77 Hz), 3,03 (2 H, s ancho), 2,78 (2 H, s ancho), 2,66 (2 H, t, *J*=7,17 Hz), 2,06 (1 H, s ancho), 1,91 (1 H, s ancho), 1,39 - 1,67 (3 H, m)

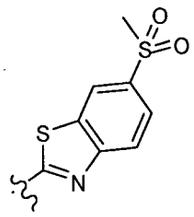
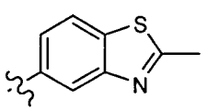
Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
52		2,05	351,2	RMN de ^1H (500 MHz, DMSO-d_6)δppm 9,01 (1 H, s ancho), 7,88 - 8,00 (1 H, m), 7,53 - 7,64 (1 H, m), 3,88 (1 H, d, *J*=10,07 Hz), 3,63 (1 H, d, *J*=10,07 Hz), 2,98 - 3,08 (2 H, m), 2,72 - 2,87 (2 H, m), 2,66 (2 H, t, *J*=7,17 Hz), 2,07 (1 H, s ancho), 1,92 (1 H, s ancho), 1,42 - 1,65 (3 H, m)
53		1,80	345,3	RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 9,03 (s, 1 H), 7,65 (d, *J*=8,55 Hz, 1 H), 7,19 (d, *J*=2,44 Hz, 1 H), 6,82 (dd, *J*=8,70, 2,59 Hz, 1 H), 3,90 (d, *J*=10,07 Hz, 1 H), 3,79 (s, 3 H), 3,64 (d, *J*=10,07 Hz, 1 H), 3,04 (d, *J*=2,44 Hz, 2 H), 2,75 - 2,84 (m, 2 H), 2,67 (t, *J*=7,78 Hz, 2 H), 2,07 (s, 1 H), 1,92 (s, 1 H), 1,55 - 1,63 (m, 2 H), 1,49 (dd, *J*=9,77, 2,75 Hz, 1 H)

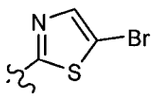
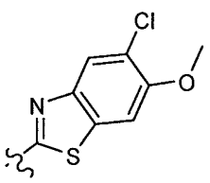
Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
54		1,23	345,2	RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 8,83 (s, 1 H), 7,37 (d, *J*=7,94 Hz, 1 H), 7,14 (t, *J*=7,93 Hz, 1 H), 6,92 (d, *J*=7,93 Hz, 1 H), 3,89 - 3,95 (m, 4 H), 3,66 (d, *J*=10,07 Hz, 1 H), 3,00 - 3,08 (m, 2 H), 2,76 - 2,85 (m, 2 H), 2,67 (t, *J*=7,78 Hz, 2 H), 2,08 (s, 1 H), 1,93 (d, *J*=3,66 Hz, 1 H), 1,60 (ddd, *J*=15,26, 6,87, 3,20 Hz, 2 H), 1,50 (ddd, *J*=7,48, 5,19, 2,59 Hz, 1 H)
55		1,72	375,2	RMN de ^1H (500 MHz, DMSO-d_6) δppm 8,89 (s, 1 H), 7,40 (s, 1 H), 7,22 (s, 1 H), 3,87 (d, *J*=10,07 Hz, 1 H), 3,79 (d, *J*=8,55 Hz, 6 H), 3,62 (d, *J*=10,07 Hz, 1 H), 2,99 - 3,07 (m, 2 H), 2,75 - 2,84 (m, 2 H), 2,67 (t, *J*=7,63 Hz, 2 H), 2,06 (s, 1 H), 1,93 (s, 1 H), 1,56 - 1,64 (m, 2 H), 1,46 - 1,55 (m, 1 H)

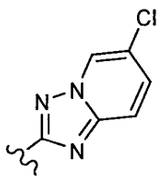
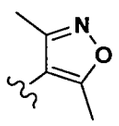
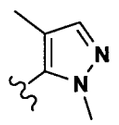
Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
56		2,14	342,1	RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 8,75 (s, 1 H), 7,84 (dd, *J*=7,93, 1,53 Hz, 3 H), 7,46 - 7,53 (m, 5 H), 3,85 (d, *J*=9,77 Hz, 2 H), 3,60 (d, *J*=10,07 Hz, 2 H), 3,01 - 3,09 (m, 3 H), 2,84 (t, *J*=7,78 Hz, 3 H), 2,67 (t, *J*=7,78 Hz, 3 H), 2,09 (s, 2 H), 1,91 - 1,99 (m, 2 H), 1,53 - 1,62 (m, 3 H)
57		1,04	386,2	RMN de ^1H (400 MHz, DMSO-d_6) δ ppm 9,05 (1 H, s ancho), 7,86 (1 H, d, *J*=1,51 Hz), 7,60 (1 H, d, *J*=8,06 Hz), 7,36 (1 H, dd, *J*=8,31, 1,76 Hz), 3,90 (1 H, d, *J*=10,07 Hz), 3,65 (1 H, d, *J*=10,07 Hz), 3,03 (2 H, s), 2,97 (6 H, s), 2,72 - 2,87 (2 H, m), 2,66 (2 H, t, *J*=7,68 Hz), 2,07 (1 H, s ancho), 1,92 (1 H, s ancho), 1,55 - 1,64 (2 H, m), 1,44 - 1,54 (1 H, m)

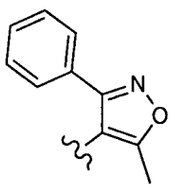
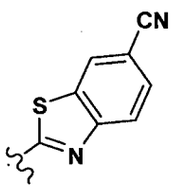
Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
58		1,57	426,2	RMN de ^1H (400 MHz, DMSO-d_6) δ ppm 9,06 (1 H, s ancho), 7,83 (1 H, d, *J*=1,51 Hz), 7,61 (1 H, d, *J*=8,31 Hz), 7,32 (1 H, dd, *J*=8,31, 1,76 Hz), 3,90 (1 H, d, *J*=10,07 Hz), 3,65 (1 H, d, *J*=10,07 Hz), 3,37 - 3,57 (4 H, m), 3,04 (2 H, d, *J*=1,76 Hz), 2,73 - 2,86 (2 H, m), 2,66 (2 H, t, *J*=7,68 Hz), 2,07 (1 H, d, *J*=2,52 Hz), 1,92 (1 H, dd, *J*=8,18, 5,67 Hz), 1,43 - 1,67 (9 H, m)
59		2,17	360,1	RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 8,74 (s, 1 H), 7,86 - 7,92 (m, 2 H), 7,31 - 7,37 (m, 2 H), 3,85 (d, *J*=9,77 Hz, 1 H), 3,60 (d, *J*=9,77 Hz, 1 H), 3,00 - 3,09 (m, 2 H), 2,84 (t, *J*=7,48 Hz, 2 H), 2,67 (t, *J*=7,32 Hz, 2 H), 2,09 (d, *J*=1,83 Hz, 1 H), 1,89 - 1,98 (m, 1 H), 1,55 - 1,61 (m, 2 H), 1,51 - 1,54 (m, *J*=11,29 Hz, 1 H)

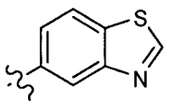
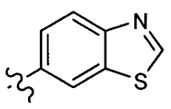
Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
60		1,67	332,2	RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 7,87 (s, 1 H), 7,01 (d, *J*=3,05 Hz, 1 H), 6,68 (dd, *J*=3,51, 1,68 Hz, 1 H), 3,84 (d, *J*=10,38 Hz, 1 H), 3,58 (d, *J*=10,07 Hz, 1 H), 3,03 (d, *J*=11,29 Hz, 2 H), 2,78 - 2,86 (m, 2 H), 2,66 (t, *J*=7,48 Hz, 2 H), 2,06 (s, 1 H), 1,87 - 1,96 (m, 1 H), 1,55 - 1,61 (m, 2 H), 1,51 - 1,54 (m, 1 H)
61		1,83	393,0	RMN de ^1H (400 MHz, DMSO-d_6) δ ppm 9,02 (1 H, s ancho), 8,04 (1 H, d, *J*=2,01 Hz), 7,49 - 7,53 (1 H, m), 7,43 - 7,47 (1 H, m), 3,88 (1 H, d, *J*=10,07 Hz), 3,63 (1 H, d, *J*=10,07 Hz), 3,02 (2 H, s), 2,74 - 2,84 (2 H, m), 2,65 (2 H, t, *J*=7,68 Hz), 2,06 (1 H, d, *J*=2,52 Hz), 1,89 (1 H, s ancho), 1,42 - 1,64 (3 H, m)

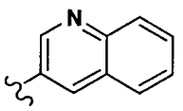
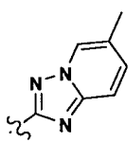
Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
62		1,16	391,1	RMN de ^1H (400 MHz, DMSO-d_6) δ ppm 9,21 (1 H, s ancho), 8,40 (1 H, d, *J*=1,51 Hz), 7,80 - 7,85 (1 H, m), 7,72 - 7,77 (1 H, m), 3,92 (1 H, d, *J*=10,32 Hz), 3,67 (1 H, d, *J*=10,07 Hz), 3,21 (3 H, s), 3,05 (2 H, d, *J*=4,03 Hz), 2,82 (2 H, d, *J*=6,80 Hz), 2,67 (2 H, t, *J*=7,43 Hz), 2,10 (1 H, s ancho), 1,94 (1 H, d, *J*=3,27 Hz), 1,45 - 1,66 (3 H, m)
63		1,35	329,1	RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 8,54 (s, 1 H), 7,32 (s, 1 H), 3,79 (d, *J*=10,07 Hz, 1 H), 3,54 (d, *J*=10,07 Hz, 1 H), 2,98 - 3,05 (m, 2 H), 2,76 - 2,85 (m, 2 H), 2,66 (t, *J*=7,63 Hz, 2 H), 2,05 (s, 1 H), 1,87 - 1,95 (m, 1 H), 1,41 - 1,68 (m, 3 H)

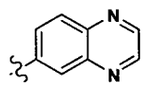
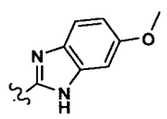
Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
64		1,02	349,9	RMN de ^1H (500 MHz, DMSO-d_6) δppm 8,54 (s, 1 H), 7,32 (s, 1 H), 3,67 (dd, *J*=126,04, 10,07 Hz, 2 H), 2,92 - 3,09 (m, 2 H), 2,72 - 2,91 (m, 2 H), 2,60 - 2,73 (m, *J*=7,63, 7,63 Hz, 2 H), 2,00 - 2,12 (m, 1 H), 1,81 - 1,99 (m, 1 H), 1,35 - 1,69 (m, 3 H)
65		2,14	380	RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 8,93 (s, 1 H), 7,54 - 7,76 (m, *J*=10,53, 3,81 Hz, 2 H), 3,79 - 4,04 (m, 1 H), 3,56 - 3,72 (m, *J*=9,92, 3,20 Hz, 1 H), 3,26 - 3,45 (m, 2 H), 2,98 - 3,12 (m, 2 H), 2,75 - 2,90 (m, 2 H), 2,61 - 2,74 (m, *J*=1,22 Hz, 2 H), 2,09 (s, 1 H), 1,87 - 2,04 (m, 1 H), 1,42 - 1,76 (m, 3 H)

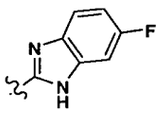
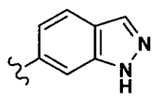
Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
66		1,26	333,1	RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 9,04 (1 H, d, *J*=1,22 Hz), 8,44 (1 H, s ancho), 7,52 - 7,69 (2 H, m), 3,77 - 3,82 (1 H, m), 3,68 (1 H, d, *J*=10,07 Hz), 3,05 - 3,12 (2 H, m), 2,94 - 3,04 (2 H, m), 2,80 - 2,91 (2 H, m), 2,19 (1 H, d, *J*=1,83 Hz), 2,01 (1 H, s ancho), 1,67 - 1,85 (3 H, m)
67		0,28	277,1	RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 6,72 - 7,61 (m, 1 H), 3,49 - 3,70 (m, 1 H), 3,31 - 3,46 (m, 1 H), 2,86 - 3,06 (m, *J*=9,46 Hz, 2 H), 2,56 - 2,84 (m, 4 H), 2,10 - 2,31 (m, 3 H), 1,91 - 2,10 (m, 4 H), 1,70 (s, 1 H), 1,49 - 1,61 (m, 2 H), 1,36 - 1,49 (m, 1 H)
68		0,44	276,2	RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 7,55 (s, 1 H), 5,63 (s, 1 H), 3,57 - 3,74 (m, *J*=8,55 Hz, 1 H), 3,48 (s, 3 H), 2,96 (s, 2 H), 2,72 - 2,88 (m, 2 H), 2,65 (s, 2 H), 1,93 - 2,17 (m, 4 H), 1,86 (s, 1 H), 1,57 (s, 3 H)

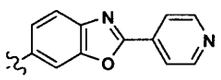
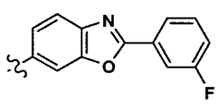
Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
69		1,35	339,1	RMN de ^1H (500 MHz, DMSO-*d6*) δ ppm 7,87 (d, *J*=6,71 Hz, 1 H), 7,80 (d, *J*=7,02 Hz, 2 H), 7,42 - 7,48 (m, 4 H), 3,49 - 3,57 (m, 1 H), 3,25 - 3,33 (m, 4 H), 2,77 (t, *J*=15,41 Hz, 2 H), 2,59 - 2,68 (m, 1 H), 2,49 - 2,57 (m, 15 H), 2,24 - 2,31 (m, 2 H), 2,21 (s, 1 H), 1,94 (s, 1 H), 1,47 (s, 2 H)
70		0,73	340,1	RMN de ^1H (300 MHz, DMSO-d_6) δ ppm 9,20 (1 H, s ancho), 8,29 - 8,42 (1 H, m), 7,63 - 7,76 (2 H, m), 3,91 (1 H, d, *J*=10,25 Hz), 3,66 (1 H, d, *J*=10,25 Hz), 3,05 (2 H, s), 2,74 - 2,90 (2 H, m), 2,66 (2 H, t, *J*=7,68 Hz), 2,09 (1 H, s ancho), 1,92 (1 H, d, *J*=4,03 Hz), 1,42 - 1,66 (3 H, m)

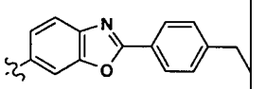
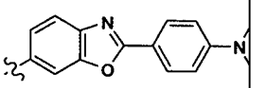
Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
71		1,00	315,1	RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 8,92 (1 H, s), 8,00 (1 H, s ancho), 7,78 (1 H, d, J=8,56 Hz), 7,42 (1 H, d, J=8,06 Hz), 3,92 (1 H, d, J=11,08 Hz), 3,55 (1 H, d, J=10,83 Hz), 3,23 (1 H, d, J=14,86 Hz), 2,83 - 2,90 (2 H, m), 2,65 - 2,83 (2 H, m), 1,89 - 2,17 (3 H, m), 1,41 - 1,75 (3 H, m)
72		0,75	315,1	RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 8,82 (1 H, s), 8,22 (1 H, s), 7,98 (1 H, d, *J*=8,56 Hz), 7,21 - 7,25 (1 H, m), 6,37 (1 H, s ancho), 3,99 (1 H, d, *J*=11,58 Hz), 3,61 (1 H, d, *J*=11,58 Hz), 3,23 (1 H, d, *J*=14,86 Hz), 2,89 (2 H, t, *J*=7,68 Hz), 2,69 - 2,84 (2 H, m), 1,91 - 2,09 (2 H, m), 1,45 - 1,73 (4 H, m)

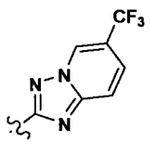
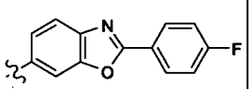
Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
73		0,85	309,2	RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 8,70 (1 H, d, *J*=1,76 Hz), 8,09 (1 H, s ancho), 8,00 (1 H, d, *J*=8,31 Hz), 7,43 - 7,58 (2 H, m), 3,90 (1 H, d, *J*=10,58 Hz), 3,54 (1 H, d, *J*=10,32 Hz), 3,26 (1 H, d, *J*=14,60 Hz), 2,65 - 3,06 (5 H, m), 2,13 (1 H, s ancho), 2,00 (1 H, s ancho), 1,34 - 1,79 (5 H, m)
74		0,65	313,2	RMN de ^1H (500 MHz, MeOD) δ ppm 8,55 (1 H, s), 7,66 - 7,70 (1 H, m), 7,59 - 7,63 (1 H, m), 4,25 (1 H, d, *J*=10,99 Hz), 4,04 (1 H, d, *J*=10,68 Hz), 3,91 (1 H, d, *J*=14,95 Hz), 3,76 (1 H, dd, *J*=14,95, 2,44 Hz), 3,45 - 3,53 (1 H, m), 3,29 - 3,40 (3 H, m), 2,61 (1 H, d, *J*=2,14 Hz), 2,40 (3 H, s), 2,31 (1 H, tt, *J*=10,26, 3,47 Hz), 2,06 - 2,16 (1 H, m, *J*=14,23, 9,35, 4,54, 4,54 Hz), 1,92 - 2,06 (2 H, m)

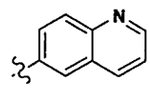
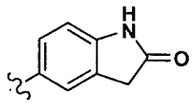
Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
75		1,24	310,1	RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 8,73 (1 H, d, *J*=1,76 Hz), 8,66 (1 H, d, *J*=2,01 Hz), 7,96 (1 H, d, *J*=9,07 Hz), 7,90 (1 H, s ancho), 7,68 (1 H, s ancho), 7,50 (1 H, s ancho), 3,93 (1 H, d, *J*=10,32 Hz), 3,56 (1 H, d, *J*=9,32 Hz), 3,29 (1 H, d, *J*=14,86 Hz), 2,97 (1 H, d, *J*=14,86 Hz), 2,88 - 2,94 (2 H, m), 2,69 - 2,87 (2 H, m), 2,12 (1 H, s ancho), 2,06 (1 H, s ancho), 1,64 - 1,73 (1 H, m), 1,46 - 1,64 (2 H, m)
76		1,58	328,2	RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 11,30 (s, 1 H), 9,16 (s, 1 H), 7,04 - 7,43 (m, 1 H), 6,70 - 7,03 (m, 1 H), 6,54 - 6,69 (m, 1 H), 3,89 (d, *J*=9,77 Hz, 1 H), 3,53 - 3,81 (m, 4 H), 3,01 (s, 2 H), 2,58 - 2,91 (m, 4 H), 2,03 (s, 1 H), 1,78 - 1,96 (m, 1 H), 1,32 - 1,73 (m, 3 H)

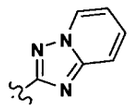
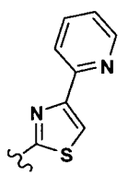
Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
77		1,40	316,1	RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 11,53 (s, 1 H), 9,12 (s, 1 H), 6,94 - 7,46 (m, 2 H), 6,83 (s, 2 H), 3,90 (d, *J*=9,77 Hz, 1 H), 3,64 (d, *J*=9,77 Hz, 1 H), 2,90 - 3,09 (m, 2 H), 2,61 - 2,87 (m, 4 H), 1,95 - 2,10 (m, 1 H), 1,88 (d, *J*=3,05 Hz, 1 H), 1,33 - 1,70 (m, 3 H)
78		0,35	298,1	RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 7,94 (1 H, s), 7,80 (1 H, s ancho), 7,26 - 7,36 (1 H, m), 7,17 - 7,25 (1 H, m), 3,97 (1 H, d, *J*=11,33 Hz), 3,59 (1 H, d, *J*=11,58 Hz), 3,23 (1 H, d, *J*=14,60 Hz), 2,65 - 3,01 (5 H, m), 1,86 - 2,16 (2 H, m), 1,35 - 1,73 (3 H, m)

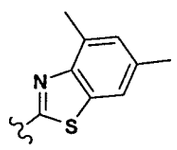
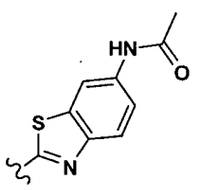
Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
79		1,10	376,1	RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 8,78 (2 H, d, *J*=5,79 Hz), 8,03 (2 H, d, *J*=6,04 Hz), 7,73 (1 H, s ancho), 7,48 (1 H, d, *J*=8,56 Hz), 7,36 (1 H, s ancho), 3,92 (1 H, d, *J*=8,81 Hz), 3,55 (1 H, d, *J*=9,06 Hz), 3,24 (1 H, d, *J*=14,10 Hz), 2,57 - 3,06 (5 H, m), 1,86 - 2,20 (2 H, m), 1,30 - 1,80 (3 H, m)
80		2,36	393,1	RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 8,00 (1 H, d, *J*=7,81 Hz), 7,83 - 7,97 (1 H, m), 7,68 (1 H, s ancho), 7,39 - 7,55 (2 H, m), 7,35 (1 H, s ancho), 7,20 (2 H, td, *J*=8,31, 2,27 Hz), 3,93 (1 H, d, *J*=10,83 Hz), 3,56 (1 H, d, *J*=10,58 Hz), 3,24 (1 H, d, *J*=15,11 Hz), 2,62 - 3,05 (5 H, m), 1,88 - 2,22 (2 H, m), 1,34 - 1,79 (3 H, m)

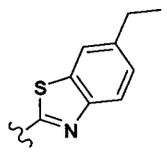
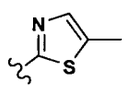
Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
81		2,81	403,1	RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 8,12 (2 H, d, *J*=8,06 Hz), 7,64 (1 H, s ancho), 7,43 (1 H, d, *J*=8,56 Hz), 7,32 (3 H, d, *J*=8,06 Hz), 3,94 (1 H, d, *J*=10,07 Hz), 3,56 (1 H, d, *J*=9,57 Hz), 3,24 (1 H, d, *J*=13,60 Hz), 2,57 - 3,03 (7 H, m), 1,88 - 2,22 (2 H, m), 1,39 - 1,74 (3 H, m), 1,27 (3 H, t, *J*=7,68 Hz)
82		2,62	418,1	RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 8,06 (2 H, d, *J*=9,07 Hz), 7,56 (1 H, s ancho), 7,30 - 7,43 (2 H, m), 6,74 (2 H, d, *J*=9,07 Hz), 3,95 (1 H, d, *J*=11,58 Hz), 3,58 (1 H, d, *J*=11,83 Hz), 3,24 (1 H, d, *J*=14,10 Hz), 3,05 (6 H, s), 2,61 - 2,99 (5 H, m), 1,88 - 2,13 (2 H, m), 1,35 - 1,81 (4 H, m)

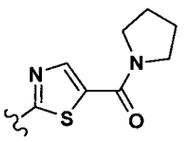
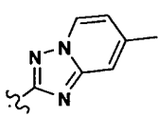
Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
83		1,15	367,1	RMN de ^1H (500 MHz, MeOD) δ ppm 9,12 (1 H, s), 7,78 - 7,82 (1 H, m), 7,70 - 7,74 (1 H, m), 4,05 (1 H, d, *J*=9,77 Hz), 3,75 (1 H, d, *J*=9,77 Hz), 3,29 (1 H, d, *J*=14,65 Hz), 3,11 - 3,18 (1 H, m), 2,98 (2 H, t, *J*=7,93 Hz), 2,80 - 2,91 (2 H, m), 2,13 - 2,22 (2 H, m), 1,71 - 1,87 (2 H, m), 1,62 - 1,71 (1 H, m)
84		1,96	393,1	RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 8,18 - 8,26 (2 H, m), 7,66 (1 H, s), 7,44 (1 H, d, *J*=8,56 Hz), 7,32 (1 H, d, *J*=8,56 Hz), 7,16 - 7,23 (2 H, m), 3,95 (1 H, d, *J*=11,33 Hz), 3,57 (1 H, d, *J*=11,33 Hz), 3,25 (1 H, d, *J*=14,60 Hz), 2,69 - 3,04 (6 H, m), 2,09 (1 H, s ancho), 1,45 - 1,74 (4 H, m)

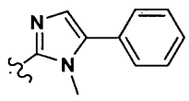
Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
85		1,34	309,1	RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 8,75 (1 H, dd, *J*=4,15, 1,64 Hz), 8,04 (1 H, d, *J*=8,06 Hz), 7,98 (2 H, d, *J*=8,81 Hz), 7,49 (1 H, d, *J*=8,81 Hz), 7,31 (1 H, dd, *J*=8,31, 4,28 Hz), 6,71 (1 H, s ancho), 4,03 (1 H, d, *J*=11,83 Hz), 3,65 (1 H, d, *J*=12,09 Hz), 3,25 (1 H, d, *J*=14,86 Hz), 2,96 (1 H, d, *J*=14,86 Hz), 2,89 (2 H, t, *J*=7,55 Hz), 2,69 - 2,84 (2 H, m), 2,07 (1 H, s ancho), 1,98 (1 H, s ancho), 1,57 - 1,73 (2 H, m), 1,44 - 1,55 (1 H, m)
86		1,16	313,1	RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 9,78 (1 H, s ancho), 7,19 (1 H, s ancho), 6,99 (1 H, d, *J*=6,80 Hz), 6,67 (1 H, d, *J*=8,31 Hz), 3,87 (1 H, d, *J*=10,32 Hz), 3,50 (1 H, d, *J*=11,08 Hz), 3,46 (2 H, s), 3,21 (1 H, d, *J*=14,60 Hz), 2,93 (1 H, d, *J*=15,11 Hz), 2,87 (2 H, t, *J*=7,68 Hz), 2,65 - 2,81 (2 H, m), 2,04 (1 H, s ancho), 1,96 (1 H, s ancho), 1,40 - 1,75 (3 H, m)

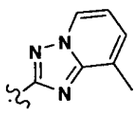
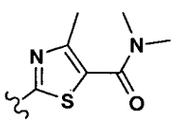
Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
87		1,13	299,2	RMN de ^1H (500 MHz, MeOD) δ ppm 8,57 - 8,63 (1 H, m), 7,55 - 7,64 (2 H, m), 7,06 - 7,12 (1 H, m), 4,04 (1 H, dd, *J*=9,92, 1,98 Hz), 3,81 (1 H, dd, *J*=10,07, 2,14 Hz), 3,46 - 3,57 (1 H, m), 3,23 (2 H, d, *J*=10,68 Hz), 3,09 - 3,18 (2 H, m), 2,82 - 3,02 (1 H, m), 2,41 (1 H, s ancho), 2,28 - 2,37 (1 H, m), 1,99 - 2,07 (1 H, m), 1,86 - 1,97 (2 H, m)
88		1,26	342,1	RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 9,20 (s, 1 H), 8,64 (s, 1 H), 8,45 - 8,56 (m, *J*=4,58, 1,53 Hz, 1 H), 8,21 - 8,38 (m, *J*=7,63 Hz, 1 H), 7,62 (s, 1 H), 7,33 - 7,50 (m, *J*=7,93, 4,88 Hz, 1 H), 3,75 (dd, *J*=128,64, 9,92 Hz, 2 H), 2,95 - 3,14 (m, 2 H), 2,62 - 2,91 (m, 4 H), 2,06 (s, 1 H), 1,92 (s, 1 H), 1,42 - 1,70 (m, 3 H)

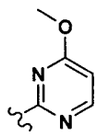
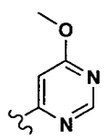
Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
89		2,13	343,1	RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 8,81 (s, 1 H), 7,39 (s, 1 H), 6,97 (s, 1 H), 3,78 (dd, *J*=130,16, 9,92 Hz, 2 H), 2,95 - 3,15 (m, 2 H), 2,74 - 2,90 (m, 2 H), 2,61 - 2,72 (m, *J*=7,78, 7,78 Hz, 2 H), 2,47 - 2,55 (m, *J*=3,66, 1,83 Hz, 3 H), 2,33 (s, 3 H), 2,07 (s, 1 H), 1,85 - 2,01 (m, 1 H), 1,41 - 1,70 (m, 3 H)
90		0,55	372,0	RMN de ^1H (300 MHz, DMSO-d_6) δ ppm 9,98 (1 H, s), 8,92 (1 H, s ancho), 8,11 (1 H, d, *J*=1,83 Hz), 7,48 - 7,53 (1 H, m), 7,34 - 7,40 (1 H, m), 3,88 (1 H, d, *J*=10,25 Hz), 3,62 (1 H, d, *J*=10,25 Hz), 3,02 (2 H, s), 2,74 - 2,83 (2 H, m), 2,66 (2 H, t, *J*=7,50 Hz), 2,04 (4 H, s), 1,90 (1 H, s ancho), 1,58 (3 H, s ancho)

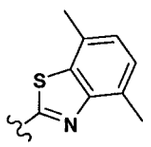
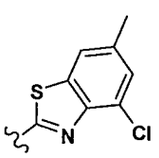
Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
91		1,60	343,3	RMN de ^1H (300 MHz, DMSO-d_6) δ ppm 7,61 (1 H, s), 7,47 - 7,53 (1 H, m), 7,16 (1 H, d, *J*=8,05 Hz), 3,84 - 3,92 (1 H, m), 3,62 (1 H, d, *J*=10,25 Hz), 3,26 - 3,46 (3 H, m), 3,02 (1 H, s), 2,79 (1 H, d, *J*=6,95 Hz), 2,65 (2 H, c, *J*=7,32 Hz), 2,01 - 2,20 (1 H, m), 1,93 (2 H, d, *J*=9,88 Hz), 1,40 - 1,64 (2 H, m), 1,15 - 1,28 (3 H, m), 1,00 (1 H, d, *J*=6,59 Hz)
92		0,45	279,1	RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 8,34 - 8,83 (m, 1 H), 6,96 (s, 1 H), 3,79 (d, *J*=9,77 Hz, 2 H), 3,53 (d, *J*=9,77 Hz, 2 H), 2,89 - 3,06 (m, 2 H), 2,71 - 2,86 (m, 2 H), 2,60 - 2,70 (m, *J*=7,78, 7,78 Hz, 2 H), 2,29 (s, 3 H), 2,01 (s, 1 H), 1,90 (d, *J*=13,43 Hz, 2 H), 1,35 - 1,65 (m, 3 H)

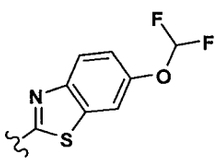
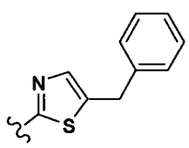
Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
93		1,79	355,1	RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 8,74 (s, 1 H), 7,62 - 7,88 (m, 1 H), 3,83 (d, *J*=10,07 Hz, 1 H), 3,63 - 3,76 (m, 2 H), 3,58 (d, *J*=10,07 Hz, 1 H), 3,40 - 3,53 (m, 2 H), 2,96 - 3,10 (m, 2 H), 2,73 - 2,90 (m, 2 H), 2,58 - 2,72 (m, *J*=7,63, 7,63 Hz, 2 H), 2,06 (s, 1 H), 1,75 - 1,99 (m, 5 H), 1,43 - 1,69 (m, 3 H)
94		1,53	313,1	RMN de ^1H (500 MHz, MeOD) δ ppm 8,63 (1 H, d, *J*=7,02 Hz), 7,55 (1 H, s), 7,19 - 7,23 (1 H, m), 4,27 (1 H, d, *J*=10,68 Hz), 4,06 (1 H, d, *J*=10,68 Hz), 3,94 (1 H, d, *J*=14,95 Hz), 3,76 - 3,83 (1 H, m), 3,54 (1 H, t, *J*=11,90 Hz), 3,36 - 3,48 (3 H, m), 2,64 (1 H, d, *J*=1,83 Hz), 2,56 (3 H, s), 2,34 - 2,42 (1 H, m, *J*=10,15, 10,15, 3,66, 3,51 Hz), 2,17 (1 H, dddd, *J*=14,19, 9,46, 4,58, 4,43 Hz), 1,97 - 2,11 (2 H, m)

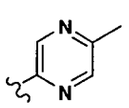
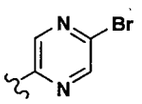
Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
95		0,63	260,2	RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 9,05 (1 H, s ancho), 8,34 (1 H, s), 8,04 (1 H, dd, *J*=2,77, 1,26 Hz), 8,00 (1 H, d, *J*=2,77 Hz), 3,91 (1 H, d, *J*=9,32 Hz), 3,57 (1 H, d, *J*=9,57 Hz), 3,31 (1 H, dd, *J*=14,98, 1,64 Hz), 2,65 - 3,02 (5 H, m), 2,10 - 2,20 (1 H, m), 2,05 - 2,09 (1 H, m), 1,63 - 1,75 (1 H, m), 1,40 - 1,60 (2 H, m)
96		1,88	338,1	RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 8,85 (s, 1 H), 7,41 - 7,47 (m, 4 H), 7,28 - 7,35 (m, 1 H), 6,85 (s, 1 H), 3,83 (d, *J*=9,77 Hz, 1 H), 3,57 (d, *J*=9,77 Hz, 1 H), 3,46 - 3,51 (m, 3 H), 3,00 (s, 2 H), 2,78 (t, *J*=7,78 Hz, 2 H), 2,67 (t, *J*=7,78 Hz, 2 H), 1,98 - 2,03 (m, 1 H), 1,85 - 1,93 (m, 1 H), 1,54 - 1,63 (m, *J*=8,16, 7,82, 7,82, 3,05 Hz, 2 H), 1,43 - 1,51 (m, 1 H)

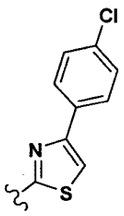
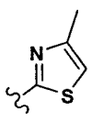
Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
97		1,57	313,1	RMN de ^1H (500 MHz, MeOD) δ ppm 8,61 (1 H, d, *J*=6,71 Hz), 7,65 (1 H, d, *J*=7,32 Hz), 7,25 (1 H, t, *J*=7,02 Hz), 4,32 (1 H, d, *J*=10,99 Hz), 4,11 (1 H, d, *J*=10,68 Hz), 3,98 (1 H, dd, *J*=14,80, 1,68 Hz), 3,82 (1 H, dd, *J*=14,95, 2,14 Hz), 3,52 - 3,61 (1 H, m), 3,35 - 3,47 (3 H, m), 2,66 - 2,71 (1 H, m), 2,62 (3 H, s), 2,34 - 2,44 (1 H, m), 2,14 - 2,24 (1 H, m), 1,99 - 2,13 (2 H, m)
98		0,57	350,1	RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 8,64 (s, 1 H), 3,82 (d, *J*=10,07 Hz, 1 H), 3,57 (d, *J*=9,77 Hz, 1 H), 3,02 (s, 2 H), 2,97 (s, 6 H), 2,79 (s, 2 H), 2,67 (t, *J*=7,63 Hz, 2 H), 2,19 (s, 3 H), 2,04 (s, 1 H), 1,85 - 1,94 (m, 1 H), 1,58 (s, 2 H), 1,49 (d, *J*=6,71 Hz, 1 H)

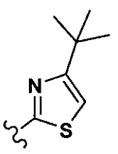
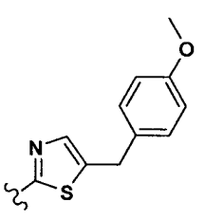
Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
99		0,87	290,1	RMN de ^1H (400 MHz, MeOD) δ ppm 8,20 (1 H, d, *J*=5,79 Hz), 6,34 (1 H, d, *J*=5,79 Hz), 3,94 - 4,04 (1 H, m), 3,91 (3 H, s), 3,55 - 3,76 (1 H, m), 3,00 - 3,28 (2 H, m), 2,63 - 2,97 (4 H, m), 1,99 - 2,21 (2 H, m), 1,44 - 1,85 (3 H, m)
100		0,91	290,1	RMN de ^1H (400 MHz, MeOD) δ ppm 8,39 (1 H, s), 6,21 (1 H, d, *J*=6,04 Hz), 3,98 (1 H, d, *J*=10,32 Hz), 3,89 (3 H, s), 3,67 (1 H, d, *J*=10,32 Hz), 3,01 - 3,24 (2 H, m), 2,65 - 2,97 (4 H, m), 1,96 - 2,17 (2 H, m), 1,43 - 1,81 (3 H, m)
101		1,18	260,1	RMN de ^1H (400 MHz, MeOD) δ ppm 8,56 (2 H, d, *J*=4,78 Hz), 6,94 - 6,99 (1 H, m), 3,98 - 4,04 (1 H, m), 3,78 (1 H, d, *J*=10,32 Hz), 3,45 - 3,52 (1 H, m), 3,35 (1 H, s), 3,15 - 3,22 (2 H, m), 3,05 - 3,12 (2 H, m), 2,22 - 2,38 (2 H, m), 1,95 - 2,03 (1 H, m), 1,80 - 1,92 (2 H, m)

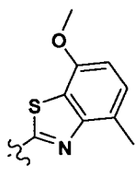
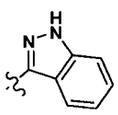
Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
102		2,19	343,4	RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 8,87 (1 H, s ancho), 7,06 (1 H, d, J=7,63 Hz), 6,91 (1 H, d, J=7,63 Hz), 3,92 (1 H, d, J=10,07 Hz), 3,66 (1 H, d, J=10,07 Hz), 3,03 (2 H, s), 2,72 - 2,85 (2 H, m), 2,64 - 2,70 (2 H, m), 2,51 (3 H, s), 2,35 (3 H, s), 2,07 (1 H, s ancho), 1,91 (1 H, s ancho), 1,55 - 1,65 (2 H, m), 1,44 - 1,53 (1 H, m)
103		2,48	363,3	RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 8,84 (1 H, s ancho), 7,71 (1 H, d, J=1,83 Hz), 7,18 (1 H, s), 3,90 (1 H, d, J=10,07 Hz), 3,64 (1 H, d, J=10,07 Hz), 3,03 (2 H, s), 2,72 - 2,85 (2 H, m), 2,66 (2 H, t, J=7,63 Hz), 2,53 (3 H, s), 2,07 (1 H, s ancho), 1,88 - 1,96 (1 H, m), 1,55 - 1,63 (2 H, m), 1,44 - 1,53 (1 H, m)

Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
104		1,45	381,0	RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 8,99 (1 H, s ancho), 7,69 (1 H, d, *J*=2,44 Hz), 7,61 (1 H, d, *J*=8,55 Hz), 7,01 - 7,34 (2 H, m), 3,89 (1 H, d, *J*=10,07 Hz), 3,64 (1 H, d, *J*=10,07 Hz), 3,03 (2 H, d, *J*=2,44 Hz), 2,72 - 2,86 (2 H, m), 2,66 (2 H, t, *J*=7,78 Hz), 2,07 (1 H, s ancho), 1,88 - 1,96 (1 H, m), 1,55 - 1,64 (2 H, m), 1,45 - 1,53 (1 H, m)
105		1,83	355,1	RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 8,57 (s, 1 H), 7,31 (t, *J*=7,32 Hz, 2 H), 7,20 - 7,26 (m, 3 H), 7,08 (s, 1 H), 4,01 (s, 2 H), 3,78 (d, *J*=9,77 Hz, 1 H), 3,53 (d, *J*=10,07 Hz, 1 H), 2,97 (s, 2 H), 2,70 - 2,78 (m, 2 H), 2,64 (t, *J*=7,78 Hz, 2 H), 1,99 (s, 1 H), 1,81 - 1,90 (m, 1 H), 1,52 - 1,60 (m, 2 H), 1,41 - 1,49 (m, *J*=6,90, 2,90, 2,67, 2,48 Hz, 1 H)

Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
106		0,71	274,2	RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 8,87 (1 H, s ancho), 8,23 (1 H, s), 7,88 (1 H, s), 3,85 (1 H, d, *J*=9,32 Hz), 3,51 (1 H, d, *J*=9,32 Hz), 3,27 (1 H, dd, *J*=14,98, 1,64 Hz), 2,60 - 2,97 (5 H, m), 2,37 (3 H, s), 2,06 - 2,16 (1 H, m, *J*=13,25, 9,85, 3,46, 3,46, 3,46 Hz), 1,99 - 2,05 (1 H, m), 1,57 - 1,70 (1 H, m), 1,36 - 1,54 (2 H, m)
107		0,93	338,1	RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 8,71 (1 H, s ancho), 8,14 (1 H, d, *J*=1,26 Hz), 8,11 (1 H, d, *J*=1,26 Hz), 3,92 (1 H, d, *J*=9,32 Hz), 3,58 (1 H, d, *J*=9,57 Hz), 3,32 (1 H, dd, *J*=14,98, 1,89 Hz), 2,68 - 3,03 (5 H, m), 2,04 - 2,19 (2 H, m), 1,63 - 1,75 (1 H, m, *J*=14,01, 9,85, 4,31, 4,31 Hz), 1,42 - 1,59 (2 H, m)

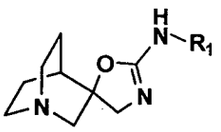
Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
108		2,34	375,0	RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 8,58 (s, 1 H), 7,98 (d, *J*=8,24 Hz, 2 H), 7,51 (s, 1 H), 7,45 (d, *J*=8,54 Hz, 2 H), 3,87 (d, *J*=10,07 Hz, 1 H), 3,62 (d, *J*=9,77 Hz, 1 H), 3,04 (s, 2 H), 2,75 - 2,87 (m, 2 H), 2,68 (t, *J*=7,63 Hz, 2 H), 2,07 (s, 1 H), 1,92 (s, 1 H), 1,40 - 1,68 (m, 3 H)
109		0,73	279,3	RMN de ^1H (400 MHz, *DMSO-D6*) δ ppm 8,61 (s, 1 H), 6,54 (d, *J*=1,01 Hz, 1 H), 3,80 (d, *J*=10,07 Hz, 1 H), 3,54 (d, *J*=9,82 Hz, 1 H), 2,98 (s, 2 H), 2,70 - 2,81 (m, 2 H), 2,65 (t, *J*=7,81 Hz, 2 H), 2,20 (s, 3 H), 1,95 - 2,05 (m, 1 H), 1,88 (s, 1 H), 1,50 - 1,61 (m, 2 H), 1,41 - 1,50 (m, 1 H)

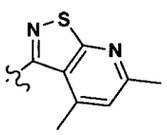
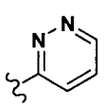
Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
110		1,76	321,4	RMN de ^1H (400 MHz, *DMSO-D6*) δ ppm 8,24 - 8,82 (m, 1 H), 6,51 (s, 1 H), 3,83 (d, *J*=9,57 Hz, 1 H), 3,57 (d, *J*=9,32 Hz, 1 H), 2,98 (s, 2 H), 2,70 - 2,82 (m, 2 H), 2,65 (t, *J*=7,68 Hz, 2 H), 1,97 - 2,04 (m, 1 H), 1,88 (s, 1 H), 1,52 - 1,61 (m, 2 H), 1,46 (dd, *J*=9,69, 2,90 Hz, 1 H), 1,24 (s, 9 H)
111		1,64	312,3	RMN de ^1H (400 MHz, DMSO-d_6) δ ppm 8,55 (s, 1 H), 7,13 (d, *J*=8,56 Hz, 2 H), 7,04 (s, 1 H), 6,86 (d, *J*=8,56 Hz, 2 H), 3,92 (s, 2 H), 3,66 - 3,85 (m, 4 H), 3,45 - 3,60 (m, *J*=10,07 Hz, 1 H), 2,95 (s, 2 H), 2,57 - 2,86 (m, 4 H), 1,98 (s, 1 H), 1,84 (s, 1 H), 1,31 - 1,66 (m, 2 H)

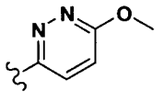
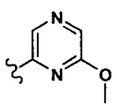
Ejemplo Número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
112		1,70	359,1	RMN de ^1H (300 MHz, DMSO-d_6) δ ppm 8,83 (1 H, d, *J*=1,83 Hz), 7,08 (1 H, d, *J*=8,42 Hz), 6,71 (1 H, d, *J*=8,05 Hz), 3,87 - 3,94 (1 H, m), 3,85 (3 H, s), 3,65 (1 H, d, *J*=9,88 Hz), 3,04 (2 H, s), 2,61 - 2,85 (4 H, m), 2,47 (3 H, s), 2,08 (1 H, d, *J*=2,20 Hz), 1,82 - 1,99 (1 H, m), 1,41 - 1,66 (3 H, m)
113		1,48	298,3	RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 12,09 (s, 1 H), 8,02 (s, 1 H), 7,63 (d, *J*=7,32 Hz, 1 H), 7,33 - 7,36 (m, 1 H), 7,30 (d, *J*=5,80 Hz, 1 H), 6,99 (t, *J*=7,02 Hz, 1 H), 3,82 (d, *J*=8,24 Hz, 1 H), 3,57 (s, 1 H), 3,00 (s, 2 H), 2,79 (s, 2 H), 2,67 (s, 2 H), 1,99 - 2,04 (m, 1 H), 1,93 (s, 1 H), 1,58 (s, 2 H), 1,47 (s, 1 H)

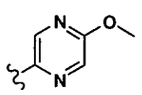
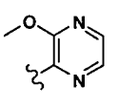
Los compuestos de la Tabla 3 se sintetizaron de acuerdo con el procedimiento del Ejemplo 21, etapas C-D usando el isotiocianato o amina apropiados y 3-(aminometil)quinuclidin-3-ol, 2 HCl racémico.

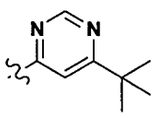
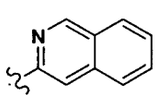
Tabla 3.

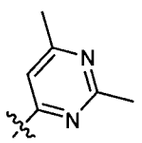
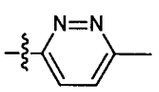


Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
114		2,06	344,3	RMN de ^1H (400 MHz, DMSO-d_6) δ ppm 9,02 (1 H, s), 7,10 (1 H, s), 3,67 - 3,88 (2 H, m), 3,07 - 3,30 (2 H, m), 2,80 - 3,05 (4 H, m), 2,78 (3 H, s), 2,55 (3 H, s), 2,22 (1 H, s ancho), 2,00 (1 H, d, *J*=12,09 Hz), 1,55 - 1,88 (3 H, m)
115		1,19	260,3	RMN de ^1H (400 MHz, MeOD) δ ppm 8,70 (1 H, dd, *J*=4,41, 1,39 Hz), 7,51 (1 H, dd, *J*=8,81, 4,53 Hz), 7,15 (1 H, d, *J*=7,81 Hz), 4,03 (1 H, d, *J*=10,07 Hz), 3,72 (1 H, d, *J*=10,07 Hz), 3,14 - 3,26 (1 H, m), 3,03 - 3,14 (1 H, m), 2,85 - 2,99 (2 H, m), 2,69 - 2,84 (2 H, m), 2,00 - 2,26 (2 H, m), 1,51 - 1,87 (3 H, m)

Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
116		0,73	290,3	RMN de ^1H (400 MHz, MeOD) δ ppm 6,99 - 7,12 (2 H, m), 3,95 - 4,02 (4 H, m), 3,68 (1 H, d, *J*=10,07 Hz), 3,20 (1 H, dd), 3,08 (1 H, dd), 2,84 - 2,95 (2 H, m), 2,69 - 2,84 (2 H, m), 1,99 - 2,21 (2 H, m), 1,47 - 1,87 (3 H, m)
117				RMN de ^1H (400 MHz, MeOD) δ ppm 8,71 (1 H, s), 8,33 (1 H, d, *J*=5,54 Hz), 6,84 (1 H, s ancho), 4,04 (1 H, d, *J*=10,32 Hz), 3,73 (1 H, d, *J*=10,32 Hz), 3,17 - 3,25 (1 H, m), 3,04 - 3,13 (1 H, m), 2,70 - 3,00 (4 H, m), 2,02 - 2,18 (2 H, m), 1,51 - 1,81 (3 H, m)
118		0,83	290,3	RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 8,48 (1 H, s ancho), 7,96 (1 H, s ancho), 7,71 (1 H, s), 3,91 (1 H, d, *J*=9,32 Hz), 3,87 (3 H, s), 3,57 (1 H, d, *J*=9,32 Hz), 3,30 (1 H, d, *J*=14,86 Hz), 2,62 - 3,03 (5 H, m), 2,09 - 2,21 (1 H, m), 2,08 (1 H, s ancho), 1,61 - 1,78 (1 H, m), 1,39 - 1,60 (2 H, m)

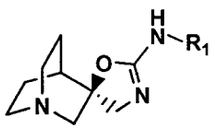
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
119		0,84	290,3	RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 8,56 (1 H, s ancho), 7,96 (1 H, d, *J*=1,26 Hz), 7,79 (1 H, d, *J*=1,51 Hz), 3,89 (3 H, s), 3,85 (1 H, s), 3,53 (1 H, d, *J*=9,06 Hz), 3,31 (1 H, d, *J*=14,86 Hz), 2,65 - 3,04 (5 H, m), 2,11 - 2,23 (1 H, m, *J*=9,85, 9,85, 6,74, 3,53 Hz), 2,08 (1 H, s ancho), 1,62 - 1,75 (1 H, m), 1,40 - 1,61 (2 H, m)
120		0,75	290,3	RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 9,30 (1 H, s ancho), 7,58 (1 H, d, *J*=3,02 Hz), 7,52 (1 H, d, *J*=3,02 Hz), 3,92 (3 H, s), 3,88 (1 H, d, *J*=9,32 Hz), 3,54 (1 H, d, *J*=9,32 Hz), 3,28 (1 H, dd, *J*=14,86, 1,51 Hz), 2,63 - 2,96 (5 H, m), 2,07 - 2,22 (1 H, m), 2,02 (1 H, s ancho), 1,57 - 1,71 (1 H, m), 1,33 - 1,55 (2 H, m)

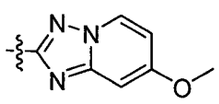
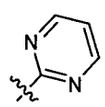
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
121		1,15	316,4	RMN de ^1H (400 MHz, MeOD) δ ppm 8,65 (1 H, d, *J*=3,02 Hz), 6,82 (1 H, s ancho), 4,02 (1 H, dd, *J*=10,32, 3,02 Hz), 3,71 (1 H, dd, *J*=10,32, 3,02 Hz), 2,98 - 3,26 (2 H, m), 2,66 - 2,96 (4 H, m), 1,97 - 2,18 (2 H, m), 1,48 - 1,86 (3 H, m), 1,29 (9 H, s)
122		1,73	309,3	RMN de ^1H (400 MHz, MeOD) δ ppm 8,99 (1 H, s), 7,90 (1 H, d, *J*=8,31 Hz), 7,70 (1 H, d, *J*=8,31 Hz), 7,57 (1 H, t, *J*=7,55 Hz), 7,39 (1 H, t, *J*=7,55 Hz), 7,30 (1 H, s ancho), 3,94 (1 H, d, *J*=9,82 Hz), 3,63 (1 H, d, *J*=10,07 Hz), 3,14 - 3,24 (1 H, m), 3,00 - 3,10 (1 H, m), 2,68 - 2,98 (4 H, m), 2,01 - 2,24 (2 H, m), 1,45 - 1,87 (3 H, m)

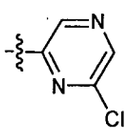
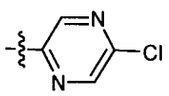
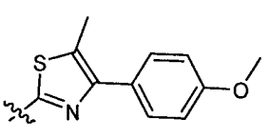
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M + H]^+$	RMN de ^1H
123		0,79	288,30	RMN de ^1H (400 MHz, MeOD-d_4) δ ppm 6,51 (1 H, s ancho), 4,03 (1 H, d, *J*=10,32 Hz), 3,71 (1 H, d, *J*=10,32 Hz), 3,12 - 3,24 (1 H, m), 3,01 - 3,12 (1 H, m), 2,72 - 3,00 (4 H, m), 2,52 (3 H, s), 2,33 (3 H, s), 1,98 - 2,20 (2 H, m), 1,51 - 1,87 (3 H, m)
124		0,72	274,30	RMN de ^1H (400 MHz, MeOD-d_4) δ ppm 7,42 (1 H, d, *J*=9,07 Hz), 7,07 (1 H, d, *J*=8,06 Hz), 4,02 (1 H, d, *J*=10,07 Hz), 3,71 (1 H, d, *J*=10,07 Hz), 3,15 - 3,25 (1 H, m), 3,04 - 3,14 (1 H, m), 2,69 - 2,98 (4 H, m), 2,55 (3 H, s), 1,99 - 2,21 (2 H, m), 1,47 - 1,89 (3 H, m)

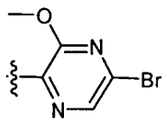
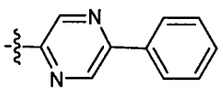
Los compuestos de la Tabla 3 se sintetizaron de acuerdo con el procedimiento del Ejemplo 21, etapas C-D usando el isotiocianato o amina apropiado y (S)-3-(aminometil)quinuclidin-3-ol, 2 HCl.

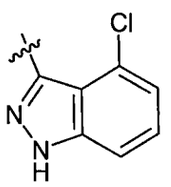
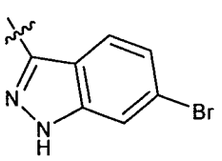
Tabla 3.

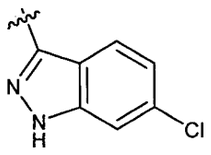
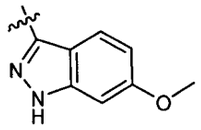
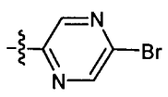


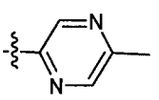
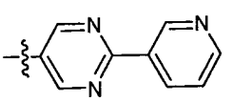
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
125		2,06	329,11	RMN de ^1H (500 MHz, MeOD-d_4) δppm 8,37 (d, *J*=7,32 Hz, 1 H), 6,92 (d, *J*=2,75 Hz, 1 H), 6,65 - 6,75 (m, 1 H), 4,01 (d, *J*=9,77 Hz, 1 H), 3,86 - 3,95 (m, 3 H), 3,70 (d, *J*=9,77 Hz, 1 H), 3,26 (d, *J*=14,95 Hz, 2 H), 3,12 (d, *J*=14,95 Hz, 1 H), 2,96 (t, *J*=7,32 Hz, 2 H), 2,76 - 2,89 (m, 2 H), 2,06 - 2,26 (m, 2 H), 1,58 - 1,86 (m, 3 H)
126		0,56	260,30	RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 8,52 (2 H, d, *J*=4,78 Hz), 6,83 (1 H, t, *J*=4,78 Hz), 3,94 - 4,10 (2 H, m), 3,87 (1 H, d, *J*=14,60 Hz), 3,62 (1 H, dd, *J*=14,48, 1,89 Hz), 3,41 - 3,56 (1 H, m), 3,29 (2 H, t, *J*=8,44 Hz), 3,04 - 3,18 (1 H, m), 2,27 - 2,50 (2 H, m), 1,88 - 2,06 (2 H, m), 1,71 - 1,87 (1 H, m)

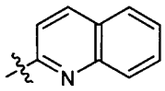
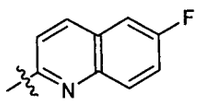
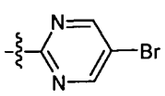
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
127		0,88	294,20	RMN de ^1H (400 MHz, *CDCl₃*) δ ppm 8,58 (1 H, s ancho), 8,18 (1 H, s), 7,97 (1 H, s), 3,93 (1 H, d, *J*=9,32 Hz), 3,58 (1 H, d, *J*=9,57 Hz), 3,28 (1 H, dd, *J*=14,86, 1,51 Hz), 2,64 - 2,98 (5 H, m), 2,02 - 2,15 (2 H, m), 1,60 - 1,73 (1 H, m), 1,38 - 1,56 (2 H, m)
128		0,86	294,20	RMN de ^1H (400 MHz, *CDCl₃*) δ ppm 8,72 (1 H, s ancho), 8,12 (1 H, d, *J*=0,76 Hz), 8,06 (1 H, d, *J*=1,26 Hz), 3,93 (1 H, d, *J*=9,32 Hz), 3,59 (1 H, d, *J*=9,32 Hz), 3,32 (1 H, dd, *J*=14,98, 1,38 Hz), 2,68 - 3,02 (5 H, m), 2,05 - 2,21 (2 H, m), 1,64 - 1,76 (1 H, m), 1,42 - 1,59 (2 H, m). P.F.. 185-8 °C
129		2,04	385,28	RMN de ^1H (500 MHz, *DMSO-D₆*) δ ppm 8,48 (s, 1 H), 7,58 (d, *J*=8,24 Hz, 2 H), 6,98 (d, *J*=8,55 Hz, 2 H), 3,73 - 3,87 (m, 4 H), 3,56 (d, *J*=9,16 Hz, 1 H), 3,00 (s, 2 H), 2,72 - 2,87 (m, 2 H), 2,61 - 2,72 (m, *J*=7,63, 7,63 Hz, 2 H), 2,38 (s, 3 H), 2,03 (s, 1 H), 1,91 (s, 1 H), 1,37 - 1,70 (m, 3 H)

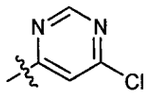
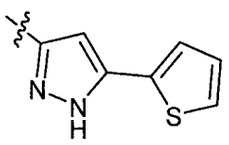
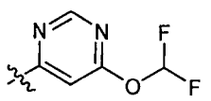
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
130		1,10	368,20	RMN de ^1H (400 MHz, *CDCl*$_3$) δ ppm 8,97 (1 H, s ancho), 7,67 (1 H, s), 3,94 (3 H, s), 3,89 (1 H, d, *J*=9,57 Hz), 3,55 (1 H, d, *J*=9,57 Hz), 3,28 (1 H, dd, *J*=14,86, 1,76 Hz), 2,63 - 2,95 (5 H, m), 2,08 - 2,19 (1 H, m), 1,99 - 2,06 (1 H, m), 1,60 - 1,70 (1 H, m, *J*=14,01, 9,85, 4,31, 4,31 Hz), 1,35 - 1,55 (2 H, m)
131		1,19	336,30	RMN de ^1H (400 MHz, *CDCl*$_3$) δ ppm 9,06 (1 H, s ancho), 8,52 (1 H, d, *J*=1,51 Hz), 8,44 (1 H, d, *J*=1,26 Hz), 7,89 - 7,93 (2 H, m), 7,40 - 7,47 (2 H, m), 7,33 - 7,39 (1 H, m), 3,94 (1 H, d, *J*=9,32 Hz), 3,60 (1 H, d, *J*=9,32 Hz), 3,34 (1 H, dd, *J*=14,86, 1,76 Hz), 2,69 - 3,05 (5 H, m), 2,13 - 2,23 (1 H, m), 2,07 - 2,12 (1 H, m), 1,65 - 1,76 (1 H, m), 1,44 - 1,60 (2 H, m)

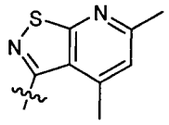
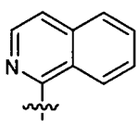
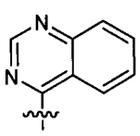
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
132		1,35	332,23	RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 12,40 (s, 1 H), 7,95 (s, 1 H), 7,30 (d, *J*=8,24 Hz, 1 H), 7,22 (t, *J*=7,78 Hz, 2 H), 6,97 (d, *J*=7,02 Hz, 1 H), 3,79 (d, *J*=6,71 Hz, 1 H), 3,53 (s, 1 H), 3,18 (d, *J*=4,58 Hz, 3 H), 3,00 (s, 2 H), 2,79 (d, *J*=2,14 Hz, 2 H), 2,74 (s, 1 H), 2,66 (d, *J*=7,93 Hz, 3 H), 1,96 - 2,04 (m, 2 H), 1,91 (s, 1 H), 1,59 (s, 3 H), 1,46 (s, 1 H)
133		1,94	378,16	RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 12,22 (s, 1 H), 8,32 (s, 1 H), 8,01 (s, 1 H), 7,58 (d, *J*=8,24 Hz, 1 H), 7,55 (s, 1 H), 7,08 - 7,14 (m, 1 H), 3,82 (d, *J*=9,77 Hz, 1 H), 3,56 (d, *J*=9,16 Hz, 1 H), 2,96 - 3,04 (m, 2 H), 2,73 - 2,82 (m, 2 H), 2,67 (t, *J*=7,48 Hz, 2 H), 2,00 - 2,05 (m, 1 H), 1,91 (s, 1 H), 1,54 - 1,63 (m, 2 H), 1,45 (s, 1 H)

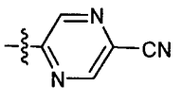
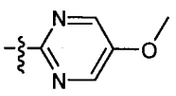
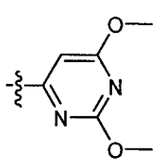
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
134		1,86	332,16	RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 12,22 (s, 1 H), 8,00 (s, 1 H), 7,63 (d, *J*=8,55 Hz, 1 H), 7,40 (s, 1 H), 7,00 (d, *J*=7,93 Hz, 1 H), 3,82 (d, *J*=9,46 Hz, 1 H), 3,56 (d, *J*=9,16 Hz, 1 H), 3,00 (s, 2 H), 2,78 (s, 2 H), 2,67 (t, *J*=7,32 Hz, 2 H), 2,02 (s, 1 H), 1,91 (s, 1 H), 1,58 (s, 2 H), 1,45 (s, 1 H)
135		1,51	328,28	RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 11,88 (s, 2 H), 8,01 (s, 1 H), 7,48 (d, *J*=8,55 Hz, 2 H), 6,73 (s, 2 H), 6,62 (dd, *J*=8,70, 1,68 Hz, 2 H), 3,77 - 3,83 (m, 7 H), 3,55 (d, *J*=8,85 Hz, 2 H), 2,97 - 3,05 (m, 4 H), 2,80 (s, 3 H), 2,65 - 2,72 (m, 4 H), 1,98 - 2,04 (m, 3 H), 1,92 (s, 2 H), 1,60 (d, *J*=2,14 Hz, 2 H), 1,59 (s, 2 H), 1,47 (s, 2 H)
136		0,91	338,20	RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 8,69 (1 H, s ancho), 8,12 (1 H, d, *J*=1,51 Hz), 8,08 (1 H, d, *J*=1,26 Hz), 3,91 (1 H, d, *J*=9,57 Hz), 3,57 (1 H, d, *J*=9,32 Hz), 3,29 (1 H, dd, *J*=14,86, 1,51 Hz), 2,62 - 3,01 (5 H, m), 2,01 - 2,18 (2 H, m), 1,61 - 1,76 (1 H, m), 1,39 - 1,59 (2 H, m)

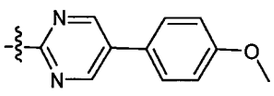
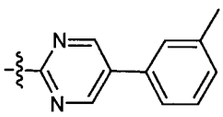
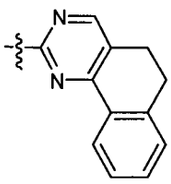
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
137		0,77	274,30	RMN de ^1H (400 MHz, *CDCl$_3$*) δ ppm 8,92 (1 H, s ancho), 8,27 (1 H, s), 7,92 (1 H, s), 3,90 (1 H, d, *J*=9,32 Hz), 3,56 (1 H, d, *J*=9,32 Hz), 3,32 (1 H, dd, *J*=14,86, 1,76 Hz), 2,67 - 3,02 (5 H, m), 2,42 (3 H, s), 2,10 - 2,21 (1 H, m, *J*=13,17, 9,84, 3,49, 3,49, 3,49 Hz), 2,04 - 2,10 (1 H, m), 1,64 - 1,74 (1 H, m), 1,39 - 1,59 (2 H, m)
138		0,84	337,40	RMN de ^1H (400 MHz, *MeOD-d$_4$*) d ppm 9,39 (1 H, s), 8,57 - 8,73 (2 H, m), 8,52 (1 H, d, *J*=5,79 Hz), 7,56 (1 H, dd, *J*=8,06, 5,04 Hz), 6,54 - 7,00 (1 H, m), 4,11 (1 H, d, *J*=10,32 Hz), 3,79 (1 H, d, *J*=10,58 Hz), 3,02 - 3,29 (2 H, m), 2,72 - 3,02 (4 H, m), 2,01 - 2,25 (2 H, m), 1,47 - 1,89 (3 H, m)

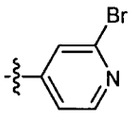
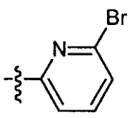
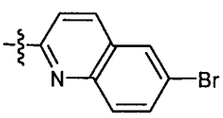
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
139		1,15	309,30	RMN de ^1H (500 MHz, *MeOD-d4*) δ ppm 8,07 (1 H, d, *J*=8,85 Hz), 7,88 (1 H, d, *J*=8,24 Hz), 7,75 (1 H, d, *J*=7,93 Hz), 7,56 - 7,66 (1 H, m), 7,39 (1 H, t, *J*=7,48 Hz), 7,06 (1 H, d, *J*=8,85 Hz), 4,09 (1 H, d, *J*=10,07 Hz), 3,78 (1 H, d, *J*=10,07 Hz), 3,27 (1 H, d, *J*=14,95 Hz), 3,06 - 3,18 (1 H, m), 2,93 - 3,01 (2 H, m), 2,75 - 2,93 (2 H, m), 2,07 - 2,29 (2 H, m), 1,57 - 1,88 (3 H, m)
140		1,26	327,30	RMN de ^1H (500 MHz, *MeOD-d4*) δ ppm 8,05 (1 H, d, *J*=8,85 Hz), 7,92 (1 H, dd, *J*=9,00, 5,34 Hz), 7,35 - 7,49 (2 H, m), 7,08 (1 H, d, *J*=8,24 Hz), 4,09 (1 H, d, *J*=10,07 Hz), 3,78 (1 H, d, *J*=10,07 Hz), 3,22 - 3,30 (1 H, m), 3,09 - 3,18 (1 H, m), 2,91 - 3,04 (2 H, m), 2,71 - 2,91 (2 H, m), 2,06 - 2,30 (2 H, m), 1,56 - 1,90 (3 H, m)
141		0,80	339,40	RMN de ^1H (400 MHz, *MeOD-d4*) δ ppm 8,58 (2 H, s), 3,99 (1 H, d, *J*=10,07 Hz), 3,69 (1 H, d, *J*=10,07 Hz), 3,16 - 3,24 (1 H, m), 3,03 - 3,12 (1 H, m), 2,85 - 2,95 (2 H, m), 2,70 - 2,85 (2 H, m), 1,96 - 2,21 (2 H, m), 1,42 - 1,87 (3 H, m)

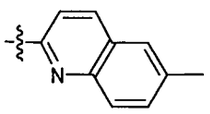
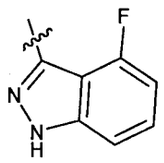
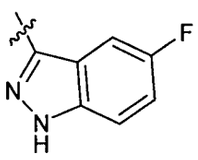
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
142		0,80	294,40	RMN de ^1H (400 MHz, *MeOD-d4*) δppm 8,54 (1 H, d, *J*=1,01 Hz), 6,83 (1 H, s ancho), 4,04 (1 H, d, *J*=10,32 Hz), 3,73 (1 H, d, *J*=10,32 Hz), 3,04 - 3,25 (2 H, m), 2,69 - 2,97 (4 H, m), 1,96 - 2,18 (2 H, m), 1,43 - 1,84 (3 H, m)
143		1,60	330,28	RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 11,95 (s, 1 H), 7,54 (s, 1 H), 7,35 (s, 1 H), 7,22 (s, 1 H), 7,04 (s, 1 H), 6,09 (s, 1 H), 3,66 (s, 1 H), 3,39 (d, *J*=7,02 Hz, 1 H), 3,04 (s, 1 H), 2,99 (s, 1 H), 2,84 (s, 2 H), 2,67 (s, 3 H), 2,02 (s, 1 H), 1,92 (s, 1 H), 1,59 (s, 2 H), 1,51 (s, 1 H)
144		1,00	326,30	RMN de ^1H (400 MHz, *MeOD-d4*) δppm 8,47 (1 H, s), 7,30 - 7,79 (1 H, m), 6,28 (1 H, s ancho), 4,02 (1 H, d, *J*=10,32 Hz), 3,71 (1 H, d, *J*=10,32 Hz), 3,16 - 3,25 (1 H, m), 3,04 - 3,13 (1 H, m), 2,85 - 2,99 (2 H, m), 2,70 - 2,86 (2 H, m), 1,94 - 2,20 (2 H, m), 1,49 - 1,84 (3 H, m). P.F. 185-90 °C

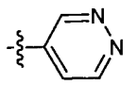
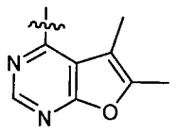
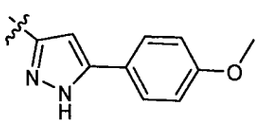
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
145		1,16	344,30	RMN de ^1H (400 MHz, *MeOD-d4*) δ ppm 7,06 (1 H, s), 3,96 (1 H, d, *J*=9,82 Hz), 3,65 (1 H, d, *J*=10,07 Hz), 3,18 - 3,26 (1 H, m), 3,05 - 3,13 (1 H, m), 2,87 - 2,98 (2 H, m), 2,70 - 2,86 (5 H, m), 2,57 (3 H, s), 2,03 - 2,20 (2 H, m), 1,51 - 1,85 (3 H, m)
146		1,20	309,30	RMN de ^1H (400 MHz, *MeOD-d4*) δ ppm 8,46 (1 H, d, *J*=8,31 Hz), 8,06 (1 H, d, *J*=6,04 Hz), 7,58 - 7,78 (2 H, m), 7,51 (1 H, td, *J*=7,68, 1,26 Hz), 7,25 (1 H, d, *J*=6,04 Hz), 3,99 (1 H, d, *J*=9,82 Hz), 3,67 (1 H, d, *J*=9,82 Hz), 3,23 (1 H, s), 3,04 - 3,13 (1 H, m), 2,89 - 2,99 (2 H, m), 2,71 - 2,88 (2 H, m), 2,04 - 2,27 (2 H, m), 1,46 - 1,85 (3 H, m)
147		0,98	310,30	RMN de ^1H (400 MHz, *MeOD-d4*) δ ppm 8,72 (1 H, s), 8,46 (1 H, d, *J*=7,81 Hz), 7,72 - 7,88 (2 H, m), 7,56 (1 H, ddd, *J*=8,25, 6,86, 1,26 Hz), 4,11 (1 H, d, *J*=10,32 Hz), 3,80 (1 H, d, *J*=10,32 Hz), 3,09 - 3,17 (1 H, m), 2,97 (2 H, t, *J*=7,43 Hz), 2,76 - 2,89 (2 H, m), 2,04 - 2,26 (2 H, m), 1,50 - 1,87 (3 H, m)

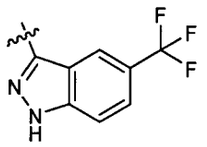
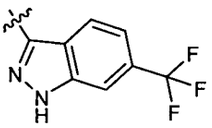
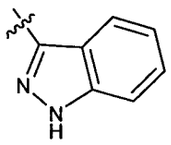
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
148		0,81	285,30	RMN de ^1H (400 MHz, *MeOD-d4*) δ ppm 8,64 (1 H, d, *J*=1,26 Hz), 8,28 (1 H, d, *J*=1,26 Hz), 4,19 (1 H, d, *J*=10,83 Hz), 3,97 (1 H, d, *J*=11,08 Hz), 3,86 (1 H, dd, *J*=14,60, 1,51 Hz), 3,72 (1 H, dd, *J*=14,86, 2,52 Hz), 3,44 - 3,56 (1 H, m), 3,31 - 3,43 (3 H, m), 2,49 - 2,58 (1 H, m), 2,28 - 2,42 (1 H, m, J=13,53, 10,07, 3,56, 3,56, 3,27 Hz), 1,91 - 2,18 (3 H, m)
149		0,73	290,30	RMN de ^1H (400 MHz, *MeOD-d4*) δ ppm 8,28 (2 H, s), 3,95 (1 H, d, *J*=9,82 Hz), 3,86 (3 H, s), 3,65 (1 H, d, *J*=9,82 Hz), 3,15 - 3,24 (1 H, m), 3,03 - 3,11 (1 H, m), 2,68 - 2,96 (4 H, m), 1,97 - 2,19 (2 H, m), 1,49 - 1,85 (3 H, m)
150		0,90	320,40	RMN de ^1H (400 MHz, *MeOD-d4*) δ ppm 5,87 (1 H, s ancho), 3,99 (1 H, d, *J*=10,32 Hz), 3,92 (3 H, s), 3,88 (3 H, s), 3,67 (1 H, d, *J*=10,32 Hz), 3,14 - 3,22 (1 H, m), 3,01 - 3,10 (1 H, m), 2,70 - 2,94 (4 H, m), 1,98 - 2,16 (2 H, m), 1,51 - 1,82 (3 H, m)

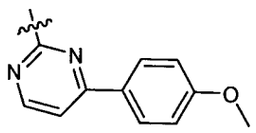
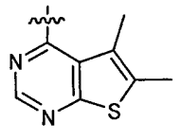
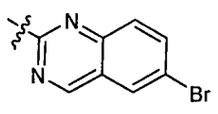
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
151		1,15	366,30	RMN de ^1H (400 MHz, *MeOD-d4*) δ ppm 8,74 (2 H, s), 7,53 (2 H, d, *J*=8,81 Hz), 7,02 (2 H, d, *J*=8,81 Hz), 4,01 (1 H, d, *J*=10,07 Hz), 3,81 (3 H, s), 3,71 (1 H, d, *J*=10,07 Hz), 3,26 (1 H, s), 3,08 - 3,18 (1 H, m), 2,73 - 3,03 (4 H, m), 2,16 (2 H, s ancho), 1,51 - 1,90 (3 H, m)
152		1,27	350,40	RMN de ^1H (400 MHz, *MeOD-d4*) δ ppm 8,78 (2 H, s), 7,27 - 7,47 (3 H, m), 7,20 (1 H, d, *J*=7,30 Hz), 4,02 (1 H, d, *J*=10,07 Hz), 3,71 (1 H, d, *J*=10,07 Hz), 3,24 (1 H, d, *J*=15,11 Hz), 3,03 - 3,14 (1 H, m), 2,70 - 3,00 (4 H, m), 2,40 (3 H, s), 2,03 - 2,22 (2 H, m), 1,53 - 1,84 (3 H, m)
153		2,13	362,28	RMN de ^1H (400 MHz, *MeOD-d4*) δ ppm 8,37 (1 H, s), 8,24 (1 H, dd, *J*=7,55, 1,51 Hz), 7,88 (1 H, s), 7,19 - 7,44 (3 H, m), 4,02 (1 H, d, *J*=10,07 Hz), 3,71 (1 H, d, *J*=10,07 Hz), 3,24 (1 H, d, *J*=16,87 Hz), 3,05 - 3,12 (1 H, m), 2,70 - 2,99 (8 H, m), 2,05 - 2,21 (2 H, m), 1,48 - 1,84 (3 H, m)

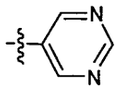
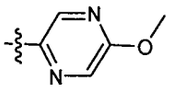
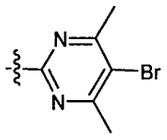
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
154		0,57	339,10	RMN de ^1H (500 MHz, *MeOD-d4*) δ ppm 8,07 (d, *J*=5,49 Hz, 1 H), 7,47 - 7,71 (m, 1 H), 7,13 - 7,34 (m, 1 H), 3,91 - 4,06 (m, 1 H), 3,56 - 3,73 (m, 1 H), 3,14 - 3,24 (m, 1 H), 3,02 - 3,14 (m, 1 H), 2,73 - 3,01 (m, 4 H), 1,98 - 2,21 (m, 2 H), 1,58 - 1,85 (m, 3 H)
155		0,64	339,04	RMN de ^1H (500 MHz, *MeOD-d4*) δ ppm 7,45 - 7,58 (m, 1 H), 7,04 - 7,16 (m, 1 H), 6,90 (d, *J*=7,32 Hz, 1 H), 3,95 - 4,09 (m, 1 H), 3,67 - 3,77 (m, 1 H), 3,18 - 3,28 (m, 1 H), 3,07 - 3,17 (m, 1 H), 2,76 - 3,05 (m, 4 H), 2,04 - 2,22 (m, 2 H), 1,50 - 1,89 (m, 3 H)
156		1,47	388,40	RMN de ^1H (500 MHz, *MeOD-d4*) δ ppm 7,96 - 8,03 (1 H, m), 7,88 - 7,95 (1 H, m), 7,75 - 7,84 (1 H, m), 7,61 - 7,73 (1 H, m), 7,06 (1 H, d, *J*=8,55 Hz), 4,01 - 4,11 (1 H, m), 3,69 - 3,82 (1 H, m), 3,20 - 3,29 (1 H, m), 3,09 - 3,19 (1 H, m), 2,76 - 3,02 (4 H, m), 2,09 - 2,23 (2 H, m), 1,58 - 1,87 (3 H, m)

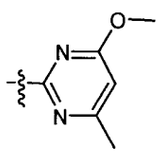
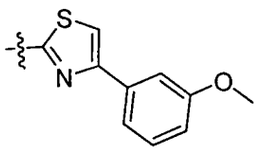
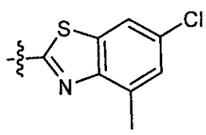
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
157		1,33	323,50	RMN de ^1H (500 MHz, *MeOD-d4*) δ ppm 7,99 (1 H, d, *J*=8,55 Hz), 7,77 (1 H, d, *J*=8,55 Hz), 7,41 - 7,57 (2 H, m), 7,02 (1 H, d, *J*=8,55 Hz), 4,08 (1 H, d, *J*=9,77 Hz), 3,76 (1 H, d, *J*=9,77 Hz), 3,26 (1 H, d, *J*=14,95 Hz), 3,08 - 3,17 (1 H, m), 2,78 - 3,02 (4 H, m), 2,49 (3 H, s), 2,08 - 2,31 (2 H, m), 1,54 - 1,89 (3 H, m)
158		1,19	316,16	RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 12,36 (s, 1 H), 7,98 (s, 1 H), 7,19 - 7,27 (m, 1 H), 7,15 (d, *J*=8,24 Hz, 1 H), 6,64 - 6,71 (m, 1 H), 3,80 (d, *J*=7,63 Hz, 1 H), 3,54 (s, 1 H), 2,95 - 3,04 (m, 2 H), 2,78 (s, 2 H), 2,66 (s, 2 H), 2,01 (s, 1 H), 1,93 (s, 1 H), 1,58 (s, 2 H), 1,46 (s, 1 H)
159		1,40	316,16	RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 12,20 (s, 1 H), 7,98 (s, 1 H), 7,38 (dd, *J*=8,55, 3,36 Hz, 1 H), 7,32 (d, *J*=8,55 Hz, 1 H), 7,18 (t, *J*=8,85 Hz, 1 H), 3,81 (d, *J*=8,85 Hz, 1 H), 3,55 (d, *J*=8,55 Hz, 1 H), 2,97 - 3,05 (m, 2 H), 2,79 (s, 2 H), 2,68 (t, *J*=7,32 Hz, 3 H), 2,02 (s, 1 H), 1,92 (s, 1 H), 1,59 (d, *J*=6,41 Hz, 2 H), 1,47 (d, *J*=8,85 Hz, 1 H)

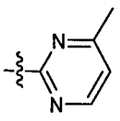
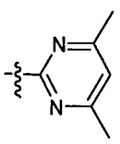
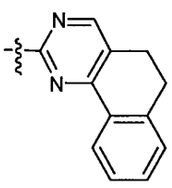
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
160		0,83	260,27	RMN de ^1H (400 MHz, *MeOD*) δ ppm 8,89 (1 H, s ancho), 8,80 (1 H, d, *J*=5,79 Hz), 7,53 (1 H, s ancho), 3,91 (1 H, d, *J*=10,83 Hz), 3,60 (1 H, d, *J*=10,83 Hz), 3,16 - 3,25 (1 H, m), 3,02 - 3,12 (1 H, m), 2,68 - 2,99 (4 H, m), 1,94 - 2,17 (2 H, m), 1,53 - 1,83 (3 H, m)
161		1,55	328,21	RMN de ^1H (400 MHz, *MeOD-d4*) δ ppm 8,35 (1 H, s), 4,01 (1 H, d, *J*=10,07 Hz), 3,70 (1 H, d, *J*=10,07 Hz), 3,20 - 3,27 (1 H, m), 3,05 - 3,13 (1 H, m), 2,69 - 2,99 (4 H, m), 2,34 (3 H, s), 2,29 (3 H, s), 2,01 - 2,22 (2 H, m), 1,51 - 1,83 (3 H, m)
162		1,85	354,25	RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 11,75 - 12,09 (m, *J*=14,95 Hz, 1 H), 7,62 (d, *J*=7,93 Hz, 2 H), 7,38 - 7,54 (m, *J*=10,99 Hz, 1 H), 6,95 (d, *J*=6,71 Hz, 2 H), 6,13 (s, 1 H), 3,76 - 3,83 (m, 4 H), 3,74 (s, 1 H), 3,38 (d, *J*=2,75 Hz, 1 H), 2,98 (s, 1 H), 2,82 (s, 2 H), 2,62 - 2,71 (m, 2 H), 2,00 (s, 1 H), 1,92 (s, 1 H), 1,58 (s, 2 H), 1,50 (s, 1 H)

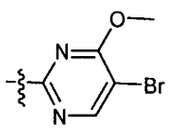
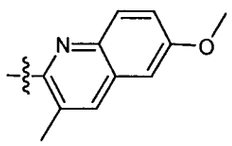
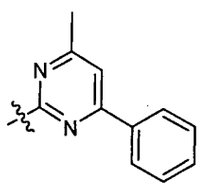
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
163		2,09	366,17	RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 12,54 (s, 1 H), 8,05 (s, 1 H), 7,97 (s, 1 H), 7,52 - 7,60 (m, 2 H), 3,82 (s, 1 H), 3,58 (s, 1 H), 3,01 (s, 2 H), 2,78 (s, 2 H), 2,64 - 2,70 (m, 2 H), 1,99 - 2,05 (m, 1 H), 1,92 (s, 1 H), 1,58 (s, 2 H), 1,47 (s, 1 H)
164		2,12	366,17	RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 12,54 (s, 1 H), 8,03 (s, 1 H), 7,85 (d, *J*=8,24 Hz, 1 H), 7,70 (s, 1 H), 7,26 (d, *J*=8,24 Hz, 1 H), 3,83 (d, *J*=9,46 Hz, 1 H), 3,57 (d, *J*=8,85 Hz, 1 H), 2,97 - 3,05 (m, 2 H), 2,79 (s, 2 H), 2,67 (t, *J*=7,48 Hz, 2 H), 2,03 (d, *J*=2,44 Hz, 1 H), 1,92 (s, 1 H), 1,59 (d, *J*=5,80 Hz, 2 H), 1,46 (s, 1 H)
165		1,24	298,16	RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 12,07 (s, 1 H), 8,02 (s, 1 H), 7,63 (d, *J*=7,63 Hz, 1 H), 7,27 - 7,36 (m, 2 H), 6,99 (t, *J*=7,32 Hz, 1 H), 3,82 (d, *J*=9,46 Hz, 1 H), 3,56 (d, *J*=8,85 Hz, 1 H), 3,00 (s, 2 H), 2,79 (s, 2 H), 2,67 (t, *J*=6,87 Hz, 2 H), 2,02 (d, *J*=2,75 Hz, 1 H), 1,93 (s, 1 H), 1,58 (s, 2 H), 1,47 (s, 1 H)

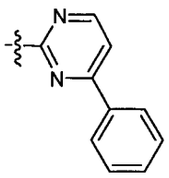
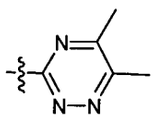
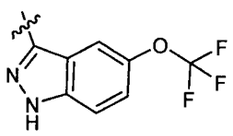
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
166		1,16	366,30	RMN de ^1H (500 MHz, *MeOD-d4*) δ ppm 8,53 (1 H, d, *J*=5,19 Hz), 8,02 - 8,15 (2 H, m), 7,39 (1 H, d, *J*=5,19 Hz), 7,01 - 7,11 (2 H, m), 4,06 (1 H, d, *J*=10,07 Hz), 3,89 (3 H, s), 3,74 (1 H, d, *J*=10,07 Hz), 3,28 (1 H, d, *J*=14,95 Hz), 3,13 (1 H, d, *J*=14,95 Hz), 2,73 - 3,02 (4 H, m), 2,07 - 2,25 (2 H, m), 1,54 - 1,86 (3 H, m)
167		1,25	344,40	RMN de ^1H (500 MHz, *MeOD-d4*) δ ppm 8,48 (1 H, s), 4,05 (1 H, d, *J*=10,07 Hz), 3,74 (1 H, d, *J*=10,07 Hz), 3,26 (1 H, s), 3,14 (1 H, d, *J*=14,65 Hz), 2,76 - 3,02 (4 H, m), 2,59 (3 H, s), 2,46 (3 H, s), 2,09 - 2,23 (2 H, m), 1,57 - 1,89 (3 H, m)
168		1,73	390,20	RMN de ^1H (500 MHz, *MeOD-d4*) δ ppm 9,27 (1 H, s), 8,14 (1 H, d, *J*=2,14 Hz), 7,93 (1 H, dd, *J*=8,85, 1,83 Hz), 7,78 (1 H, d, *J*=8,85 Hz), 4,11 (1 H, d, *J*=10,07 Hz), 3,80 (1 H, d, *J*=10,07 Hz), 3,28 (1 H, s), 3,15 (1 H, d, *J*=14,95 Hz), 2,78 - 3,02 (4 H, m), 2,05 - 2,25 (2 H, m), 1,52 - 1,88 (3 H, m)

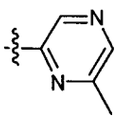
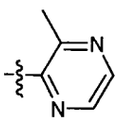
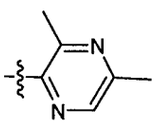
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
169		0,71	260,40	RMN de ^1H (500 MHz, *MeOD-d4*) δ ppm 8,73 (1 H, s), 8,59 (2 H, s ancho), 3,86 (1 H, d, *J*=9,77 Hz), 3,56 (1 H, d, *J*=9,77 Hz), 3,18 - 3,26 (1 H, m), 3,05 - 3,12 (1 H, m), 2,72 - 2,99 (4 H, m), 2,17 (1 H, s ancho), 2,01 (1 H, s ancho), 1,54 - 1,86 (3 H, m)
170		0,78	290,30	RMN de ^1H (400 MHz, *CDCl3*) δ ppm 8,57 (1 H, s ancho), 7,97 (1 H, d, *J*=1,51 Hz), 7,80 (1 H, d, *J*=1,26 Hz), 3,90 (3 H, s), 3,87 (1 H, d, *J*=9,06 Hz), 3,54 (1 H, d, *J*=9,06 Hz), 3,32 (1 H, dd, *J*=14,86, 1,76 Hz), 2,69 - 3,04 (5 H, m), 2,13 - 2,23 (1 H, m), 2,06 - 2,11 (1 H, m), 1,63 - 1,76 (1 H, m), 1,41 - 1,61 (2 H, m)
171		1,06	368,40	RMN de ^1H (400 MHz, *MeOD-d4*) δ ppm 3,99 (1 H, d, *J*=10,07 Hz), 3,68 (1 H, d, *J*=10,07 Hz), 3,15 - 3,24 (1 H, m), 3,02 - 3,10 (1 H, m), 2,68 - 2,96 (4 H, m), 2,53 (6 H, s), 2,02 - 2,19 (2 H, m), 1,46 - 1,83 (3 H, m)

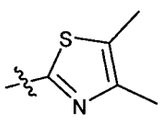
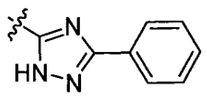
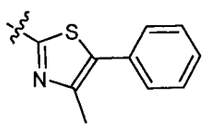
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
172		0,89	304,25	RMN de ^1H (400 MHz, *MeOD-d4*) δ ppm 6,22 (1 H, s), 3,99 (1 H, d, *J*=10,07 Hz), 3,89 (3 H, s), 3,67 (1 H, d, *J*=10,07 Hz), 3,15 - 3,25 (1 H, m), 3,00 - 3,11 (1 H, m), 2,67 - 2,97 (4 H, m), 2,32 (3 H, s), 2,00 - 2,19 (2 H, m), 1,42 - 1,83 (3 H, m)
173		1,07	371,17	RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 8,57 (s, 1 H), 7,46 - 7,54 (m, 6 H), 7,31 (t, *J*=7,93 Hz, 2 H), 6,87 (dd, *J*=8,24, 2,44 Hz, 2 H), 3,87 (d, *J*=9,77 Hz, 2 H), 3,82 (s, 6 H), 3,61 (d, *J*=9,77 Hz, 2 H), 3,03 (s, 4 H), 2,75 - 2,84 (m, 4 H), 2,68 (t, *J*=7,63 Hz, 4 H), 2,06 (s, 2 H), 1,93 (s, 2 H), 1,56 - 1,64 (m, 4 H), 1,50 (dd, *J*=9,46, 2,44 Hz, 2 H)
174		1,32	363,44	RMN de ^1H (500 MHz, *DMSO-d6*) δ ppm 8,73 - 8,93 (m, 1 H), 7,73 (s, 1 H), 7,20 (s, 1 H), 3,91 (d, *J*=9,77 Hz, 1 H), 3,66 (d, *J*=10,07 Hz, 1 H), 3,05 (s, 2 H), 2,74 - 2,89 (m, 1 H), 2,68 (t, *J*=7,63 Hz, 1 H), 2,54 (s, 3 H), 2,09 (s ancho, 2 H), 1,83 - 1,98 (m, 1 H), 1,42 - 1,69 (m, 2 H)

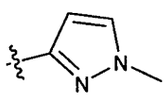
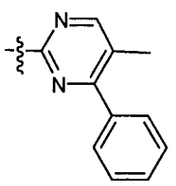
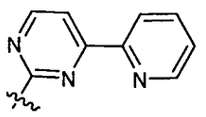
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
175		0,40	274,26	RMN de ^1H (400 MHz, *MeOD-d4*) δ ppm 8,36 (1 H, d, *J*=5,04 Hz), 6,82 (1 H, d, *J*=5,04 Hz), 3,98 (1 H, d, *J*=10,07 Hz), 3,67 (1 H, d, *J*=10,07 Hz), 3,17 - 3,25 (1 H, m), 3,03 - 3,10 (1 H, m), 2,70 - 2,96 (4 H, m), 2,41 (3 H, s), 1,98 - 2,22 (2 H, m), 1,44 - 1,87 (3 H, m)
176		0,72	288,25	RMN de ^1H (400 MHz, *MeOD-d4*) δ ppm 6,72 (1 H, s), 3,98 (1 H, d, *J*=10,07 Hz), 3,67 (1 H, d, *J*=9,82 Hz), 3,18 - 3,24 (1 H, m), 3,02 - 3,12 (1 H, m), 2,65 - 2,96 (4 H, m), 2,36 (6 H, s), 2,02 - 2,21 (2 H, m), 1,45 - 1,83 (3 H, m)
177		2,13	362,28	RMN de ^1H (400 MHz, *MeOD-d4*) δ ppm 8,37 (1 H, s), 8,24 (1 H, dd, *J*=7,55, 1,51 Hz), 7,88 (1 H, s), 7,19 - 7,44 (3 H, m), 4,02 (1 H, d, *J*=10,07 Hz), 3,71 (1 H, d, *J*=10,07 Hz), 3,24 (1 H, d, *J*=16,87 Hz), 3,05 - 3,12 (1 H, m), 2,70 - 2,99 (8 H, m), 2,05 - 2,21 (2 H, m), 1,48 - 1,84 (3 H, m)

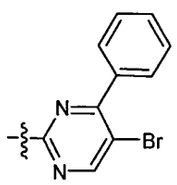
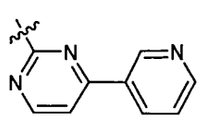
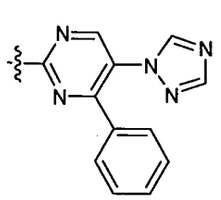
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
178		1,31	370,18	RMN de ^1H (400 MHz, *MeOD-d4*) δ ppm 8,32 (1 H, s), 3,94 - 4,03 (4 H, m), 3,68 (1 H, d, *J*=10,07 Hz), 3,15 - 3,26 (1 H, m), 3,01 - 3,12 (1 H, m), 2,68 - 2,96 (4 H, m), 2,01 - 2,16 (2 H, m), 1,51 - 1,84 (3 H, m)
179		1,87	353,28	RMN de ^1H (500 MHz, *MeOD-d4*) δ ppm 7,83 (1 H, s), 7,63 - 7,76 (1 H, m), 7,19 (1 H, dd, *J*=9,00, 2,90 Hz), 7,09 (1 H, d, *J*=2,75 Hz), 3,93 - 4,02 (1 H, m), 3,84 - 3,93 (3 H, m), 3,69 (1 H, d, *J*=9,77 Hz), 3,26 (1 H, d, *J*=14,65 Hz), 3,11 (1 H, d, *J*=14,95 Hz), 2,70 - 3,01 (4 H, m), 2,39 (3 H, s), 2,06 - 2,27 (2 H, m), 1,57 - 1,85 (3 H, m)
180		1,94	350,30	RMN de ^1H (400 MHz, *MeOD-d4*) δ ppm 7,91 - 8,15 (2 H, m), 7,38 - 7,53 (3 H, m), 7,31 (1 H, s), 4,02 (1 H, d, *J*=10,07 Hz), 3,70 (1 H, d, *J*=10,07 Hz), 3,17 - 3,26 (1 H, m), 3,02 - 3,14 (1 H, m), 2,66 - 2,98 (4 H, m), 2,48 (3 H, s), 2,03 - 2,20 (2 H, m), 1,49 - 1,83 (3 H, m)

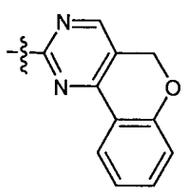
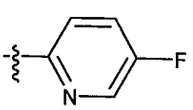
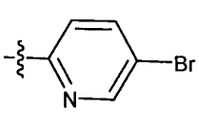
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
181		1,17	336,40	RMN de ^1H (400 MHz, *MeOD-d4*) δ ppm 8,55 (1 H, d, *J*=5,29 Hz), 8,08 (2 H, dd, *J*=6,67, 2,90 Hz), 7,44 - 7,53 (3 H, m), 7,40 (1 H, d, *J*=5,29 Hz), 4,01 (1 H, d, *J*=10,07 Hz), 3,70 (1 H, d, *J*=10,07 Hz), 3,20 - 3,28 (1 H, m), 3,04 - 3,14 (1 H, m), 2,67 - 2,99 (4 H, m), 2,05 - 2,24 (2 H, m), 1,49 - 1,85 (3 H, m)
182		0,42	289,22	RMN de ^1H (400 MHz, *MeOD-d4*) δ ppm 4,02 (1 H, d, *J*=10,32 Hz), 3,71 (1 H, d, *J*=10,32 Hz), 3,23 (1 H, d, *J*=15,36 Hz), 3,03 - 3,13 (1 H, m), 2,69 - 2,98 (4 H, m), 2,54 (3 H, s), 2,48 (3 H, s), 2,01 - 2,21 (2 H, m), 1,41 - 1,85 (3 H, m)
183		1,19	382,19	RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 12,37 (s, 1 H), 8,01 (s, 1 H), 7,53 (s, 1 H), 7,45 (d, *J*=9,16 Hz, 1 H), 7,28 (d, *J*=8,85 Hz, 1 H), 3,82 (d, *J*=9,16 Hz, 1 H), 3,57 (d, *J*=9,46 Hz, 1 H), 3,00 (s, 2 H), 2,78 (s, 2 H), 2,67 (t, *J*=7,48 Hz, 2 H), 1,96 - 2,04 (m, 1 H), 1,91 (d, *J*=8,85 Hz, 1 H), 1,55 - 1,63 (m, 2 H), 1,47 (d, *J*=7,02 Hz, 1 H)

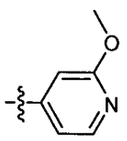
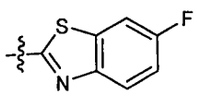
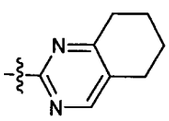
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
184		0,75	274,30	RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 9,08 (1 H, s ancho), 8,12 (1 H, s), 7,85 (1 H, s), 3,89 (1 H, d, *J*=9,32 Hz), 3,55 (1 H, d, *J*=9,32 Hz), 3,28 (1 H, dd, *J*=14,86, 1,26 Hz), 2,62 - 2,97 (5 H, m), 2,35 (3 H, s), 2,06 - 2,17 (1 H, m, *J*=13,13, 9,82, 3,53, 3,38, 3,38 Hz), 2,04 (1 H, s ancho), 1,59 - 1,73 (1 H, m), 1,37 - 1,57 (2 H, m)
185		0,75	274,30	RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 9,29 (1 H, s ancho), 7,90 (2 H, s ancho), 3,90 (1 H, d, *J*=9,32 Hz), 3,55 (1 H, d, *J*=9,06 Hz), 3,35 (1 H, d, *J*=14,86 Hz), 2,65 - 3,08 (5 H, m), 2,56 (3 H, s), 2,12 - 2,27 (1 H, m), 2,08 (1 H, s ancho), 1,62 - 1,77 (1 H, m), 1,38 - 1,61 (2 H, m)
186		0,79	288,30	RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 9,16 (1 H, s ancho), 7,78 (1 H, s), 3,88 (1 H, d, *J*=9,06 Hz), 3,53 (1 H, d, *J*=9,32 Hz), 3,34 (1 H, dd, *J*=14,86, 2,01 Hz), 2,64 - 3,07 (5 H, m), 2,55 (3 H, s), 2,38 (3 H, s), 2,14 - 2,25 (1 H, m), 2,04 - 2,11 (1 H, m), 1,68 (1 H, dddd, *J*=13,94, 9,66, 4,53, 4,34 Hz), 1,41 - 1,61 (2 H, m)

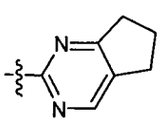
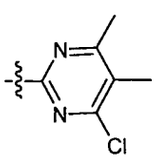
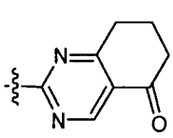
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
187		0,58	293,06	RMN de ^1H (500 MHz, *DMSO-d*$_6$) d ppm 3,73 - 3,87 (m, 1 H), 3,47 - 3,58 (m, 1 H), 2,98 (s, 2 H), 2,71 - 2,85 (m, 2 H), 2,65 (t, *J*=7,78 Hz, 2 H), 2,18 (s, 3 H), 2,11 (s, 3 H), 2,00 (s ancho, 1 H), 1,80 - 1,96 (m, 1 H), 1,57 (dd, *J*=8,24, 2,75 Hz, 3 H)
188		0,86	325,20	RMN de ^1H (500 MHz, *DMSO-d*$_6$) δ ppm 8,07 (d, *J*=7,32 Hz, 2 H), 7,42 (d, *J*=7,63 Hz, 3 H), 3,87 (s, 1 H), 3,55 - 3,70 (m, 1 H), 3,02 (s, 2 H), 2,72 - 2,88 (m, 2 H), 2,68 (s, 2 H), 1,98 - 2,10 (m, 1 H), 1,81 - 1,97 (m, 1 H), 1,40 - 1,68 (m, 3 H)
189		1,04	355,24	RMN de ^1H (500 MHz, *DMSO-d*$_6$) δ ppm 7,36 - 7,47 (m, 3 H), 7,24 - 7,34 (m, 2 H), 3,84 (d, *J*=10,07 Hz, 1 H), 3,58 (d, *J*=9,77 Hz, 1 H), 3,01 (s, 2 H), 2,71 - 2,87 (m, 2 H), 2,66 (t, *J*=7,63 Hz, 2 H), 2,32 (s, 3 H), 2,04 (s ancho, 1 H), 1,83 - 1,98 (m, 1 H), 1,43 - 1,64 (m, 3 H)

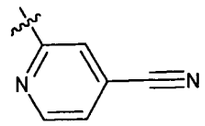
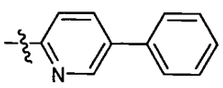
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
190		0,26	262,11	RMN de ^1H (500 MHz, *DMSO-d*$_6$) d ppm 7,43 (s ancho, 1 H), 5,56 - 5,76 (m, 1 H), 3,58 - 3,83 (m, 4 H), 3,37 - 3,52 (m, 1 H), 2,94 (s, 2 H), 2,68 - 2,88 (m, 2 H), 2,60 - 2,68 (m, 2 H), 1,94 (s ancho, 2 H), 1,37 - 1,65 (m, 3 H)
191		1,65	350,30	RMN de ^1H (400 MHz, *MeOD*) δ ppm 8,43 (1 H, s), 7,58 (2 H, dd, *J*=7,55, 1,76 Hz), 7,39 - 7,52 (3 H, m), 3,96 (1 H, d, *J*=10,07 Hz), 3,66 (1 H, d, *J*=9,82 Hz), 3,25 (1 H, d, *J*=16,12 Hz), 3,05 - 3,14 (1 H, m), 2,88 - 2,98 (2 H, m), 2,68 - 2,87 (2 H, m), 2,24 (3 H, s), 2,03 - 2,17 (2 H, m), 1,45 - 1,84 (3 H, m)
192		1,02	337,28	RMN de ^1H (400 MHz, *MeOD*) δ ppm 8,64 (2 H, d, *J*=5,29 Hz), 8,40 (1 H, d, *J*=7,81 Hz), 7,86 - 7,97 (1 H, m), 7,80 (1 H, d, *J*=5,04 Hz), 7,47 (1 H, dd, *J*=6,55, 5,04 Hz), 4,03 (1 H, d, *J*=10,07 Hz), 3,74 (1 H, d, *J*=10,07 Hz), 3,29 (1 H, d, *J*=1,51 Hz), 3,12 - 3,22 (1 H, m), 2,99 (2 H, t, *J*=7,68 Hz), 2,78 - 2,92 (2 H, m), 2,03 - 2,26 (2 H, m), 1,45 - 1,88 (3 H, m)

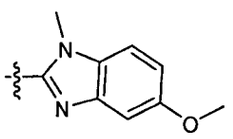
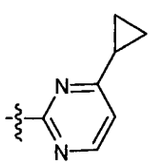
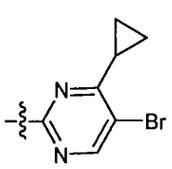
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
193		NA	NA	RMN de ^1H (400 MHz, *MeOD*) δ ppm 8,69 (1 H, s), 7,61 - 7,78 (2 H, m), 7,34 - 7,56 (3 H, m), 3,99 (1 H, d, *J*=10,07 Hz), 3,68 (1 H, d, *J*=10,32 Hz), 3,15 - 3,25 (1 H, m), 3,02 - 3,11 (1 H, m), 2,92 (2 H, t, *J*=7,55 Hz), 2,69 - 2,86 (2 H, m), 2,01 - 2,20 (2 H, m), 1,47 - 1,81 (3 H, m)
194		NA	NA	RMN de ^1H (400 MHz, *MeOD*) δ ppm 9,24 (1 H, d, *J*=1,51 Hz), 8,60 - 8,68 (2 H, m), 8,53 (1 H, dt, *J*=7,99, 1,92 Hz), 7,40 - 7,64 (2 H, m), 4,05 (1 H, d, *J*=10,32 Hz), 3,76 (1 H, d, *J*=10,07 Hz), 3,33 - 3,40 (1 H, m), 3,17 - 3,26 (1 H, m), 2,82 - 3,09 (4 H, m), 2,09 - 2,31 (2 H, m), 1,55 - 1,91 (3 H, m)
195		1,41	403,36	RMN de ^1H (400 MHz, *MeOD*) δ ppm 8,65 (1 H, s), 8,40 (1 H, s), 8,17 (1 H, s), 7,25 - 7,47 (5 H, m), 4,04 (1 H, d, *J*=10,32 Hz), 3,73 (1 H, d, *J*=10,32 Hz), 3,17 - 3,27 (1 H, m), 3,04 - 3,13 (1 H, m), 2,63 - 3,00 (4 H, m), 2,00 - 2,22 (2 H, m), 1,48 - 1,87 (3 H, m)

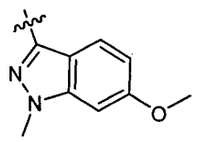
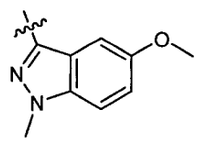
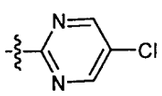
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
196		1,69	364,36	RMN de ^1H (400 MHz, *MeOD*) δ ppm 8,33 (1 H, s), 8,16 (1 H, dd, *J*=7,81, 1,51 Hz), 7,30 - 7,44 (1 H, m), 7,08 (1 H, t, *J*=7,55 Hz), 6,95 (1 H, d, *J*=8,31 Hz), 5,16 (2 H, s), 4,02 (1 H, d, *J*=9,82 Hz), 3,71 (1 H, d, *J*=10,07 Hz), 3,18 - 3,26 (1 H, m), 3,04 - 3,13 (1 H, m), 2,93 (2 H, t, *J*=7,68 Hz), 2,71 - 2,86 (2 H, m), 2,01 - 2,23 (2 H, m), 1,50 - 1,83 (3 H, m)
197		0,53	277,13	RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 8,76 (s, 1 H), 8,15 (d, *J*=2,44 Hz, 1 H), 7,55 (s, 1 H), 6,83 (s, 1 H), 3,79 (s, 1 H), 3,54 (d, *J*=10,07 Hz, 1 H), 2,92 - 3,00 (m, 3 H), 2,70 - 2,80 (m, 3 H), 2,66 (t, *J*=7,78 Hz, 3 H), 1,97 (s, 1 H), 1,88 (s, 1 H), 1,53 - 1,61 (m, 3 H), 1,41 - 1,49 (m, 1 H)
198		0,77	337,07	RMN de ^1H (500 MHz, *DMSO-d_6*) δ ppm 8,26 (s ancho, 1 H), 7,76 (s ancho, 1 H), 6,75 (s ancho, 1 H), 3,81 (s ancho, 1 H), 3,56 (d, *J*=9,46 Hz, 1 H), 2,85 - 3,10 (m, 2 H), 2,56 - 2,85 (m, 4 H), 1,97 (s ancho, 2 H), 1,36 - 1,67 (m, 3 H)

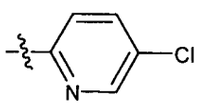
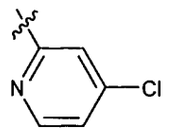
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
199		0,16	289,19	RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,90 (d, *J*=6,10 Hz, 1 H), 6,74 - 7,00 (m, 2 H), 3,93 - 4,09 (m, 1 H), 3,88 (s, 3 H), 3,61 - 3,71 (m, 1 H), 3,14 - 3,25 (m, 1 H), 3,06 (d, *J*=1,83 Hz, 1 H), 2,69 - 2,99 (m, 3 H), 2,07 (s ancho, 2 H), 1,74 (d, *J*=8,24 Hz, 3 H), 1,18 (d, *J*=6,41 Hz, 1 H)
200		0,82	332,97	RMN de ^1H (400 MHz, *DMSO-d*$_6$) δ ppm 7,71 (dd, *J*=8,78, 2,76 Hz, 1 H), 7,59 (dd, *J*=8,91, 4,89 Hz, 1 H), 7,17 (td, *J*=9,03, 2,76 Hz, 1 H), 3,89 (d, *J*=10,04 Hz, 1 H), 3,64 (d, *J*=10,04 Hz, 1 H), 2,97 - 3,13 (m, 2 H), 2,75 - 2,88 (m, 2 H), 2,67 (t, *J*=7,65 Hz, 2 H), 2,02 - 2,12 (m, 1 H), 1,81 - 1,98 (m, 1 H), 1,36 - 1,69 (m, 3 H)
201		1,16	314,35	RMN de ^1H (400 MHz, *MeOD*) δ ppm 8,20 (1 H, s), 3,96 (1 H, d, *J*=10,07 Hz), 3,65 (1 H, d, *J*=9,82 Hz), 3,20 (1 H, d), 3,06 (1 H, d), 2,91 (2 H, t, *J*=7,43 Hz), 2,71 - 2,84 (4 H, m), 2,66 (2 H, t, *J*=6,04 Hz), 1,98 - 2,21 (2 H, m), 1,43 - 1,94 (7 H, m)

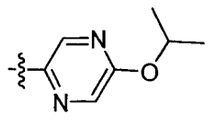
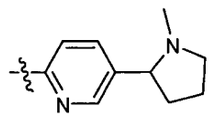
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
202		0,69	300,29	RMN de ^1H (400 MHz, *MeOD*) δ ppm 8,30 (1 H, s), 3,97 (1 H, d, *J*=9,82 Hz), 3,66 (1 H, d, *J*=10,07 Hz), 3,21 (1 H, d), 3,06 (1 H, d), 2,74 - 2,97 (8 H, m), 2,11 (4 H, dc, *J*=7,68, 7,51 Hz), 1,39 - 1,85 (3 H, m)
203		1,19	322,25	RMN de ^1H (400 MHz, *MeOD*) δ ppm 4,00 (1 H, d, *J*=10,07 Hz), 3,69 (1 H, d, *J*=10,07 Hz), 3,22 (1 H, d, *J*=14,60 Hz), 3,03 - 3,14 (1 H, m), 2,69 - 2,97 (4 H, m), 2,46 (3 H, s), 2,26 (3 H, s), 2,03 - 2,17 (2 H, m), 1,51 - 1,84 (3 H, m)
204		0,67	328,28	RMN de ^1H (400 MHz, *MeOD*) δ ppm 8,92 (1 H, s), 4,05 (1 H, d, *J*=10,32 Hz), 3,75 (1 H, d, *J*=10,32 Hz), 3,24 (1 H, d, *J*=1,26 Hz), 3,06 - 3,17 (1 H, m), 2,75 - 3,03 (6 H, m), 2,56 - 2,68 (2 H, m), 2,13 (4 H, ddd, *J*=12,72, 6,30, 6,17 Hz), 1,54 - 1,84 (3 H, m)

Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
205		0,15	284,10	RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 9,01 (s, 1 H), 8,40 (d, *J*=4,88 Hz, 1 H), 7,21 (s, 1 H), 7,16 (s, 1 H), 3,84 (s, 1 H), 3,59 (d, *J*=10,07 Hz, 1 H), 2,94 - 3,02 (m, 3 H), 2,70 - 2,79 (m, 3 H), 2,62 - 2,68 (m, 3 H), 1,99 (s, 1 H), 1,87 (s, 1 H), 1,57 (d, *J*=3,05 Hz, 2 H), 1,56 (s, 1 H), 1,41 - 1,49 (m, 1 H)
206		0,78	366,10	RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 12,63 (s, 1 H), 7,95 (d, *J*=7,63 Hz, 2 H), 7,68 (d, *J*=6,71 Hz, 1 H), 7,16 (t, *J*=7,32 Hz, 1 H), 3,84 (s, 1 H), 3,60 (s, 1 H), 3,03 (s, 2 H), 2,80 (s, 2 H), 2,64 - 2,72 (m, 2 H), 2,05 (s, 1 H), 1,92 (s, 1 H), 1,60 (d, *J*=8,24 Hz, 2 H), 1,48 (s, 1 H)
207		0,77	335,17	RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 9,05 (s, 1 H), 8,52 (d, *J*=2,44 Hz, 1 H), 7,91 (s, 1 H), 7,66 (d, *J*=7,63 Hz, 2 H), 7,47 (t, *J*=7,63 Hz, 2 H), 7,36 (t, *J*=7,32 Hz, 1 H), 6,87 (s, 1 H), 3,84 (s, 1 H), 3,59 (d, *J*=10,07 Hz, 1 H), 2,99 (s, 2 H), 2,72 - 2,81 (m, 2 H), 2,63 - 2,71 (m, 3 H), 1,99 (s, 1 H), 1,90 (s, 1 H), 1,59 (s, 2 H), 1,42 - 1,50 (m, 1 H)

Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
208		0,63	342,25	RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 9,30 (s, 1 H), 7,19 (d, *J*=8,55 Hz, 1 H), 6,94 (d, *J*=2,44 Hz, 1 H), 6,69 (dd, *J*=8,55, 2,14 Hz, 1 H), 3,92 (d, *J*=10,07 Hz, 1 H), 3,75 (s, 3 H), 3,66 (d, *J*=9,77 Hz, 1 H), 3,54 (s, 3 H), 2,99 - 3,07 (m, 2 H), 2,79 (t, *J*=7,78 Hz, 2 H), 2,68 (t, *J*=7,78 Hz, 2 H), 2,02 - 2,07 (m, 1 H), 1,89 (dd, *J*=6,41, 3,36 Hz, 1 H), 1,56 - 1,64 (m, 2 H), 1,44 - 1,52 (m, 1 H)
209		0,96	300,34	RMN de ^1H (400 MHz, *MeOD*) d ppm 8,27 (1 H, d, *J*=5,04 Hz), 6,78 (1 H, d, *J*=5,29 Hz), 3,98 (1 H, d, *J*=10,07 Hz), 3,66 (1 H, d, *J*=10,07 Hz), 3,21 (1 H, d), 3,06 (1 H, d), 2,64 - 2,99 (4 H, m), 2,02 - 2,17 (2 H, m), 1,92 - 2,05 (1 H, m), 1,54 - 1,82 (3 H, m), 0,92 - 1,11 (4 H, m)
210		1,64	378,23	RMN de ^1H (400 MHz, *MeOD*) d ppm 8,42 (1 H, s), 3,97 (1 H, d, *J*=10,07 Hz), 3,66 (1 H, d, *J*=10,07 Hz), 3,20 (1 H, d), 3,06 (1 H, d), 2,63 - 2,97 (4 H, m), 2,35 - 2,50 (1 H, m), 1,99 - 2,16 (2 H, m), 1,50 - 1,83 (3 H, m), 0,98 - 1,24 (4 H, m)

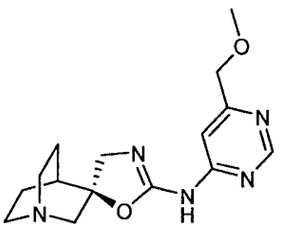
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
211		0,64	342,18	RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 7,98 (s, 1 H), 7,46 (t, *J*=7,93 Hz, 1 H), 6,91 (d, *J*=5,49 Hz, 1 H), 6,59 - 6,65 (m, 1 H), 3,82 - 3,88 (m, 6 H), 3,82 (s, 2 H), 3,55 (s, 1 H), 3,00 (s, 2 H), 2,78 (s, 2 H), 2,67 (d, *J*=6,71 Hz, 2 H), 2,01 (s, 1 H), 1,91 (s, 1 H), 1,59 (s, 2 H), 1,46 (s, 1 H)
212		0,63	342,25	RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 7,94 (s, 1 H), 7,37 (d, *J*=9,16 Hz, 1 H), 7,02 (d, *J*=9,46 Hz, 1 H), 6,99 (d, *J*=1,83 Hz, 1 H), 3,87 (s, 3 H), 3,82 (d, *J*=9,46 Hz, 1 H), 3,78 (s, 3 H), 3,56 (d, *J*=9,16 Hz, 1 H), 3,00 (s, 2 H), 2,78 (s, 2 H), 2,63 - 2,70 (m, 2 H), 2,01 (s, 1 H), 1,91 (s, 1 H), 1,58 (s, 2 H), 1,46 (s, 1 H)
213		0,35	294,25	RMN de ^1H (400 MHz, *MeOD*) d ppm 8,51 (2 H, s), 4,00 (1 H, d, *J*=10,32 Hz), 3,69 (1 H, d, *J*=10,32 Hz), 3,22 (1 H, d), 3,08 (1 H, d), 2,70 - 2,98 (4 H, m), 2,01 - 2,21 (2 H, m), 1,50 - 1,84 (3 H, m)

Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
214		0,36	293,14	RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 8,80 (s, 1 H), 8,19 (s, 1 H), 7,66 (s, 1 H), 6,80 (s, 1 H), 3,81 (s, 1 H), 3,56 (d, *J*=10,07 Hz, 1 H), 2,92 - 3,01 (m, 2 H), 2,70 - 2,79 (m, 2 H), 2,62 - 2,68 (m, 2 H), 1,97 (s, 1 H), 1,87 (s, 1 H), 1,57 (d, *J*=7,32 Hz, 2 H), 1,40 - 1,49 (m, 1 H)
215		0,35	293,14	RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 9,01 (s, 1 H), 8,17 (d, *J*=5,49 Hz, 2 H), 6,97 (s, 2 H), 6,83 (s, 1 H), 3,83 (s, 2 H), 3,57 (d, *J*=10,38 Hz, 2 H), 2,93 - 3,01 (m, 3 H), 2,74 - 2,82 (m, 3 H), 2,73 (s, 1 H), 2,66 (t, *J*=7,63 Hz, 3 H), 1,98 (s, 2 H), 1,87 (s, 2 H), 1,53 - 1,62 (m, 3 H), 1,41 - 1,49 (m, 2 H)

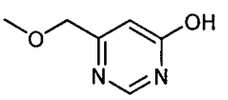
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
216		0,82	318,30	RMN de ^1H (400 MHz, *CDCl3*) δ ppm 8,56 (1 H, s ancho), 7,94 (1 H, d, *J*=1,26 Hz), 7,72 (1 H, d, *J*=1,26 Hz), 5,14 (1 H, spt, *J*=6,13 Hz), 3,85 (1 H, d, *J*=9,06 Hz), 3,52 (1 H, d, *J*=9,06 Hz), 3,30 (1 H, dd, *J*=14,86, 1,51 Hz), 2,67 - 3,03 (5 H, m), 2,11 - 2,26 (1 H, m, *J*=13,17, 9,84, 3,65, 3,42, 3,42 Hz), 2,07 (1 H, s ancho), 1,62 - 1,75 (1 H, m), 1,41 - 1,59 (2 H, m), 1,30 (6 H, d, *J*=6,30 Hz)
217		0,18	342,19	RMN de ^1H (400 MHz, *DMSO-D6*) δ ppm 8,09 (s, 1 H), 7,53 (s, 1 H), 3,80 (s, 1 H), 3,54 (d, *J*=10,32 Hz, 1 H), 3,07 - 3,18 (m, 1 H), 2,91 - 3,01 (m, 3 H), 2,75 (d, *J*=8,31 Hz, 2 H), 2,60 - 2,71 (m, 2 H), 2,19 (c, *J*=8,90 Hz, 1 H), 2,01 - 2,12 (m, 4 H), 1,94 (s, 1 H), 1,83 (d, *J*=15,11 Hz, 2 H), 1,56 (s, 3 H), 1,43 (s, 1 H)

Ejemplo 218

(R)-N-(6-(metoximetil)pirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

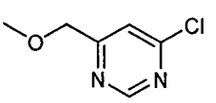


Etapa A: 6-(Metoximetil)pirimidin-4-ol



A una solución de 4-metoxi-3-oxobutanoato de metilo (3,54 ml, 26,5 mmol) en metanol (30 ml) se añadió acetato de formamidina (3,07 g, 29,2 mmol) y metóxido sódico (13 ml, 58,4 mmol). La mezcla se calentó entonces hasta reflujo durante 18 horas y se enfrió hasta temperatura ambiente, luego se concentró. El residuo se suspendió en agua y se ajustó el pH hasta 7 con HCl 1N. La mezcla acuosa se extrajo con cloroformo. Las fases orgánicas reunidas se secaron sobre sulfato de magnesio, se filtraron y concentraron proporcionando 6-(metoximetil)pirimidin-4-ol (1,38 g, 9,85 mmol, 37,1 % de rendimiento). MS (LC/MS) T. R. = 0,19; $[M+H]^+$ = 141,20.

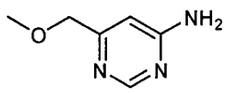
Etapa B: 4-Cloro-6-(metoximetil)pirimidina



Se suspendió 6-(metoximetil)pirimidin-4-ol (1,38 g, 9,85 mmol) en diclorometano (14 ml) y se añadió oxicloruro de fósforo (9 ml, 97 mmol) a temperatura ambiente. La mezcla se agitó a temperatura ambiente durante 18 horas y se concentró. El residuo se suspendió en hielo-agua y el pH se ajustó hasta 7 con hidróxido sódico 1N. La mezcla se extrajo con cloroformo y se secó

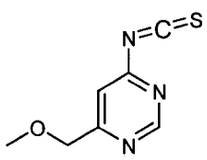
sobre sulfato sódico, se filtró y concentró a vacío. El residuo se purificó por cromatografía en columna (5 -10 % de acetato de etilo/cloroformo) proporcionando 4-cloro-6-(metoximetil)pirimidina (1,2 g, 7,57 mmol, 77 % de rendimiento) como un aceite amarillo pálido, que solidificó en reposo. RMN de ^{1}H (400 MHz, *CDCl$_3$*) δ ppm 8,88 (1 H, d, *J*=1,01 Hz), 7,52 (1 H, d, *J*=1,01 Hz), 4,53 (2 H, s), 3,50 (3 H, s). MS (LC/MS) T. R. = 0,98; $[M+H]^+$ = 159,10.

Etapa C: 6-(Metoximetil)pirimidin-4-amina



Una mezcla de 4-cloro-6-(metoximetil)pirimidina (1,2 g, 7,57 mmol) y hidróxido amónico (20 ml) se calentó en un tubo sellado durante 3 horas. La mezcla se enfrió hasta temperatura ambiente y se concentró. El residuo se trituró con éter proporcionando 6-(metoximetil)pirimidin-4-amina (0,50 g, 3,59 mmol, 48 % de rendimiento) como un sólido amarillo pálido. RMN de ^{1}H (400 MHz, *CDCl$_3$*) δ ppm 8,47 (1 H, s), 6,55 (1 H, s), 5,12 (2 H, s ancho), 4,38 (2 H, s), 3,45 (3 H, s). MS (LC/MS) T. R. = 0,42; $[M+H]^+$ = 140,20.

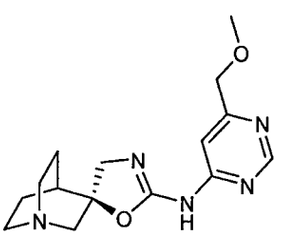
Etapa D: 4-Isotiocianato-6-(metoximetil)pirimidina



A una solución naranja brillante de 1,1'-tiocarbonildipiridin-2(1H)-ona (0,84 g, 3,59 mmol) en diclorometano a temperatura ambiente se añadió 6-(metoximetil)pirimidin-4-amina (0,5 g, 3,59 mmol). La solución naranja se agitó

a temperatura ambiente durante 18 h. La solución se purificó por cromatografía en columna (0-40 % de acetato de etilo/hexanos) proporcionando 4-isotiocianato-6-(metoximetil)pirimidina (0,32 g, 1,77 mmol, 49 % de rendimiento) como un sólido amarillo. RMN de ^{1}H (400 MHz, *CDCl$_3$*) δ ppm 8,91 (1 H, d, *J*=1,26 Hz), 7,19 (1 H, d, *J*=1,01 Hz), 4,52 (2 H, s), 3,49 (3 H, s). MS (LC/MS) T. R. = 1,39; $[M+H]^+$ = 182,10.

Etapa E: (R)-N-(6-(Metoximetil)pirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

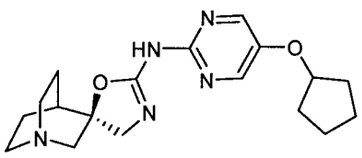


A diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (0,39 g, 1,71 mmol) en dimetilformamida se añadió carbonato de cesio (1,39 g, 4,28 mmol) y 4-isotiocianato-6-(metoximetil)pirimidina (0,31 g, 1,71 mmol). La suspensión se agitó a temperatura ambiente durante 15 min. A la mezcla de reacción se añadió N,N'-diisopropilcarbodiimida (0,80 ml, 5,13 mmol) y la mezcla se agitó durante la noche y luego se concentró. El residuo se purificó por cromatografía en columna (5-25% de metanol/hidróxido amónico 9:1 en acetato de etilo) proporcionando (R)-N-(6-(metoximetil)pirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,18 g, 0,58 mmol, 34 % de rendimiento) como un sólido amarillo. RMN de ^{1}H (400 MHz, *MeOD-d$_4$*) δ ppm 8,65 (1 H, d, *J*=1,01 Hz), 6,92 (1 H, s ancho), 4,40 (3 H, s), 4,03 (1 H, d, *J*=10,32 Hz), 3,72 (1 H, d, *J*=10,32 Hz), 3,44 (2 H, s), 3,18 - 3,26 (1 H, m), 3,06 - 3,13 (1 H, m), 2,69 - 2,96

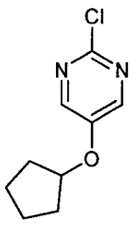
(4 H, m), 1,94 - 2,19 (2 H, m), 1,45 - 1,86 (3 H, m). MS (LC/MS) T. R. = 0,76; $[M+H]^+$ = 304,30.

EJEMPLO 219

(R)-N-(5-(Ciclopentiloxi)pirimidin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

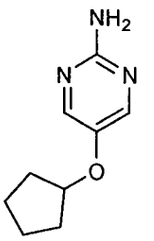


Etapa A: 2-Cloro-5-(ciclopentiloxi)pirimidina



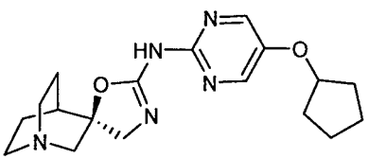
Una mezcla de 2-cloropirimidin-5-ol (1 g, 7,66 mmol), clorociclopentano (2,39 ml, 22,98 mmol) y carbonato potásico (3,18 g, 22,98 mmol) en N,N-dimetilformamida se calentó 65ºC durante 16 h a temperatura ambiente. Se añadió agua y la mezcla se extrajo con acetato de etilo. La fase orgánica se lavó con agua y salmuera, se secó sobre sulfato sódico y se concentró a vacío. El residuo se purificó por cromatografía en columna (acetato de etilo del 0-25%/hexanos) proporcionando 2-cloro-5-(ciclopentiloxi)pirimidina (831 mg, 4,18 mmol, 54,6 % de rendimiento) como un sólido blanco. MS (LC/MS) T. R. = 2,32; $[M+H]^+$ = 199,23.

Etapa B: 5-(Ciclopentiloxi)pirimidin-2-amina



5-(Ciclopentiloxi)pirimidin-2-amina se preparó a partir de 2-cloro-5-(ciclopentiloxi)pirimidina siguiendo los procedimientos generales del **Ejemplo 218, Etapa C**. RMN de ^{1}H (400 MHz, *DMSO-d$_6$*) δ ppm 7,99 (2 H, s), 6,18 (2 H, s), 4,54 - 4,75 (1 H, m), 1,30 - 1,91 (8 H, m). MS (LC/MS) T. R. = 1,47; $[M+H]^+$ = 180,24.

Etapa C: (R)-N-(5-(Ciclopentiloxi)pirimidin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

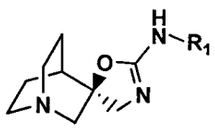


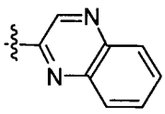
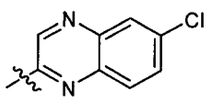
(R)-N-(5-(Ciclopentiloxi)pirimidin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina se preparó a partir de 5-(ciclopentiloxi)pirimidin-2-amina siguiendo los procedimientos generales del **Ejemplo 23, Etapas A-B**. RMN de ^{1}H (400 MHz, *MeOD-d$_4$*) δ ppm 8,24 (2 H, s), 4,76 - 4,86 (1 H, m), 3,98 (1 H, d, *J*=10,07 Hz), 3,69 (1 H, d, *J*=10,07 Hz), 3,33 (1 H, d), 3,20 (1 H, d), 2,77 - 3,08 (4 H, m), 2,04 - 2,26 (2 H, m), 1,49 - 2,03 (11 H, m). MS (LC/MS) T. R. = 1,56; $[M+H]^+$ = 344,32.

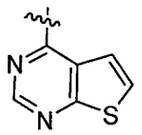
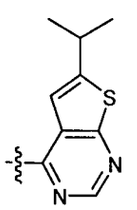
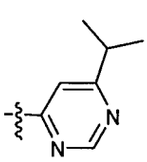
Los compuestos de la Tabla 5 se sintetizaron de acuerdo con el

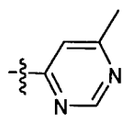
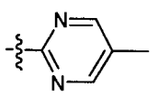
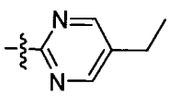
procedimiento del Ejemplo **218** usando los cloruros disponibles comercialmente apropiados como en el Ejemplo **218, Etapa C**.

Tabla 4.



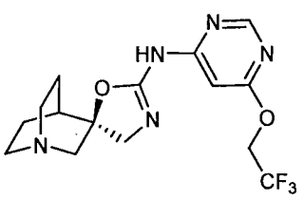
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
220		0,99	310,30	RMN de ^1H (400 MHz, *CDCl₃*) δ ppm 9,82 (1 H, s ancho), 8,62 (1 H, s), 7,95 (1 H, dd, *J*=8,18, 1,13 Hz), 7,72 (1 H, dd, *J*=8,18, 1,13 Hz), 7,58 - 7,64 (1 H, m, *J*=7,62, 7,62, 7,05, 1,39 Hz), 7,51 (1 H, ddd, *J*=7,68, 7,05, 1,26 Hz), 4,05 (1 H, d, *J*=9,32 Hz), 3,70 (1 H, d, *J*=9,57 Hz), 3,39 (1 H, dd, *J*=14,86, 1,51 Hz), 2,72 - 3,06 (5 H, m), 2,12 - 2,26 (2 H, m), 1,69 - 1,80 (1 H, m), 1,45 - 1,64 (2 H, m). P.F. 212-5 °C.
221		1,32	180,09	RMN de ^1H (400 MHz, *DMSO-d₆*) δ ppm 8,31 (1 H, s), 7,80 (1 H, d, *J*=2,52 Hz), 7,55 (1 H, dd, *J*=8,81, 2,52 Hz), 7,50 (1 H, d, *J*=9,06 Hz), 7,13 (2 H, s)

Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
222		0,90	316,30	RMN de ^1H (400 MHz, *MeOD-d4*) δ ppm 8,60 (s, 1 H), 7,60 (d, *J*=6,04 Hz, 1 H), 7,52 (s, 1 H), 4,04 - 4,17 (m, 1 H), 3,73 - 3,87 (m, 1 H), 3,23 - 3,26 (m, 1 H), 3,07 - 3,19 (m, 1 H), 2,88 - 3,01 (m, 2 H), 2,75 - 2,88 (m, 2 H), 2,08 - 2,27 (m, 2 H), 1,56 - 1,86 (m, 3 H)
223		2,28	358,20	RMN de ^1H (400 MHz, *MeOD-d4*) δ ppm 8,52 (1 H, s), 7,30 (1 H, d, *J*=1,01 Hz), 4,03 - 4,09 (1 H, m), 3,76 (1 H, d, *J*=10,07 Hz), 3,16 - 3,27 (2 H, m), 3,06 - 3,14 (1 H, m), 2,68 - 3,01 (4 H, m), 2,01 - 2,23 (2 H, m), 1,54 - 1,82 (3 H, m), 1,37 (6 H, d, *J*=6,80 Hz)
224		0,86	302,24	RMN de ^1H (400 MHz, *MeOD-d4*) δ ppm 8,63 (1 H, s), 6,73 (1 H, s ancho), 4,02 (1 H, d, *J*=10,32 Hz), 3,72 (1 H, d, *J*=10,32 Hz), 3,17 - 3,25 (1 H, m), 3,01 - 3,13 (1 H, m), 2,68 - 2,97 (5 H, m), 1,98 - 2,16 (2 H, m), 1,51 - 1,82 (3 H, m), 1,24 (6 H, d, *J*=7,05 Hz)

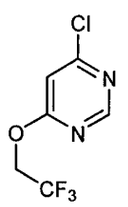
Ejemplo número	R_1	LCMS TR (min)	LCMS Ion $[M+H]^+$	RMN de ^1H
225		0,25	274,19	RMN de ^1H (400 MHz, *MeOD-d4*) δ ppm 8,60 (1 H, s), 6,71 (1 H, s ancho), 4,02 (1 H, d, *J*=10,32 Hz), 3,71 (1 H, d, *J*=10,32 Hz), 3,17 - 3,24 (1 H, m), 3,04 - 3,13 (1 H, m), 2,65 - 3,02 (4 H, m), 2,37 (3 H, s), 1,99 - 2,20 (2 H, m), 1,32 - 1,88 (3 H, m)
226		0,37	274,26	RMN de ^1H (400 MHz, *MeOD-d4*) δ ppm 8,38 (2 H, s), 3,97 (1 H, d, *J*=10,07 Hz), 3,66 (1 H, d, *J*=10,07 Hz), 3,16 - 3,25 (1 H, m), 3,02 - 3,13 (1 H, m), 2,92 (2 H, t, *J*=7,55 Hz), 2,73 - 2,86 (2 H, m), 2,21 (3 H, s), 2,03 - 2,16 (2 H, m), 1,45 - 1,86 (3 H, m)
227		0,96	288,31	RMN de ^1H (400 MHz, *MeOD-d4*)δ ppm 8,41 (2 H, s), 3,98 (1 H, d, *J*=10,07 Hz), 3,67 (1 H, d, *J*=10,07 Hz), 3,17 - 3,25 (1 H, m), 3,02 - 3,13 (1 H, m), 2,92 (2 H, t, *J*=7,43 Hz), 2,72 - 2,87 (2 H, m), 2,57 (2 H, c, *J*=7,55 Hz), 2,01 - 2,23 (2 H, m), 1,48 - 1,84 (3 H, m), 1,22 (3 H, t, *J*=7,68 Hz)

EJEMPLO 228

(R)-N-(6-(2,2,2-Trifluoroetoxi)pirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

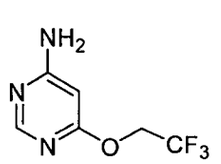


Etapa A: 4-Cloro-6-(2,2,2-trifluoroetoxi)pirimidina



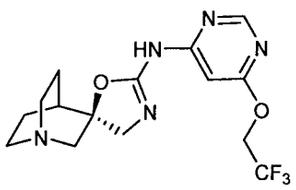
Una solución de 2,2,2-trifluoroetanol (2,61 g, 26,10 mmol) en tetrahidrofurano (12 ml) se añadió gota a gota a una suspensión de hidruro sódico (1,31 g, 32,60 mmol) en tetrahidrofurano (48 ml) a 0 °C. La mezcla se agitó a 0°C durante 30 min y se añadió una solución de 4,6-dicloropirimidina (3,6 g, 24,16 mmol) en tetrahidrofurano (12 ml) a 0 °C. La mezcla de reacción se agitó a temperatura ambiente durante 3 h y se vertió en cloruro amónico acuoso saturado y se extrajo con acetato de etilo. El extracto de acetato de etilo se lavó con agua, se secó sobre sulfato de magnesio y se concentró a vacío. El residuo naranja se purificó por cromatografía en columna (acetato de etilo del 10-40%/hexanos) proporcionando 4-cloro-6-(2,2,2-trifluoroetoxi)pirimidina (2,0 g, 2,41 mmol, 38,9 % de rendimiento) como un aceite amarillo pálido. MS (LC/MS) T. R. = 2,78; $[M+H]^+$ = 213,12.

Etapa B: 6-(2,2,2-Trifluoroetoxi)pirimidin-4-amina



6-(2,2,2-trifluoroetoxi)pirimidin-4-amina se preparó a partir de 4-cloro-6-(2,2,2-trifluoroetoxi)pirimidina siguiendo el procedimiento general del Ejemplo **218, Etapa C.** MS (LC/MS) T. R. = 1,16; $[M+H]^+$ = 194,07.

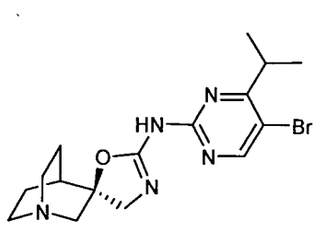
Etapa C: (R)-N-(6-(2,2,2-Trifluoroetoxi)pirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



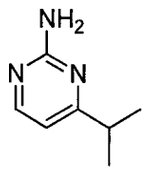
(R)-N-(6-(2,2,2-trifluoroetoxi)pirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina se preparó a partir de 6-(2,2,2-trifluoroetoxi)pirimidin-4-amina siguiendo los procedimientos generales del **Ejemplo 23, Etapas A-B**. RMN de ^1H (400 MHz, *CDCl*$_3$) δ ppm 9,30 (1 H, s ancho), 8,39 (1 H, s), 6,38 (1 H, s ancho), 4,59 - 4,84 (2 H, m), 3,94 (1 H, d, *J*=9,32 Hz), 3,59 (1 H, d, *J*=9,57 Hz), 3,33 (1 H, d, *J*=16,62 Hz), 2,61 - 3,01 (5 H, m), 1,97 - 2,25 (2 H, m), 1,37 - 1,81 (3 H, m). MS (LC/MS) T. R. = 1,42; $[M+H]^+$ = 358,33.

EJEMPLO 229

(R)-N-(5-Bromo-4-isopropilpirimidin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

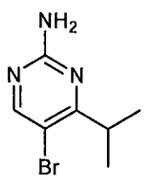


Etapa A: 4-Isopropilpirimidin-2-amina



4-Isopropilpirimidin-2-amina se preparó a partir de 2-cloro-4-isopropilpirimidina siguiendo el procedimiento general del Ejemplo **218, Etapa C.** RMN de ^{1}H (400 MHz, *DMSO-d*$_6$) d ppm 8,10 (1 H, d, *J*=5,04 Hz), 6,45 (3 H, d, *J*=5,04 Hz), 2,59 - 2,80 (1 H, m), 1,15 (6 H, d, *J*=7,05 Hz). MS (LC/MS) T. R. = 0,76; $[M+H]^+$ = 138,12.

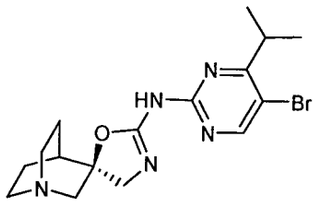
Etapa B: 5-Bromo-4-isopropilpirimidin-2-amina



Se añadió N-bromosuccinimida (0,5 g, 2,8 mmol) a una solución de 4-isopropilpirimidin-2-amina (0,39 g, 2,81 mmol) en cloroformo. La solución amarilla resultante se agitó a temperatura ambiente durante 1 h y se concentró a vacío. El residuo se purificó por cromatografía en columna (3-10% de metanol:hidróxido amónico 9:1 en cloroformo) proporcionando 5-bromo-4-isopropilpirimidin-2-amina (0,69 g, 3,18 mmol, 113 %) como un sólido amarillo pálido. RMN de ^{1}H (400 MHz, *DMSO-d*$_6$) δ ppm 8,21 (1 H, s), 6,75 (2 H, s), 3,10 - 3,23 (1 H, m), 1,14 (6 H, d, *J*=6,80 Hz). MS (LC/MS) T. R. = 2,58; $[M]^+$ = 216,09.

Etapa C: (R)-N-(5-Bromo-4-isopropilpirimidin-2-il)-4H-1'-azaspiro[oxazol-5,3'-

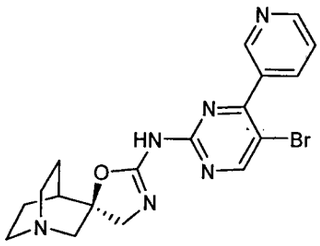
biciclo[2.2.2]octan]-2-amina



(R)-N-(5-Bromo-4-isopropilpirimidin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina se preparó a partir de 5-bromo-4-isopropilpirimidin-2-amina siguiendo los procedimientos generales del **Ejemplo 23, Etapas A-B**. RMN de ^{1}H (400 MHz, *MeOD-d$_4$*) δ ppm 8,49 (1 H, s), 4,02 (1 H, d, *J*=10,07 Hz), 3,72 (1 H, d, *J*=10,07 Hz), 3,34 - 3,44 (1 H, m), 3,23 (1 H, s), 3,06 - 3,15 (1 H, m), 2,95 (2 H, t, *J*=7,55 Hz), 2,75 - 2,89 (2 H, m), 2,00 - 2,21 (2 H, m), 1,52 - 1,83 (3 H, m), 1,24 (6 H, d, *J*=6,80 Hz). MS (LC/MS) T. R. = 1,84; $[M+H]^+$ = 382,24.

EJEMPLO 230

(R)-N-(5-Bromo-4-(piridin-3-il)pirimidin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

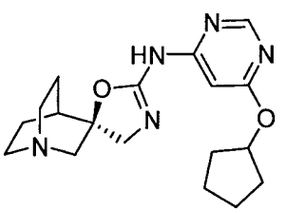


(R)-N-(5-Bromo-4-(piridin-3-il)pirimidin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina se preparó a partir de 4-(piridin-3-il)pirimidin-2-amina siguiendo los procedimientos generales del **Ejemplo 229, Etapas B-C**. RMN de ^{1}H (400 MHz, *MeOD-d$_4$*) δ ppm 8,92 (1 H, d, *J*=1,51 Hz), 8,73 (1 H, s),

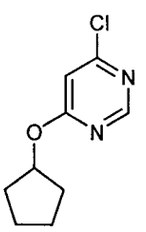
8,64 (1 H, dd, *J*=4,91, 1,64 Hz), 8,23 (1 H, dt, *J*=8,06, 1,89 Hz), 7,56 (1 H, dd, *J*=7,93, 4,91 Hz), 4,00 (1 H, d, *J*=10,07 Hz), 3,69 (1 H, d, *J*=10,07 Hz), 3,22 (1 H, d), 3,07 (1 H, d), 2,60 - 2,99 (4 H, m), 2,00 - 2,21 (2 H, m), 1,50 - 1,83 (3 H, m). MS (LC/MS) T. R. = 0,76; $[M+H]^+$ = 416,30.

EJEMPLO 231

(R)-N-(6-(Ciclopentiloxi)pirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



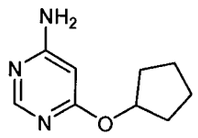
Etapa A: 4-Cloro-6-(ciclopentiloxi)pirimidina



Se añadió una solución de ciclopentanol (2,25 g, 26,1 mmol) en tetrahidrofurano (12 ml) gota a gota a una suspensión de hidruro sódico (1,31 g, 32,6 mmol) en tetrahidrofurano (48 ml) a 0º C. La mezcla se agitó a 0ºC durante 30 min y se añadió una solución de 4,6-dicloropirimidina (3,6 g, 24,16 mmol) en tetrahidrofurano (12 ml) a 0º C. La mezcla de reacción se agitó a temperatura ambiente durante 3 h y se vertió en cloruro amónico acuoso

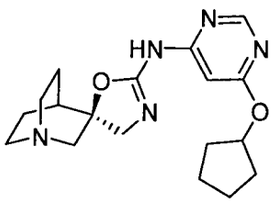
saturado y se extrajo con acetato de etilo. Las fases orgánicas se lavaron con agua, se secaron sobre sulfato de magnesio y se concentró a vacío. El residuo naranja se purificó por cromatografía en columna (acetato de etilo del 10-40%/hexanos). Se proporcionó 4-cloro-6-(ciclopentiloxi)pirimidina como un aceite amarillo pálido. Este material se usó directamente para la siguiente reacción.

Etapa B: 6-(Ciclopentiloxi)pirimidin-4-amina



6-(Ciclopentiloxi)pirimidin-4-amina se preparó a partir de 4-cloro-6-(ciclopentiloxi)pirimidina siguiendo el procedimiento general del Ejemplo **218, Etapa C.** MS (LC/MS) T. R. = 1,64; $[M+H]^+$ = 180,22.

Etapa C: (R)-N-(6-(Ciclopentiloxi)pirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

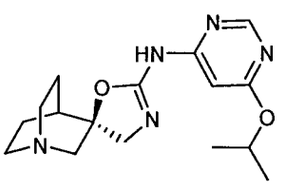


(R)-N-(6-(ciclopentiloxi)pirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina se preparó a partir de 6-(ciclopentiloxi)pirimidin-4-amina siguiendo los procedimientos generales del **Ejemplo 23, Etapas A-B**. RMN de ^{1}H (400 MHz, *MeOD-d$_4$*) δ ppm 8,37 (1 H, s), 6,16 (1 H, s ancho), 5,27 (1 H, s ancho), 3,98 (1 H, d, *J*=10,32 Hz), 3,67 (1 H, d, *J*=10,32 Hz), 3,15 - 3,24

(1 H, m), 3,02 - 3,12 (1 H, m), 2,71 - 2,97 (4 H, m), 2,01 - 2,14 (2 H, m), 1,87 - 2,00 (3 H, m), 1,49 - 1,84 (8 H, m). MS (LC/MS) T. R. = 1,96; $[M+H]^+$ = 344,34.

EJEMPLO 232

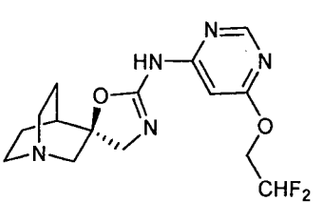
(R)-N-(6-Isopropoxipirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



(R)-N-(6-Isopropoxipirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina se preparó a partir de 4,6-dicloropirimidina siguiendo los procedimientos generales del **Ejemplo 231, Etapas A-C**. RMN de ^{1}H (400 MHz, *MeOD-d$_4$*) δ ppm 8,37 (1 H, s), 6,13 (1 H, s ancho), 5,09 - 5,30 (1 H, m), 3,98 (1 H, d, *J*=10,32 Hz), 3,67 (1 H, d, *J*=10,32 Hz), 3,13 - 3,24 (1 H, m), 3,01 - 3,09 (1 H, m), 2,68 - 2,98 (4 H, m), 1,98 - 2,17 (2 H, m), 1,49 - 1,83 (3 H, m), 1,30 (6 H, d, *J*=6,04 Hz). MS (LC/MS) T. R. = 1,36; $[M+H]^+$ = 318,24.

EJEMPLO 233

(R)-N-(6-(2,2-Difluoroetoxi)pirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

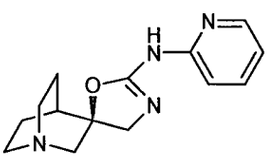


(R)-N-(6-(2,2-Difluoroetoxi)pirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-

biciclo[2.2.2]octan]-2-amina se preparó a partir de 4,6-dicloropirimidina siguiendo los procedimientos generales del **Ejemplo 231, Etapas A-C**. P.F. 83-8 °C. RMN de ^{1}H (400 MHz, *MeOD-d$_4$*) δ ppm 8,42 (1 H, s), 5,93 - 6,37 (2 H, m), 4,52 (2 H, td, *J*=13,98, 3,78 Hz), 3,99 (1 H, d, *J*=10,32 Hz), 3,68 (1 H, d, *J*=10,32 Hz), 3,19 (1 H, d), 3,07 (1 H, d), 2,67 - 2,97 (4 H, m), 1,99 - 2,19 (2 H, m), 1,51 - 1,82 (3 H, m). MS (LC/MS) T. R. = 0,99; $[M+H]^+$ = 340,26.

EJEMPLO 234

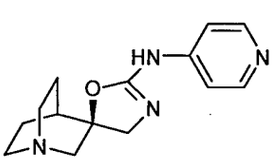
(R)-N-(Piridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



(R)-N-(Piridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina se preparó a partir de (R)-N-(6-bromopiridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (a partir del **Ejemplo 155**) de acuerdo con el procedimiento general del **Ejemplo 19, Etapa C**. RMN de ^{1}H (500 MHz, *MeOD-d$_4$*) δ ppm 8,26 (d, *J*=4,88 Hz, 1 H), 7,58 - 7,74 (m, 1 H), 6,85 - 7,02 (m, 2 H), 4,00 (d, *J*=10,07 Hz, 1 H), 3,70 (d, *J*=10,07 Hz, 1 H), 3,26 - 3,35 (m, 1 H), 3,14 - 3,21 (m, 1 H), 3,02 (d, *J*=8,24 Hz, 2 H), 2,84 - 2,97 (m, 2 H), 2,11 - 2,25 (m, 2 H), 1,58 - 1,92 (m, 3 H). MS (LC/MS) T. R. = 0,30; $[M+H]^+$ = 259,16.

EJEMPLO 235

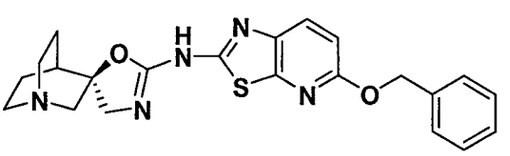
(R)-N-(Piridin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



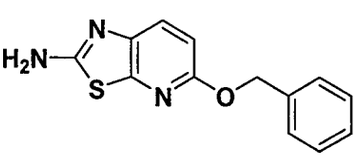
(R)-N-(Piridin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina se preparó a partir de (R)-N-(2-bromopiridin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (a partir del **Ejemplo 154)** de acuerdo con el procedimiento del **Ejemplo 19, Etapa C.** RMN de ^{1}H (500 MHz, *MeOD-d$_4$*) δ ppm 8,31 (d, *J*=6,41 Hz, 2 H), 7,39 (d, *J*=3,97 Hz, 2 H), 4,01 (d, *J*=12,21 Hz, 1 H), 3,70 (d, *J*=11,90 Hz, 1 H), 3,37 (s, 1 H), 3,29 (s, 1 H), 3,18 (d, *J*=1,83 Hz, 1 H), 3,15 (d, *J*=2,14 Hz, 1 H), 2,86 - 3,09 (m, 3 H), 2,02 - 2,20 (m, 1 H), 1,59 - 1,88 (m, 3 H). MS (LC/MS) T. R. = 0,22; $[M+H]^+$ = 259,16.

Ejemplo 236

(R)-N-(5-(Benciloxi)tiazolo[5,4-b]piridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



Etapa A: 5-(Benciloxi)tiazolo[5,4-b]piridin-2-amina

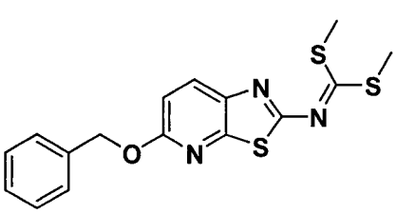


Se suspendió tiocianato potásico (12,42 g, 128 mmol) en ácido acético (45,0 ml) y se enfrió hasta 0 °C. Se añadió 6-(benciloxi)piridin-3-amina (3,2 g, 15,98 mmol), preparada de acuerdo con el documento WO2006/044707. Se añadió bromo (2,55 ml, 49,5 mmol) en ácido acético (15 ml) gota a gota durante

30 minutos tiempo durante el cual la mezcla de reacción se hizo muy densa. Se dejó calentar hasta temperatura ambiente lentamente y se agitó durante la noche.

Se añadió agua (20ml) y la mezcla de reacción se calentó hasta 90 °C y se filtró caliente. Se guardó el filtrado y la torta del filtro se devolvió al matraz de reacción, al que se añadieron otros 40 ml de HOAc. La mezcla se calentó de nuevo hasta 90ºC y se filtró caliente. Los filtrados reunidos se enfriaron en baño de hielo y se añadió NH_4OH gota a gota hasta pH >8. Se formó un precipitado amarillo que se recogió por filtración. Los sólidos se secaron a vacío durante 1h proporcionando 5-(benciloxi)tiazolo[5,4-b]piridin-2-amina (1,95 g, 7,58 mmol, 47,4 % de rendimiento), que se usó sin purificación posterior. RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 7,70 (d, *J*=8,78 Hz, 1 H) 7,48 (d, *J*=7,28 Hz, 2 H) 7,39 (t, *J*=7,28 Hz, 2 H) 7,30 - 7,36 (m, 1 H) 6,78 (d, *J*=8,78 Hz, 1 H) 5,39 (s, 2 H) 5,14 (s ancho, 2 H).

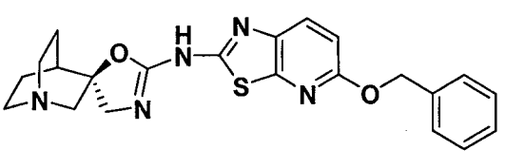
Etapa B: 5-(Benciloxi)tiazolo[5,4-b]piridin-2-ilcarbonimidoditioato de dimetilo



A una suspensión de 5-(benciloxi)tiazolo[5,4-b]piridin-2-amina (800 mg, 3,11 mmol) en DMF (3,1 ml) se añadió hidróxido sódico 20,0M (0,3 ml, 6,22 mmol). La mezcla se dejó agitar 10 min a temperatura ambiente momento en el que se añadió disulfuro de carbono (0,47 ml, 7,77 mmol) y la mezcla se agitó

durante 10 minutos. Se añadió una porción adicional de hidróxido sódico 20,0M (0,3 ml, 6,22 mmol) y la mezcla se agitó de nuevo durante 10 minutos. Finalmente, se añadió gota a gota yodometano (0,47 ml, 7,46 mmol). La mezcla se agitó durante 1 hora, momento en el que se vertió en agua y se extrajo con EtOAc (3x). Los orgánicos reunidos se lavaron con salmuera, se secaron sobre sulfato sódico, se filtraron y concentraron a vacío. La mezcla bruta se purificó por cromatografía sobre gel de sílice (EtOAC al 2-20%/$CHCl_3$) proporcionando 5-(benciloxi)tiazolo[5,4-b]piridin-2-ilcarbonimidoditioato de dimetilo (1,02 g, 91% de rendimiento) como un sólido cristalino amarillo. RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 8,02 (d, *J*=8,78 Hz, 1 H) 7,51 (d, *J*=7,28 Hz, 2 H) 7,38 - 7,45 (m, 2 H) 7,32 - 7,38 (m, 1 H) 6,89 (d, *J*=8,53 Hz, 1 H) 5,46 (s, 2 H) 2,65 (s, 6 H).

Etapa C: (R)-N-(5-(benciloxi)tiazolo[5,4-b]piridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

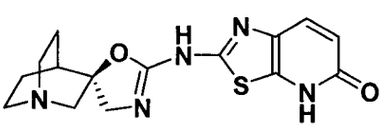


Una mezcla de 5-(benciloxi)tiazolo[5,4-b]piridin-2-ilcarbonimidoditioato de dimetilo (500 mg, 1,38 mmol), diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (317 mg, 1,38 mmol) y carbonato de cesio (1,0 g, 3,07 mmol) en DMF (7 ml) se calentó hasta 100 °C durante 2 horas. La mezcla de reacción se enfrió hasta temperatura ambiente, se vertió en agua y se extrajo con cloroformo (4x). Los orgánicos reunidos se lavaron con salmuera, se secaron sobre sulfato sódico, se filtraron y concentraron a vacío. La mezcla se purificó por

cromatografía sobre gel de sílice (2-20 % [metanol:hidróxido amónico 9:1]-cloroformo) proporcionando (R)-N-(5-(benciloxi)tiazolo[5,4-b]piridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (390mg, 67% de rendimiento). RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 9,18 (s ancho, 1 H) 7,76 (d, *J*=8,85 Hz, 1 H) 7,50 (d, *J*=7,32 Hz, 2 H) 7,41 (t, *J*=7,32 Hz, 2 H) 7,32 - 7,37 (m, 1 H) 5,42 (s, 2 H) 4,02 (d, *J*=9,46 Hz, 1 H) 3,68 (d, *J*=9,46 Hz, 1 H) 3,37 - 3,44 (m, 1 H) 2,75 - 3,06 (m, 5 H) 2,13 - 2,25 (m, 2 H) 1,73 - 1,82 (m, 1 H) 1,49 - 1,70 (m, 3 H). MS (LC/MS) T. R. = 1,69; $[M+H]^+$ = 421,98.

Ejemplo 237

(R)-2-(4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octano]-2-ilamino)tiazolo[5,4-b]piridin-5(4H)-ona

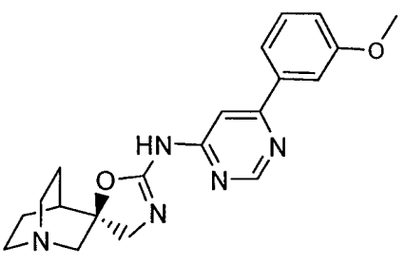


Se disolvió (R)-N-(5-(benciloxi)tiazolo[5,4-b]piridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (390 mg, 0,925 mmol) en TFA y se dejó reaccionar durante 4 horas a temperatura ambiente, momento en el que la LCMS y TLC mostró que se había consumido la mayor parte de material de partida. Se eliminó el TFA a vacío y la mezcla bruta se purificó por HPLC preparativa. Las fracciones de producto reunidas se concentraron a vacío y se trituraron con éter proporcionando (R)-2-(4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octano]-2-ilamino)tiazolo[5,4-b]piridin-5(4H)-ona, TFA (164 mg, 0,368 mmol, 39,8 % de rendimiento). P.F. 245 (desc). RMN de ^{1}H (400 MHz, DMSO-d_6) δ ppm 9,99 (s ancho, 1 H) 9,05 (s ancho, 1 H) 7,81 (d, *J*=8,53 Hz, 1 H) 6,65 (d, *J*=8,78 Hz, 1 H) 3,96 (d, *J*=10,29 Hz, 1 H) 3,82 (d, *J*=10,54 Hz, 1 H)

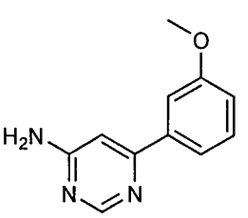
3,63 - 3,78 (m, 2 H) 3,36 - 3,47 (m, 1 H) 3,16 - 3,34 (m, 3 H) 2,43 (s ancho, 1 H) 2,16 (s ancho, 1 H) 1,76 - 2,07 (m, 3 H). MS (LC/MS) T. R. = 0,50; $[M+H]^+$ = 332,15.

Ejemplo 238

(R)-N-(6-(3-Metoxifenil)pirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



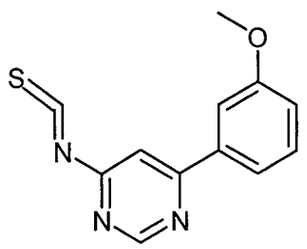
Etapa A: 6-(3-Metoxifenil)pirimidin-4-amina



Una mezcla de 6-cloropirimidin-4-amina (0,324 g, 2,5 mmol), ácido 3-metoxifenilborónico (0,475 g, 3,13 mmol), Na_2CO_3 (0,795 g, 7,50 mmol) y cloruro de bis(trifenilfosfina)paladio(II) (0,035 g, 0,050 mmol) se suspendió en DME/EtOH/agua(15:2:3 ml), se calentó en el sintetizador de microondas a 125 ºC durante 20 min y se concentró. El residuo se purificó por cromatografía sobre gel de sílice (acetato de etilo del 10-60%-hexanos) proporcionando 6-(3-metoxifenil)pirimidin-4-amina (0,35 g, 1,74 mmol, 70 % de rendimiento) como

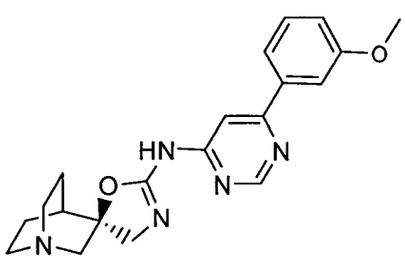
un sólido blanquecino. LCMS T. R. = 1,28; $[M+H]^+$ = 201,98.

Etapa B: 4-Isotiocianato-6-(3-metoxifenil)pirimidina



A una solución de 1,1'-tiocarbonildipiridin-2(1H)-ona (0,970 g, 4,17 mmol) en diclorometano a temperatura ambiente se añadió 6-(3-metoxifenil)pirimidin-4-amina (0,7 g, 3,48 mmol). La reacción se agitó a temperatura ambiente durante 18 horas. La LC/MS mostró el pico de producto deseado como un pico principal. La solución naranja intenso se concentró y el residuo restante se filtró. El filtrado se purificó por cromatografía sobre gel de sílice (acetato de etilo del 0-10%-hexanos) proporcionando 4-isotiocianato-6-(3-metoxifenil)pirimidina (0,39 g, 4,31 mmol, 46 % de rendimiento) como un aceite amarillo. LCMS T. R. = 2,91; $[M+H]^+$ = 244,03.

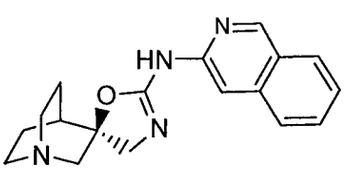
Etapa C: R)-N-(6-(3-Metoxifenil)pirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



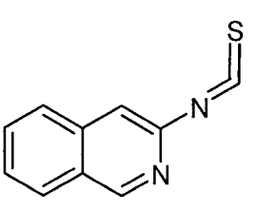
A diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (0,363 g, 1,583 mmol) en N,N-dimetilformamida (20 ml) se añadió Cs_2CO_3 (1,289 g, 3,96 mmol) y 4-isotiocianato-6-(3-metoxifenil)pirimidina. La suspensión se agitó a temperatura ambiente durante 30 minutos. Se añadió entonces N,N'-diisopropilcarbodiimida (0,740 ml, 4,75 mmol) y se continuó agitando la mezcla a temperatura ambiente durante 18 horas. La mezcla se concentró y se purificó por cromatografía sobre gel de sílice (5-25% de metanol:hidróxido amónico 9:1-acetato de etilo) proporcionando (R)-N-(6-metoxipirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,294 g, 0,788 mmol, 50 % de rendimiento) como un sólido amarillo pálido. P.F.80-5 °C. RMN de ^1H (400 MHz, MeOD) δ ppm 8,77 (1 H, s), 7,47 - 7,58 (2 H, m), 7,39 (1 H, t), 7,20 (1 H, s ancho), 7,04 (1 H, dd), 4,05 (1 H, d), 3,85 (3 H, s), 3,74 (1 H, d), 3,23 (1 H, d), 3,10 (1 H, d), 2,71 - 3,00 (4 H, m), 2,03 - 2,22 (2 H, m), 1,53 - 1,85 (3 H, m). MS (LC/MS) T. R. = 1,58; $[M+H]^+$ = 366,15.

Ejemplo 239

(R)-N-(Isoquinolin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

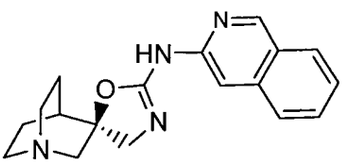


Etapa A: 3-Isotiocianatoisoquinolina



A una solución de 1,1'-tiocarbonildipiridin-2(1H)-ona (0,805 g, 3,47 mmol) en diclorometano a temperatura ambiente se añadió isoquinolin-3-amina (0,5 g, 3,47 mmol). La reacción se agitó a temperatura ambiente durante 18 horas. La LC/MS mostró el pico de producto deseado como un pico principal. La solución naranja intenso se concentró y se filtró. El filtrado se purificó por cromatografía sobre gel de sílice (acetato de etilo del 0-40%-hexanos) proporcionando 4-isotiocianato-6-(3-metoxifenil)pirimidina (0,55 g, 2,96 mmol, 85 % de rendimiento) como sólido blanco. LCMS T. R. = 2,47; $[M+H]^+$ = 187,23.

Etapa B: (R)-N-(Isoquinolin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

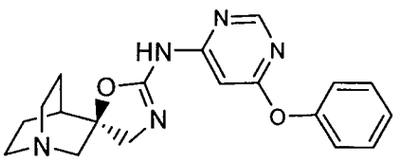


A diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (0,2 g, 0,873 mmol) en N,N-dimetilformamida (20 ml) se añadió Cs_2CO_3 (0,711 g, 2,182 mmol) y 3-isotiocianatoisoquinolina (0,163 g, 0,873 mmol). La suspensión se agitó a temperatura ambiente durante 30 minutos. Se añadió entonces N,N'-diisopropilcarbodiimida (0,408 ml, 2,62 mmol) y la mezcla se agitó a temperatura ambiente durante 18 horas. La mezcla se concentró y se purificó por cromatografía sobre gel de sílice (5-25% [metanol:hidróxido amónico 9:1]-acetato de etilo) proporcionando (R)-N-(isoquinolin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,16 g, 0,508 mmol, 58 % de rendimiento) como un sólido blanquecino. P.F. 196-200 °C. RMN de ^1H (400 MHz, *MeOD*) δ

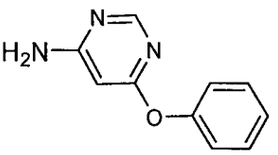
ppm 9,00 (1 H, s), 7,92 (1 H, d), 7,71 (1 H, d), 7,59 (1 H, t), 7,20 - 7,45 (2 H, m), 3,96 (1 H, d), 3,65 (1 H, d), 3,22 (1 H, d), 3,08 (1 H, d), 2,66 - 3,00 (4 H, m), 2,05 - 2,23 (2 H, m), 1,50 - 1,86 (3 H, m). T. R. = 1,37; $[M+H]^+$ = 309,31.

Ejemplo 240

(R)-N-(6-Fenoxipirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

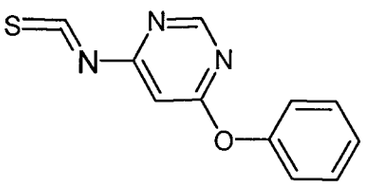


Etapa A: 6-Fenoxipirimidin-4-amina



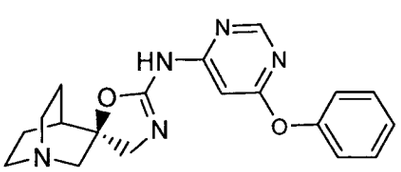
6-Cloropirimidin-4-amina (3,00 g, 23,14 mmol) se añadió a una solución de sodio (0,197 g, 8,57 mmol) en fenol (11,29 g, 120 mmol) a 55 °C. La mezcla se calentó a 140 °C durante 2 h, luego se mantuvo a temperatura ambiente durante 20 h. La mezcla de reacción se vertió en NaOH acuoso al 32% en hielo/agua manteniendo la temperatura de la mezcla por debajo de 20 °C. La mezcla se extrajo con cloroformo y el extracto orgánico se secó sobre cloruro de calcio y se concentró. El residuo se purificó por cromatografía sobre gel de sílice (2-20 % de acetato de etilo en hexanos) proporcionando 6-fenoxipirimidin-4-amina (0,6 g, 3,21 mmol, 75 % de rendimiento) como un sólido blanco. LCMS T. R. = 1,37; $[M+H]^+$ = 197,95.

Etapa B: 4-Isotiocianato-6-fenoxipirimidina



Una mezcla de 6-fenoxipirimidin-4-amina (0,288 g, 1,538 mmol) y 1,1'-tiocarbonildipiridin-2(1H)-ona (0,357 g, 1,538 mmol) en DCM se agitó a ta durante 18 h. La mezcla naranja pálido se purificó por cromatografía sobre gel de sílice (5-35 % de acetato de etilo-hexanos) proporcionando 4-isotiocianato-6-fenoxipirimidina (0,55 g, 2,96 mmol, 85 % de rendimiento) como un aceite amarillo. LCMS T. R. = 2,78; $[M+H]^+$ = 229,94.

Etapa C: (R)-N-(6-Fenoxipirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

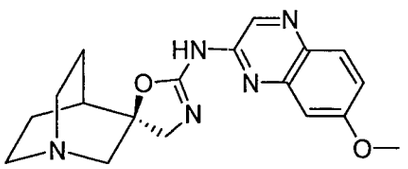


A diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (0,170 g, 0,742 mmol) en N,N-dimetilformamida (20 ml) se añadió Cs_2CO_3 (0,604 g, 1,854 mmol) y 4-isotiocianato-6-fenoxipirimidina (0,17 g, 0,742 mmol). La suspensión se agitó a temperatura ambiente durante 30 minutos. Se añadió entonces N,N'-diisopropilcarbodiimida (0,347 ml, 2,225 mmol) y se continuó agitando la mezcla a temperatura ambiente durante 18 horas. La mezcla se concentró y se

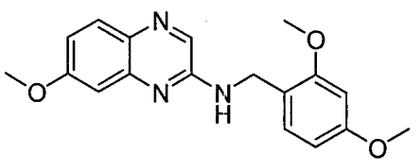
purificó por cromatografía sobre gel de sílice (5-25 % de metanol:hidróxido amónico 9:1-acetato de etilo) proporcionando (R)-N-(6-fenoxipirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,21 g, 0,72 mmol, 48,2% de rendimiento) como un sólido amarillo pálido. RMN de ^{1}H (500 MHz, *MeOD*) δ ppm 8,43 (1 H, s), 7,47 (2 H, t), 7,30 (1 H, t), 7,16 (2 H, d), 6,21 (1 H, s ancho), 4,03 (1 H, d), 3,72 (1 H, d), 3,22 (1 H, d), 3,11 (1 H, d), 2,73 - 2,99 (4 H, m), 2,00 - 2,18 (2 H, m), 1,54 - 1,88 (3 H, m). LCMS T. R. = 1,46; $[M+H]^+$ = 352,19.

EJEMPLO 241

(R)-N-(7-metoxiquinoxalin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



Etapa A: N-(2,4-Dimetoxibencil)-7-metoxiquinoxalin-2-amina

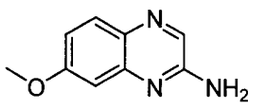


2-Cloro-7-metoxiquinoxalina (0,51 g, 2,62 mmol), preparado de acuerdo con *J. Chem. Soc. Perk Trans. 1*, **2001**, 978-984, y (2,4-dimetoxifenil)metanamina (1,181 ml, 7,86 mmol) se trataron en microondas en DMSO (2,5 ml) durante 30 min a 150 °C. Esto se diluyó en 150 ml de EtOAc y

se extrajo tres veces con 100 ml de salmuera. El producto bruto se purificó por cromatografía ultrarrápida en un cartucho de gel de sílice de 90 g con EtOAc del 20 al 80% en hexano, 50 min, a 40 ml/min proporcionando N-(2,4-dimetoxibencil)-7-metoxiquinoxalin-2-amina (795 mg, 2,443 mmol, 93 % de rendimiento).

RMN de ^{1}H (400 MHz, *CDCl$_3$*) δ ppm 8,00 (1 H, s), 7,70 (1 H, d, *J*=8,81 Hz), 7,29 (1 H, d, *J*=8,31 Hz), 7,05 (1 H, d, *J*=2,77 Hz), 6,97 (1 H, dd, *J*=9,06, 2,77 Hz), 6,47 (1 H, d, *J*=2,27 Hz), 6,43 (1 H, dd, *J*=8,18, 2,39 Hz), 5,22 (1 H, t, *J*=5,29 Hz), 4,63 (2 H, d, *J*=5,54 Hz), 3,91 (3 H, s), 3,83 (3 H, s), 3,78 (3 H, s)
LCMS: TR = 1,91 min, MH+ = 326,15.

Etapa B : 2,2,2-Trifluoroacetato de 7-metoxiquinoxalin-2-amina



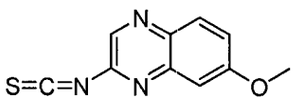
TFA

N-(2,4-Dimetoxibencil)-7-metoxiquinoxalin-2-amina (0,79 g, 2,428 mmol) se agitó en TFA (10 ml, 130 mmol)/CH_2Cl_2 (10 ml) a temperatura ambiente durante 30 min. Se eliminaron los disolvente en el evaporador rotatorio. Se añadió $NaHCO_3$ acuoso saturado (200 ml) al residuo rojo, que precipitó un sólido amarillo. La mezcla se extrajo minuciosamente con DCM. La fase orgánica se concentró y se secó a vacío proporcionando 2,2,2-trifluoroacetato de 7-metoxiquinoxalin-2-amina (0,70 g, 2,4 mmol, 99 % de rendimiento).

RMN de ^{1}H (400 MHz, *DMSO-d_6*) δ ppm 8,10 (1 H, s), 7,63 (1 H, d, *J*=9,07 Hz), 6,95 (1 H, dd, *J*=9,06, 2,77 Hz), 6,89 (1 H, d, *J*=2,77 Hz), 6,85 (2 H, s ancho), 3,84 (3 H, s)

LCMS: TR = 1,04 min, MH+ = 176,14.

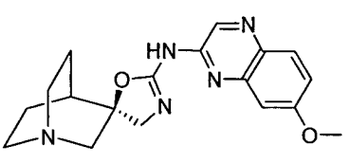
Etapa C: 2-Isotiocianato-7-metoxiquinoxalina



Una mezcla de 2,2,2-trifluoroacetato de 7-metoxiquinoxalin-2-amina (578 mg, 2 mmol), trietilamina (335 µl, 2,400 mmol) y 1,1'-tiocarbonildipiridin-2(1H)-ona (557 mg, 2,400 mmol) se agitó en 5 ml de DCM durante 24 h. La reacción se eluyó directamente en un cartucho de gel de sílice de 120 g con 0 a 25% de EtOAc en hexano, 25 min, a 35 ml/min proporcionando 2-isotiocianato-7-metoxiquinoxalina (84 mg, 0,387 mmol, 19 % de rendimiento).

LCMS: TR = 2,49 min, MH+ = 218,06.

Etapa D: (R)-N-(7-Metoxiquinoxalin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



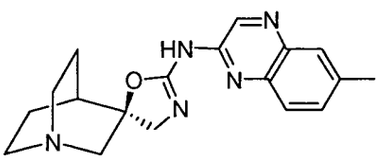
(R)-N-(7-Metoxiquinoxalin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina se sintetizó por el procedimiento del Ejemplo 23, Etapa B. La cromatografía ultrarrápida en un cartucho de gel de sílice de 120 g con 1-4% de [MeOH/NH_4OH 9:1] en $CHCl_3$, 50 min, proporcionó 24 mg (17 % de rendimiento).

RMN de ^1H (400 MHz, *$CDCl_3$*) δ ppm 9,73 (1 H, s ancho), 8,45 (1 H, s), 7,80 (1 H, d, J=9,07 Hz), 7,12 (1 H, dd, J=9,06, 2,77 Hz), 7,03 (1 H, d, J=2,52 Hz), 4,02 (1 H, d, J=9,32 Hz), 3,90 (3 H, s), 3,67 (1 H, d, J=9,32 Hz), 3,36 (1 H, dd, J=14,86, 1,51 Hz), 2,69 - 3,06 (5 H, m), 2,10 - 2,26 (2 H, m), 1,66 - 1,80 (1 H, m), 1,43 - 1,63 (2 H, m)

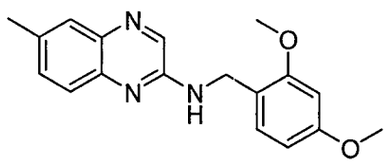
LCMS: TR = 0,835 min, MH- = 338,2, MH+ = 340,1.

EJEMPLO 242

(R)-N-(6-Metilquinoxalin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



Etapa A: N-(2,4-Dimetoxibencil)-6-metilquinoxalin-2-amina

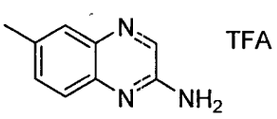


2-Cloro-6-metilquinoxalina (0,51 g, 2,86 mmol), preparada de acuerdo con *J. Chem. Soc.* **1948** ,1310-1313, y (2,4-dimetoxifenil)metanamina (1,29 ml, 8,57 mmol) se trataron en microondas en DMSO (2,5 ml) durante 30 min a 150 °C. Esto se diluyó en 150 ml de EtOAc y se extrajo tres veces con 100 ml de salmuera. El producto bruto se purificó por cromatografía ultrarrápida en un cartucho de gel de sílice de 90 g con 20 a 60% de EtOAc en hexano, 50 min, a 40 ml/min proporcionando N-(2,4-dimetoxibencil)-6-metilquinoxalin-2-amina (848 mg, 2,74 mmol, 96 % de rendimiento).

RMN de ^{1}H (400 MHz, *$CDCl_3$*) δ ppm 8,12 (1 H, s), 7,60 (1 H, s), 7,59 (1 H, d, *J*=5,79 Hz), 7,38 (1 H, dd, *J*=8,56, 1,76 Hz), 7,30 (1 H, d, *J*=8,31 Hz), 6,46 (1 H, d, *J*=2,27 Hz), 6,42 (1 H, dd, *J*=8,18, 2,39 Hz), 5,20 (1 H, t, *J*=5,41 Hz), 4,62 (2 H, d, *J*=5,54 Hz), 3,83 (3 H, s), 3,77 (3 H, s), 2,46 (3 H, s)

LCMS: TR = 1,93 min, MH+ = 310,20.

Etapa B: 2,2,2-Trifluoroacetato de 6-metilquinoxalin-2-amina



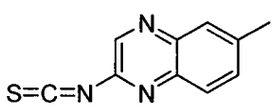
N-(2,4-Dimetoxibencil)-6-metilquinoxalin-2-amina (0,84 g, 2,72 mmol) se

agitó en TFA (10 ml, 130 mmol)/CH_2Cl_2 (10 ml) a temperatura ambiente durante 30 min. Se eliminaron los disolventes en el evaporador rotatorio. Se añadió Na_2CO_3 saturado (200 ml) al residuo rojo, que luego precipitó un sólido color castaño. La mezcla se extrajo minuciosamente con DCM. La fase orgánica se secó sobre sulfato sódico, se concentró y se secó a vacío proporcionando 2,2,2-trifluoroacetato de 6-metilquinoxalin-2-amina (640 mg, 2,343 mmol, 86 % de rendimiento).

RMN de ^{1}H (400 MHz, *DMSO-d_6*) δ ppm 8,24 (1 H, s), 7,55 (1 H, s), 7,34 - 7,45 (2 H, m), 6,82 (2 H, s), 2,41 (3 H, s)

LCMS: TR = 1,07 min, MH+ = 160,12.

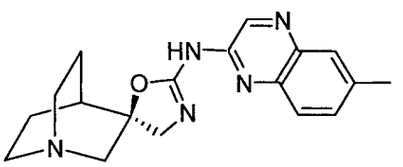
Etapa C : 2-Isotiocianato-6-metilquinoxalina



Una mezcla de 2,2,2-trifluoroacetato de 6-metilquinoxalin-2-amina (546 mg, 2 mmol), trietilamina (243 mg, 2,400 mmol) y 1,1'-tiocarbonildipiridin-2(1H)-ona (557 mg, 2,40 mmol) se agitó en 5 ml DCM durante 4 h. La reacción se eluyó directamente en un cartucho de gel de sílice de 120 g con 0 a 25% de EtOAc en hexano, 25 min, a 35 ml/min proporcionando 2-isotiocianato-6-metilquinoxalina (153 mg, 0,760 mmol, 38 % de rendimiento).

LCMS: TR = 2,59 min, MH+ = 202,04

Etapa D : (R)-N-(6-Metilquinoxalin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



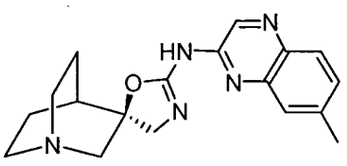
(R)-N-(6-Metilquinoxalin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina se sintetizó por el procedimiento del Ejemplo 23, Etapa B. La cromatografía ultrarrápida en un cartucho de gel de sílice de 120 g con 1 a 4% de [MeOH/NH_4OH 9 :1] en $CHCl_3$, 50 min, proporcionó 46 mg (19 % de rendimiento).

RMN de ^{1}H (400 MHz, *$CDCl_3$*) δ ppm 9,75 (1 H, s ancho), 8,57 (1 H, s), 7,71 (1 H, s), 7,60 (1 H, d, J=8,56 Hz), 7,42 (1 H, dd, J=8,44, 1,89 Hz), 4,01 (1 H, d, J=9,57 Hz), 3,68 (1 H, d, J=9,32 Hz), 3,38 (1 H, dd, J=14,86, 1,01 Hz), 2,73 - 3,08 (5 H, m), 2,50 (3 H, s), 2,16 - 2,26 (1 H, m), 2,14 (1 H, s ancho), 1,67 - 1,79 (1 H, m), 1,45 - 1,65 (2 H, m)

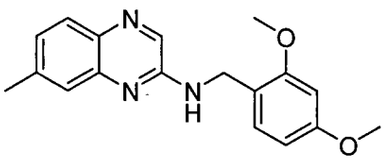
LCMS: TR = 0,838 min, MH- = 322,2, MH+ = 324,2.

EJEMPLO 243

(R)-N-(7-Metilquinoxalin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



Etapa A: N-(2,4-Dimetoxibencil)-7-metilquinoxalin-2-amina

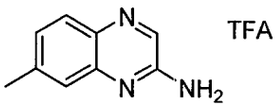


2-Cloro-7-metilquinoxalina (0,51 g, 2,86 mmol),), preparada de acuerdo con *J. Chem. Soc.* **1948** 1310-1313, y (2,4-dimetoxifenil)metanamina (1,29 ml, 8,57 mmol) se trataron en microondas en DMSO (2,5 ml) durante 30 min a 150 °C. Esto se diluyó en 150 ml de EtOAc y se extrajo tres veces con 100 ml de salmuera. El producto bruto se purificó por cromatografía ultrarrápida en un cartucho de gel de sílice de 90 g con EtOAc del 20 al 80% en hexano, 50 min, a 40 ml/min proporcionando N-(2,4-dimetoxibencil)-7-metilquinoxalin-2-amina (860 mg, 2,78 mmol, 97 % de rendimiento).

RMN de ^{1}H (400 MHz, *$CDCl_3$*) δ ppm 8,08 (1 H, s), 7,70 (1 H, d, *J*=8,31 Hz), 7,49 (1 H, s), 7,30 (1 H, d, *J*=8,06 Hz), 7,17 (1 H, dd, *J*=8,31, 2,01 Hz), 6,47 (1 H, d, *J*=2,52 Hz), 6,42 (1 H, dd, *J*=8,31, 2,52 Hz), 5,23 (1 H, t, *J*=5,16 Hz), 4,63 (2 H, d, *J*=5,79 Hz), 3,83 (3 H, s), 3,78 (3 H, s), 2,48 (3 H, s)

LCMS: TR = 1,93 min, MH+ = 310,20.

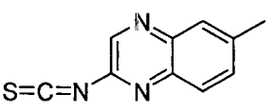
Etapa B: 2,2,2-Trifluoroacetato de 7-metilquinoxalin-2-amina



N-(2,4-Dimetoxibencil)-7-metilquinoxalin-2-amina (0,85 g, 2,75 mmol) se agitó en TFA (10 ml, 130 mmol)/CH_2Cl_2 (10 ml) a temperatura ambiente durante 30 min. Se eliminaron los disolventes en el evaporador rotatorio. Se añadió $NaHCO_3$ acuoso saturado (200 ml) al residuo rojo, que luego precipitó un sólido rosa. La mezcla se extrajo minuciosamente con DCM. La fase orgánica se secó sobre sulfato sódico, se concentró y se secó a vacío proporcionando 2,2,2-trifluoroacetato de 7-metilquinoxalin-2-amina (640 mg, 2,34 mmol, 85 % de rendimiento).

RMN de ^{1}H (400 MHz, *DMSO-d_6*) δ ppm 8,20 (1 H, s), 7,64 (1 H, d, *J*=8,31 Hz), 7,28 (1 H, s), 7,15 (1 H, dd, *J*=8,31, 1,76 Hz), 6,89 (2 H, s), 2,42 (3 H, s)
LCMS: TR = 1,07 min, MH+ = 160,12.

Etapa C : 2-Isotiocianato-6-metilquinoxalina

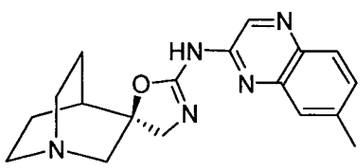


Una mezcla de 2,2,2-trifluoroacetato de 7-metilquinoxalin-2-amina (546 mg, 2 mmol) 78263-058-01, trietilamina (243 mg, 2,40 mmol) y 1,1'-

tiocarbonildipiridin-2(1H)-ona (557 mg, 2,40 mmol) se agitó en 5 ml de DCM durante 2 h. La reacción se eluyó directamente en un cartucho de gel de sílice de 120 g con 0 a 25% de EtOAc en hexano, 25 min, a 35 ml/min proporcionando 2-isotiocianato-7-metilquinoxalina (185 mg, 0,919 mmol, 46 % de rendimiento).

LCMS: TR = 2,58 min, MH+ = 202,04

Etapa D : (R)-N-(7-Metilquinoxalin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



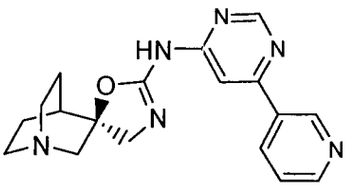
(R)-N-(7-Metilquinoxalin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina se sintetizó por el procedimiento del Ejemplo 23, Etapa B. La cromatografía ultrarrápida en un cartucho de gel de sílice de 120 g con 1 a 3% de [MeOH/NH_4OH 9:1] en $CHCl_3$, 50 min, proporcionó 22 mg (7 % de rendimiento).

RMN de ^{1}H (400 MHz, *$CDCl_3$*) δ ppm 9,80 (1 H, s ancho), 8,53 (1 H, s), 7,81 (1 H, d, *J*=8,31 Hz), 7,50 (1 H, s), 7,31 (1 H, dd, *J*=8,56, 1,76 Hz), 4,01 (1 H, d, *J*=9,57 Hz), 3,66 (1 H, d, *J*=9,32 Hz), 3,36 (1 H, d, *J*=14,86 Hz), 2,70 - 3,04 (5 H, m), 2,50 (3 H, s), 2,15 - 2,24 (1 H, m), 2,13 (1 H, s ancho), 1,66 - 1,79 (1 H, m), 1,44 - 1,63 (2 H, m)

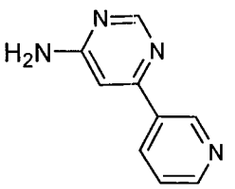
LCMS: TR = 8,67 min, MH- = 322,6, MH+ = 324,1.

Ejemplo 244

(R)-N-(6-(Piridin-3-il)pirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

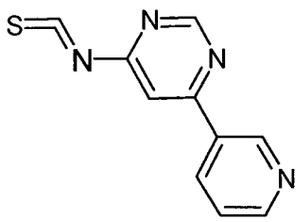


Etapa A: 6-(Piridin-3-il)pirimidin-4-amina



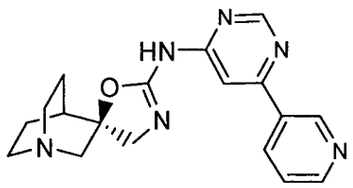
Una mezcla de 6-cloropirimidin-4-amina (0,324 g, 2,5 mmol), ácido piridin-3-ilborónico (0,384 g, 3,13 mmol), Na_2CO_3 (0,795 g, 7,50 mmol) y cloruro de bis(trifenilfosfina)paladio(II) (0,035 g, 0,050 mmol) se suspendió en una mezcla de DME/EtOH/agua. La mezcla se calentó en el sintetizador de microondas a 125 ºC durante 20 min y se concentró. El residuo se purificó por cromatografía sobre gel de sílice (acetato de etilo del 10-60% en hexanos, luego 5-25% de metanol:hidróxido amónico 9:1-acetato de etilo) proporcionando 6-(piridin-3-il)pirimidin-4-amina (0,17 g, 0,987 mmol, 40 % de rendimiento) como un sólido blanquecino. LCMS T. R. = 0,31; $[M+H]^+$ = 173,11.

Etapa B: 4-Isotiocianato-6-(piridin-3-il)pirimidina



A una solución de 1,1'-tiocarbonildipiridin-2(1H)-ona (0,682 g, 2,94 mmol) en diclorometano/N,N-dimetilformamida a temperatura ambiente se añadió 6-(piridin-3-il)pirimidin-4-amina (0,337 g, 1,957 mmol). La mezcla se calentó a 60 ºC durante 18 horas. La LC/MS mostró el pico del producto deseado como el pico principal. La mezcla naranja intenso se purificó por cromatografía sobre gel de sílice (1-40 % de acetato de etilo-hexanos) proporcionando 4-isotiocianato-6-metoxipirimidina (0,12 g, 0,56 mmol, 28,6 % de rendimiento) como un aceite naranja.

Etapa C: (R)-N-(6-(Piridin-3-il)pirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

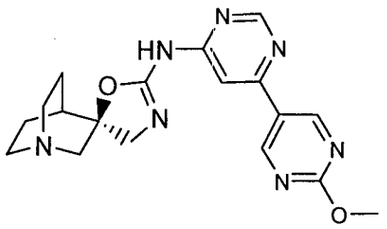


A diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (0,13 g, 0,560 mmol) en N,N-dimetilformamida (20 ml) se añadió Cs_2CO_3 (0,46 g, 1,4 mmol) y 4-isotiocianato-6-(piridin-3-il)pirimidina (0,12 g, 0,56 mmol). La suspensión se agitó a temperatura ambiente durante 30 minutos. A continuación se añadió N,N'-diisopropilcarbodiimida (0,26 ml, 1,7 mmol) y la mezcla se agitó a temperatura ambiente durante 18 horas. La mezcla se concentró y se purificó por cromatografía sobre gel de sílice (0-10% de [metanol:hidróxido amónico

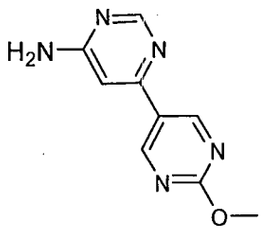
9:1]-acetato de etilo) proporcionando (S)-N-(5-cloropirazin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,182 g, 0,613 mmol, 35 % de rendimiento) como un sólido blanquecino. RMN de ^{1}H (400 MHz, MeOD) δ ppm 9,13 - 9,21 (1 H, m), 8,82 (1 H, d), 8,63 (1 H, dd), 8,44 (1 H, dt), 7,56 (1 H, dd), 7,31 (1 H, s), 4,06 (1 H, d), 3,76 (1 H, d), 3,20 - 3,28 (1 H, m), 3,08 - 3,16 (1 H, m), 2,72 - 3,01 (4 H, m), 2,00 - 2,24 (2 H, m), 1,52 - 1,83 (3 H, m). LCMS T. R. = 0,72; $[M+H]^+$ = 337,2.

Ejemplo 245

(R)-N-(2'-Metoxi-4,5'-bipirimidin-6-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



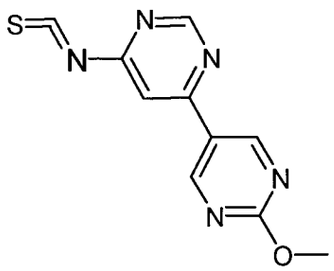
Etapa A: 2'-Metoxi-4,5'-bipirimidin-6-amina



Se suspendieron 6-cloropirimidin-4-amina (0,35 g, 2,70 mmol), ácido 2-metoxipirimidin-5-ilborónico (0,520 g, 3,38 mmol), Na_2CO_3 (0,859 g, 8,11 mmol) y cloruro de bis(trifenilfosfina)paladio(II) (0,038 g, 0,054 mmol) en una mezcla de DME/EtOH/agua. (15:2:3 ml). La mezcla se calentó en el sintetizador de microondas a 125 ºC durante 20 min y se concentró. El residuo se purificó por cromatografía sobre gel de sílice (0-5 % de metanol:hidróxido amónico 9:1-

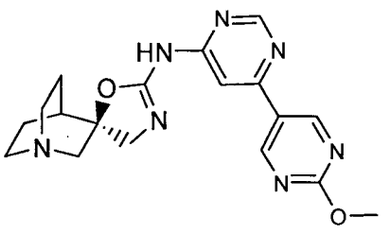
acetato de etilo) proporcionando 6-(piridin-3-il)pirimidin-4-amina (0,28 g, 1,378 mmol, 51 % de rendimiento) como un sólido blanquecino. LCMS T. R. = 0,53; $[M+H]^+$ = 204,11.

Etapa B: 6-Isotiocianato-2'-metoxi-4,5'-bipirimidina



A una solución de 1,1'-tiocarbonildipiridin-2(1H)-ona (0,832 g, 3,58 mmol) en diclorometano/N,N-dimetilformamida a temperatura ambiente se añadió 2'-metoxi-4,5'-bipirimidin-6-amina (0,56 g, 2,76 mmol). La mezcla naranja se calentó a 60 ºC durante 18 horas. La LC/MS mostró el pico del producto deseado como el pico principal. La mezcla naranja intenso se purificó por cromatografía sobre gel de sílice (0-40 % de acetato de etilo-hexanos) proporcionando 4-isotiocianato-6-metoxipirimidina (0,1 g, 0,408 mmol, 15 % de rendimiento) como un sólido naranja. LCMS T. R. = 2,29; $[M+H]^+$ = 246,03.

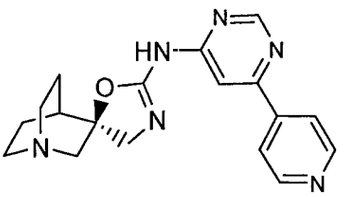
Etapa C: (R)-N-(2'-Metoxi-4,5'-bipirimidin-6-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



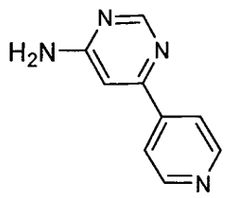
A diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (0,093 g, 0,41 mmol) en N,N-dimetilformamida (20 ml) se añadió Cs_2CO_3 (0,33 g, 1 mmol)) y 6-isotiocianato-2'-metoxi-4,5'-bipirimidina (0,1 g, 0,41 mmol). La suspensión se agitó a temperatura ambiente durante 30 minutos. Se añadió entonces N,N'-diisopropilcarbodiimida (0,19 ml, 1,2 mmol) se añadió entonces y la mezcla se agitó a temperatura ambiente durante 18 horas. La mezcla se concentró y se purificó por cromatografía sobre gel de sílice (5-25 % de [metanol:hidróxido amónico 9:1]-acetato de etilo) proporcionando (R)-N-(2'-metoxi-4,5'-bipirimidin-6-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,072 g, 0,188 mmol, 46 % de rendimiento) como un sólido blanquecino. RMN de ^1H (400 MHz, MeOD) δ ppm 9,19 (2 H, s), 8,80 (1 H, d), 7,24 (1 H, s ancho), 4,00 - 4,09 (4 H, m), 3,76 (1 H, d), 3,23 (1 H, s), 3,08 - 3,15 (1 H, m), 2,72 - 3,04 (4 H, m), 1,97 - 2,22 (2 H, m), 1,38 - 1,85 (3 H, m). T. R. = 1,22; $[M+H]^+$ = 368,22.

Ejemplo 246

(R)-N-(6-(Piridin-4-il)pirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

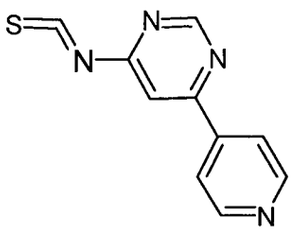


Etapa A: 6-(Piridin-4-il)pirimidin-4-amina



Se suspendieron 6-cloropirimidin-4-amina (0,324 g, 2,5 mmol), ácido piridin-4-ilborónico (0,384 g, 3,13 mmol), Na_2CO_3 (0,795 g, 7,50 mmol) y cloruro de bis(trifenilfosfina)paladio(II) (0,035 g, 0,050 mmol) en una mezcla de DME/EtOH/agua (15:2:3 ml). La mezcla se calentó en el sintetizador de microondas a 125 ºC durante 20 min y se concentró. El residuo se purificó por cromatografía sobre gel de sílice (5-25 % de [metanol:hidróxido amónico 9:1]-acetato de etilo) proporcionando 6-(piridin-3-il)pirimidin-4-amina (0,15 g, 0,871 mmol, 35 % de rendimiento) como un sólido blanquecino. LCMS T. R. = 0,30; $[M+H]^+$ = 173,11.

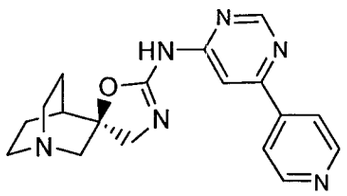
Etapa B: 4-Isotiocianato-6-(piridin-4-il)pirimidina



A una solución de 1,1'-tiocarbonildipiridin-2(1H)-ona (0,601 g, 2,59 mmol) en diclorometano/N,N-dimetilformamida a temperatura ambiente se añadió 6-(piridin-4-il)pirimidin-4-amina (0,297 g, 1,725 mmol). La mezcla naranja se calentó a 60 ºC durante 18 horas. La LC/MS mostró el pico del producto deseado como el pico principal. La mezcla naranja intenso se purificó por cromatografía sobre gel de sílice (acetato de etilo del 0-40%-hexanos) proporcionando 4-isotiocianato-6-(piridin-4-il)pirimidina (0,055 g, 0,257 mmol,

15 % de rendimiento) como un sólido naranja. LCMS T. R. = 1,46; $[M+H]^+$ = 215,09.

Etapa C: (R)-N-(6-(Piridin-4-il)pirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

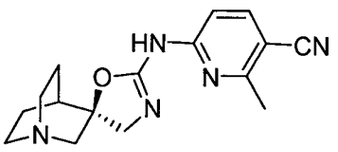


A diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (0,059 g, 0,257 mmol) en N,N-dimetilformamida (15 ml) se añadió Cs_2CO_3 (0,209 g, 0,642 mmol) y 4-isotiocianato-6-(piridin-4-il)pirimidina (0,055 g, 0,257 mmol). La suspensión se agitó a temperatura ambiente durante 30 minutos. Se añadió entonces N,N'-diisopropilcarbodiimida (0,12 ml, 0,77 mmol) y se continuó agitando la mezcla a temperatura ambiente durante 18 horas. La mezcla se concentró y se purificó por cromatografía sobre gel de sílice (0-10 % de [metanol:hidróxido amónico 9:1]-acetato de etilo) proporcionando (R)-N-(6-(piridin-4-il)pirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,014 g, 0,04 mmol, 16 % de rendimiento) como una película amarilla. RMN de ^1H (400 MHz, MeOD) δ ppm 8,85 (1 H, d), 8,67 (2 H, dd), 8,04 (2 H, dd), 7,34 (1 H, s ancho), 4,06 (1 H, d), 3,76 (1 H, d), 3,23 (1 H, d), 3,10 (1 H, d), 2,70 - 2,99 (4 H, m), 2,01 - 2,22 (2 H, m), 1,53 - 1,86 (3 H, m). LCMS T. R. = 0,42; $[M+H]^+$ = 337,14.

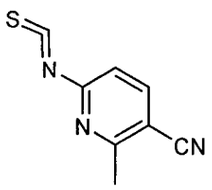
EJEMPLO 247

(R)-6-(4H-1'-Azaspiro[oxazol-5,3'-biciclo[2.2.2]octano]-2-ilamino)-2-

metilnicotinonitrilo

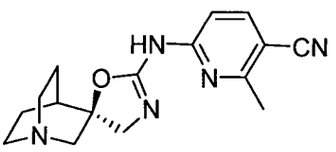


Etapa A: 6-Isotiocianato-2-metilnicotinonitrilo



A 6-amino-2-metilnicotinonitrilo (0,41 g, 3,08 mmol) en diclorometano (20 ml) se añadió 1,1'-tiocarbonildipiridin-2(1H)-ona (0,75 g, 3,23 mmol). La reacción se agitó a 40 °C durante 3 horas. La reacción se enfrió hasta temperatura ambiente. El bruto se purificó por cromatografía (Biotage: acetato de etilo del 25-100%/hexano) proporcionando 6-isotiocianato-2-metilnicotinonitrilo (0,52 g, 2,97 mmol, 96 % de rendimiento). RMN de ^{1}H (500 MHz, *DMSO-D6*) δ ppm 8,36 (d, *J*=8,24 Hz, 1 H), 7,39 (d, *J*=8,24 Hz, 1 H), 2,65 (s, 3 H). MS (LC/MS) T. R. = 2,09; $[M+H]^+$ = 176,0.

Etapa B: (R)-6-(4H-1'-Azaspiro[oxazol-5,3'-biciclo[2.2.2]octano]-2-ilamino)-2-metilnicotinonitrilo

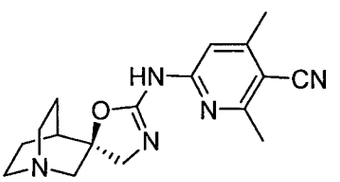


A 6-isotiocianato-2-metilnicotinonitrilo (0,25 g, 1,43 mmol) en N, N-dimetilformamida (20 ml) se añadió trietilamina (0,5 ml, 3,666 mmol) y

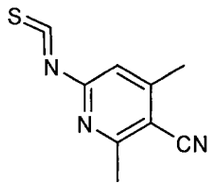
diclorhidrato de 3-(aminometil)quinuclidin-3-ol (0,33 g, 1,46 mmol) a temperatura ambiente. La reacción se agitó a 70 °C durante 2 horas. La reacción se enfrió hasta temperatura ambiente y se concentró a vacío. La urea bruta se purificó por cromatografía (Biotage: 85% de $CHCl_3$, 14% de MeOH, 1% de NH_4OH). El producto se trató entonces con N, N-dimetilformamida (20 ml) y N,N'-diisopropilcarbodiimida (0,67 ml, 4,28 mmol). La reacción se calentó hasta 70°C durante 2 horas. La reacción se enfrió hasta temperatura ambiente y se concentró a vacío proporcionando el producto bruto. El producto bruto se purificó por cromatografía (Biotage: 85% de $CHCl_3$, 14% de MeOH, 1% de NH_4OH) proporcionando (R)-6-(4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octano]-2-ilamino)-2-metilnicotinonitrilo (0,09 g, 0,3 mmol, 21 % de rendimiento) como un polvo blanco. RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 9,11 (s, 1 H), 7,87 (d, *J*=7,93 Hz, 2 H), 6,69 (s, 1 H), 3,89 (d, *J*=10,38 Hz, 2 H), 3,63 (d, *J*=10,38 Hz, 3 H), 3,00 (s, 5 H), 2,72 - 2,80 (m, 4 H), 2,64 - 2,69 (m, 5 H), 2,60 (s, 7 H), 2,00 (d, *J*=2,14 Hz, 3 H), 1,91 (s, 1 H), 1,87 (s, 2 H), 1,58 (s, 5 H), 1,42 - 1,50 (m, 2 H). MS (LC/MS) T. R. = 0,48; $[M+H]^+$ = 298,13.

EJEMPLO 248

(R)-6-(4H-1'-Azaspiro[oxazol-5,3'-biciclo[2.2.2]octano]-2-ilamino)-2,4-dimetilnicotinonitrilo

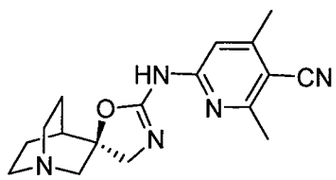


Etapa A: 6-Isotiocianato-2,4-dimetilnicotinonitrilo



A 6-amino-2,4-dimetilnicotinonitrilo (0,14 g, 0,95 mmol) en diclorometano (20 ml) se añadió 1,1'-tiocarbonildipiridin-2(1H)-ona (0,23 g, 0,1 mmol). La reacción se agitó a 40 °C durante 3 horas. La reacción se enfrió hasta temperatura ambiente. El bruto se purificó por cromatografía (Biotage: acetato de etilo del 25-100%/hexano) proporcionando 6-isotiocianato-2,4-dimetilnicotinonitrilo (0,15 g, 0,79 mmol, 83 % de rendimiento). RMN de ^{1}H (500 MHz, *DMSO-D6*) δ ppm 7,37 (s, 1 H), 2,63 (s, 3 H). MS (LC/MS) T. R. = 2,40; $[M+H]^+$ = 190.

Etapa B: (R)-6-(4H-1'-Azaspiro[oxazol-5,3'-biciclo[2.2.2]octano]-2-ilamino)-2,4-dimetilnicotinonitrilo

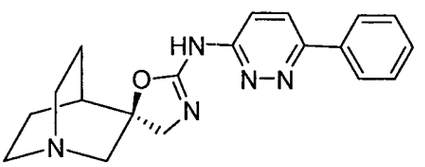


A 6-isotiocianato-2,4-dimetilnicotinonitrilo (0,09 g, 0,48 mmol) en N, N-dimetilformamida (20 ml) se añadió trietilamina (0,17 ml, 1,19 mmol) y diclorhidrato de 3-(aminometil)quinuclidin-3-ol (0,11 g, 0,49 mmol) a temperatura ambiente. La reacción se agitó a 70 °C durante 2 horas. La reacción se enfrió hasta temperatura ambiente y se concentró a vacío. La urea bruta se purificó por cromatografía (Biotage: 85% de $CHCl_3$, 14% de MeOH, 1% de NH_4OH). El producto se trató entonces con N, N-dimetilformamida (20

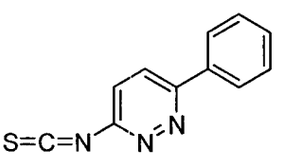
ml) y N,N'-diisopropilcarbodiimida (0,22 ml, 1,43 mmol). La reacción se calentó hasta 70 °C durante 2 horas. La reacción se enfrió hasta temperatura ambiente y se concentró a vacío proporcionando el producto bruto. El producto bruto se purificó por cromatografía (Biotage: 85% de $CHCl_3$, 14% de MeOH, 1% de NH_4OH) proporcionando (R)-6-(4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octano]-2-ilamino)-2,4-dimetilnicotinonitrilo (0,10 g, 0,32 mmol, 66 % de rendimiento) como un polvo blanco. RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 9,08 (s, 1 H), 6,60 (s, 1 H), 3,88 (d, *J*=10,38 Hz, 1 H), 3,61 (d, *J*=10,38 Hz, 1 H), 2,98 (s, 2 H), 2,70 - 2,79 (m, 2 H), 2,63 - 2,69 (m, 2 H), 2,55 - 2,60 (m, 4 H), 2,31 - 2,39 (m, 4 H), 1,99 (s, 1 H), 1,89 (s, 1 H), 1,54 - 1,62 (m, 2 H), 1,41 - 1,49 (m, 1 H). MS (LC/MS) T. R. = 0,78; $[M+H]^+$ = 312,1.

EJEMPLO 249

(R)-N-(6-Fenilpiridazin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



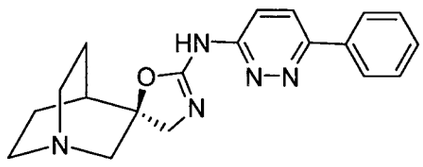
Etapa A: 3-Isotiocianato-6-fenilpiridazina



Se sintetizó 3-isotiocianato-6-fenilpiridazina por el procedimiento del Ejemplo 23, Etapa B. La cromatografía ultrarrápida en un cartucho de gel de sílice de 120 g con 0 a 25% de EtOAc en hexano, 25 min, a 35 ml/min proporcionó 420 mg (49 % de rendimiento).

LCMS: TR = 2,17 min, MH+ = 214,06.

Etapa B : (R)-N-(6-Fenilpiridazin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



Se sintetizó (R)-N-(6-fenilpiridazin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina por el procedimiento del Ejemplo 23, Etapa B. La cromatografía ultrarrápida en un cartucho de gel de sílice de 160 g con 1-4 % de [MeOH/NH_4OH 9:1] en $CHCl_3$, 50 min, a 40 ml/min proporcionó 67 mg (R)-N-(6-fenilpiridazin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (17 % de rendimiento).

RMN de ^1H (400 MHz, *$CDCl_3$*) δ ppm 9,61 (1 H, s ancho), 7,95 - 7,99 (2 H, m), 7,74 (1 H, d, *J*=9,32 Hz), 7,39 - 7,52 (3 H, m), 7,22 (1 H, d parcial), 3,97 (1 H, d, *J*=9,32 Hz), 3,64 (1 H, d, *J*=9,32 Hz), 3,37 (1 H, dd, *J*=14,73, 1,38 Hz), 2,69 -

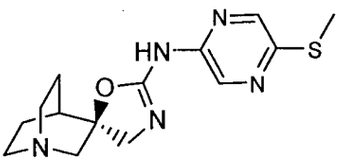
3,06 (5 H, m), 2,16 - 2,26 (1 H, m), 2,14 (1 H, s ancho), 1,66 - 1,79 (1 H, m), 1,45 - 1,60 (2 H, m)

RMN de ^{1}H (400 MHz, *MeOD*) δ ppm 7,87 - 8,02 (3 H, m), 7,44 - 7,55 (3 H, m), 7,13 - 7,29 (1 H, m), 4,05 (1 H, d, *J*=9,82 Hz), 3,74 (1 H, d, *J*=10,07 Hz), 3,17 (2 H, dd, *J*=49,35, 14,60 Hz), 2,73 - 3,04 (4 H, m), 2,16 (2 H, s ancho), 1,55 - 1,85 (3 H, m)

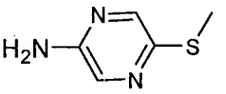
LCMS: TR = 0,82 min, MH- = 334,2, MH+ = 336,2.

EJEMPLO 250

(R)-N-(5-(Metiltio)pirazin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



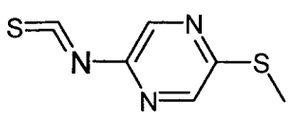
Etapa A: 5-(Metiltio)pirazin-2-amina



A una solución de 5-bromopirazin-2-amina (2 g, 11,49 mmol) en N,N-dimetilformamida (20 ml) se añadió tiometóxido sódico (1,611 g, 22,99 mmol). La mezcla se agitó y se calentó a 100 °C en nitrógeno durante 18 h y se concentró. El residuo se trató con agua y la mezcla se extrajo con diclorometano. Los orgánicos reunidos se secaron con sulfato sódico, se filtraron y concentraron. El residuo se purificó por cromatografía sobre gel de sílice (0-10% de metanol:hidróxido amónico 9:1-acetato de etilo) proporcionando 6-(piridin-3-il)pirimidin-4-amina (0,15 g, 0,871 mmol, 35 % de

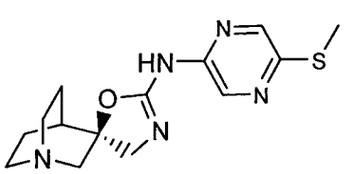
rendimiento) como un sólido amarillo. LCMS T. R. = 0,91; $[M+H]^+$ = 141,89.

Etapa B: 2-Isotiocianato-5-(metiltio)pirazina



A una solución de 1,1'-tiocarbonildipiridin-2(1H)-ona (1,069 g, 4,60 mmol) en diclorometano a temperatura ambiente se añadió 5-(metiltio)pirazin-2-amina (0,50 g, 3,54 mmol). La reacción se agitó a temperatura ambiente durante 18 horas. La LC/MS mostró el pico del producto deseado como el pico principal. La mezcla naranja intenso se purificó por cromatografía sobre gel de sílice (acetato de etilo del 0-40%-hexanos) proporcionando 2-isotiocianato-5-(metiltio)pirazina (0,545 g, 0,257 mmol, 84 % de rendimiento) como un aceite naranja. LCMS T. R. = 2,65; $[M+H]^+$ = 184,02.

Etapa C: (R)-N-(5-(Metiltio)pirazin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

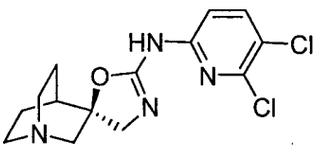


A diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (0,375 g, 1,637 mmol) en N,N-dimetilformamida (15 ml) se añadió Cs_2CO_3 (1,333 g, 4,09 mmol) y 2-isotiocianato-5-(metiltio)pirazina (0,3 g, 1,637 mmol). La suspensión se agitó a temperatura ambiente durante 30 minutos. Se añadió entonces N,N'-diisopropilcarbodiimida (0,765 ml, 4,9 mmol) y se continuó agitando la mezcla a

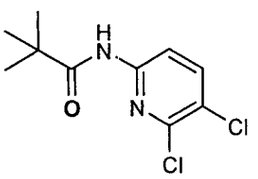
temperatura ambiente durante 18 horas. La mezcla se concentró y se purificó por cromatografía sobre gel de sílice (5-25 % de metanol:hidróxido amónico 9:1-acetato de etilo) proporcionando (R)-N-(5-(metiltio)pirazin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,014 g, 0,04 mmol, 16 % de rendimiento) como un sólido amarillo. P.F. 155-60 °C. RMN de ^{1}H (400 MHz, MeOD) δ ppm 8,13 (1 H, d), 8,06 (1 H, s), 3,96 (1 H, d), 3,66 (1 H, d), 3,20 (1 H, d), 3,08 (1 H, d), 2,87 - 2,96 (2 H, m), 2,72 - 2,82 (2 H, m), 2,52 (3 H, s), 2,00 - 2,19 (2 H, m), 1,51 - 1,81 (3 H, m). LCMS T. R. = 1,01; $[M+H]^+$ = 306,12.

EJEMPLO 251

(R)-N-(5,6-Dicloropiridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



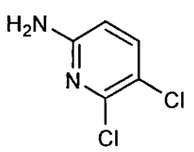
Etapa A: N-(5,6-Dicloropiridin-2-il)pivalamida



A una solución de N-(6-cloropiridin-2-il)pivalamida, sintetizada como en *J. Org. Chem* **2005**, *70*, 1771, (1,02 g, 4,80 mmol) en cloroformo (25 ml) se añadió 1-cloropirrolidin-2,5-diona (0,62 g, 4,67 mmol) y la mezcla se llevó a reflujo en un baño de aceite durante 3 horas. Se dejó enfriar hasta temperatura ambiente durante la noche. La mezcla de reacción se evaporó a vacío y se

volvió a disolver en DMF (15 ml). Se añadieron otros 480 mg de 1-cloropirrolidin-2,5-diona y la solución resultante se calentó durante la noche en un baño de aceite a 95-100°, luego se enfrió de nuevo hasta temperatura ambiente. El disolvente se eliminó a vacío y el residuo se repartió entre agua y acetato de etilo. La fase acuosa se lavó dos veces más con acetato de etilo y las fases orgánicas reunidas se lavaron con salmuera, se secaron sobre sulfato de magnesio y se evaporaron a vacío. La TLC (acetato de etilo al 10%/hexano) mostró una mancha robusta a Rf 0,6 con manchas más pequeñas a Rf 0,4 y 0,2. Se sometió el material a Biotage en acetato de etilo del 5-10%/hexano, recogiendo la fracción de Rf 0,6 dando 790 mg (66%) de sólido blanco, N-(5,6-dicloropiridin-2-il)pivalamida. RMN de ^{1}H (500 MHz, *CDCl$_3$*) δ ppm 8,17 (s, 1 H), 7,96 (s, 1 H), 7,72 (s, 1 H), 1,31 (s, 10 H). MS (LC/MS) T. R. = 1,85; $[M+H]^+$ = 248,8.

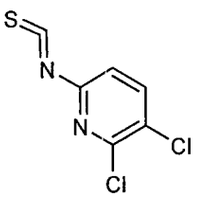
Etapa B: 5,6-Dicloropiridin-2-amina



Se calentó una mezcla de N-(5,6-dicloropiridin-2-il)pivalamida (790 mg, 3,20 mmol), ácido clorhídrico, 37% (1,25 ml), agua (1,25 ml), y EtOH (3 ml) durante 4 horas en un baño de aceite a 85-90°C. La LCMS mostró conversión casi completa al producto. La reacción se enfrió hasta temperatura ambiente y la mezcla de reacción se evaporó hasta un pequeño volumen, luego se transfirió a un embudo de separación en el que se repartió entre carbonato sódico acuoso y acetato de etilo. Se separaron las fases, se lavó de nuevo la fase acuosa con acetato de etilo y las fases orgánicas reunidas se lavaron con

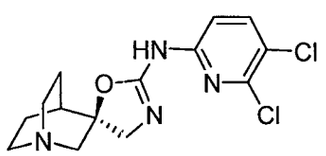
salmuera, se secaron sobre $MgSO_4$, se filtraron y evaporaron dando un sólido blanco. El material se sometió a una columna Biotage en acetato de etilo al 20%/hexano, recogiendo el componente principal. Se obtuvo 5,6-dicloropiridin-2-amina (0,49 g, 2,98 mmol, 93%) como un sólido blanco. RMN de ^1H (500 MHz, *CDCl₃*) δ ppm 7,44 (d, *J*=8,55 Hz, 1 H), 6,36 (d, *J*=8,24 Hz, 1 H), 4,58 (s, 2 H). MS (LC/MS) T. R. = 1,28; $[M+H]^+$ = 164,8.

Etapa C: 5,6-Dicloro-2-isotiocianatopiridina



A 5,6-dicloropiridin-2-amina (0,47 g, 2,88 mmol) en diclorometano (25 ml) se añadió 1,1'-tiocarbonildipiridin-2(1H)-ona (0,68 g, 2,94 mmol). La reacción se agitó a 40 °C durante 3 horas, luego se enfrió hasta temperatura ambiente. El material bruto se purificó por cromatografía (Biotage: acetato de etilo del 25-100%/hexano) dando 2,3-dicloro-6-isotiocianatopiridina (0,48 g, 2,34 mmol, 81 % de rendimiento) como un polvo blanco. RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 8,26 (d, *J*=8,55 Hz, 1 H), 7,47 (d, *J*=8,24 Hz, 1 H). MS (LC/MS) T. R. = 2,83; $[M+H]^+$ = 204,8.

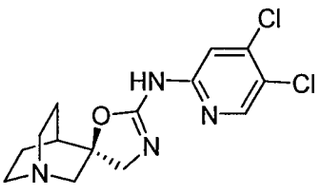
Etapa D: (R)-N-(5,6-Dicloropiridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



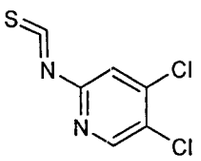
A 2,3-dicloro-6-isotiocianatopiridina (0,47 g, 2,29 mmol) en N,N-dimetilformamida (20 ml) se añadió trietilamina (0,8 ml, 5,7 mmol) y diclorhidrato de 3-(aminometil)quinuclidin-3-ol (0,54 g, 2,34 mmol) a temperatura ambiente. La reacción se agitó a 70 °C durante 2 horas, se enfrió hasta temperatura ambiente y se concentró a vacío. La urea bruta se purificó por cromatografía (Biotage: 85% de $CHCl_3$, 14% de MeOH, 1% de NH_4OH). El producto se trató entonces con N,N-dimetilformamida (20 ml) y N,N'-diisopropilcarbodiimida (1,07 ml, 6,88 mmol). La reacción se calentó hasta 70°C durante 2 horas. La reacción se enfrió hasta temperatura ambiente y se concentró a vacío. El producto bruto se purificó por cromatografía (Biotage: 85% de $CHCl_3$, 14% de MeOH, 1% de NH_4OH) proporcionando (R)-N-(5,6-dicloropiridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,36 g, 1,08 mmol, 47 % de rendimiento) como un polvo blanco. RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 8,31 (d, *J*=1,22 Hz, 1 H), 7,84 (s, 1 H), 6,80 (s, 1 H), 3,85 (d, *J*=10,07 Hz, 1 H), 3,57 (d, *J*=10,38 Hz, 2 H), 2,98 (s, 3 H), 2,69 - 2,78 (m, 3 H), 2,65 (t, *J*=7,78 Hz, 3 H), 2,00 (s, 2 H), 1,86 (s, 2 H), 1,58 (dd, *J*=7,48, 2,90 Hz, 2 H), 1,56 (s, 1 H), 1,41 - 1,49 (m, 2 H). MS (LC/MS) T. R. = 0,81; $[M+H]^+$ = 327,1.

EJEMPLO 252

(R)-N-(4,5-Dicloropiridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

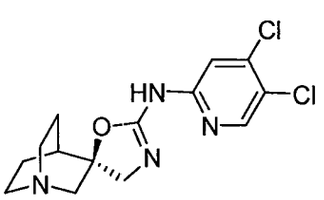


Etapa A: 4,5-Dicloro-2-isotiocianatopiridina



A 4,5-dicloropiridin-2-amina (0,25 g, 1,53 mmol) en diclorometano (25 ml) se añadió 1,1'-tiocarbonildipiridin-2(1H)-ona (0,36 g, 1,56 mmol). La reacción se agitó a 40°C durante 3 horas, luego se enfrió hasta temperatura ambiente. El material bruto se purificó por cromatografía (Biotage: acetato de etilo del 25-100%/hexano) proporcionando 4,5-dicloro-2-isotiocianatopiridina (0,26 g, 1,27 mmol, 83 % de rendimiento) como un polvo amarillo. El producto se llevó directamente a la etapa siguiente.

Etapa B: (R)-N-(4,5-Dicloropiridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

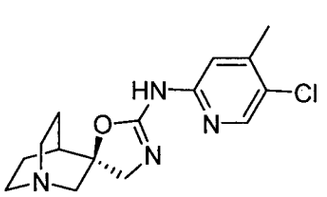


A 4,5-dicloro-2-isotiocianatopiridina (0,25 g, 1,22 mmol) en N,N-dimetilformamida (20 ml) se añadió trietilamina (0,43 ml, 3,05 mmol) y diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (0,29 g, 1,24 mmol) a

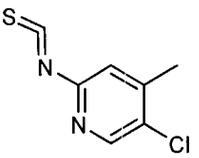
temperatura ambiente. La reacción se agitó a 70 °C durante 2 horas. La reacción se enfrió hasta temperatura ambiente y se concentró a vacío. La urea bruta se purificó por cromatografía (Biotage: 85% de $CHCl_3$, 14% de MeOH, 1% de NH_4OH). El producto se trató entonces con N,N-dimetilformamida (20 ml) y N,N'-diisopropilcarbodiimida (0,57 ml, 3,66 mmol). La reacción se calentó hasta 70 °C durante 2 horas. La reacción se enfrió hasta temperatura ambiente y se concentró proporcionando el producto bruto. El producto bruto se purificó por cromatografía (Biotage: 85% de $CHCl_3$, 14% de MeOH, 1% de NH_4OH) proporcionando (R)-N-(4,5-dicloropiridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,09 g, 0,27 mmol, 22 % de rendimiento) como un polvo blanco. RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 8,81 (s, 1 H), 8,32 (d, *J*=6,10 Hz, 1 H), 7,03 (s, 1 H), 3,83 (d, *J*=9,46 Hz, 1 H), 3,57 (d, *J*=9,77 Hz, 1 H), 2,98 (s, 2 H), 2,71 - 2,79 (m, 2 H), 2,65 (t, *J*=7,78 Hz, 2 H), 1,99 (s, 1 H), 1,86 (s, 1 H), 1,53 - 1,61 (m, 2 H), 1,41 - 1,49 (m, 1 H). MS (LC/MS) T. R. = 0,78; $[M+H]^+$ = 327,0.

EJEMPLO 253

(R)-N-(5-Cloro-4-metilpiridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

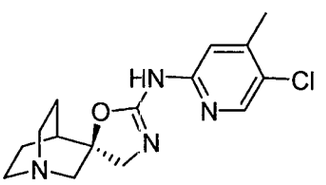


Etapa A: 5-Cloro-2-isotiocianato-4-metilpiridina



A 5-cloro-4-metilpiridin-2-amina (0,41 g, 2,88 mmol) en diclorometano (25 ml) se añadió 1,1'-tiocarbonildipiridin-2(1H)-ona (0,70 g, 3,0 mmol). La reacción se agitó a 40 °C durante 3 horas. La reacción se enfrió hasta temperatura ambiente. La mezcla bruta se purificó por cromatografía (Biotage: acetato de etilo del 25-100%/hexano) proporcionando 5-cloro-2-isotiocianato-4-metilpiridina (0,45 g, 2,44 mmol, 85 % de rendimiento). RMN de ^{1}H (500 MHz, *DMSO-D6*) δ ppm 8,45 (s, 1 H), 7,47 (s, 1 H), 2,37 (s, 3 H). LC/MS RT=2,79; $[M+H]^+$ = 184,9.

Etapa B: (R)-N-(5-Cloro-4-metilpiridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

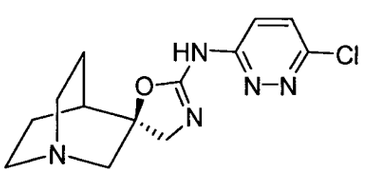


A 5-cloro-2-isotiocianato-4-metilpiridina (0,37 g, 2,0 mmol) en N,N-dimetilformamida (20 ml) se añadió trietilamina (0,7 ml, 5,0 mmol) y diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (de la Etapa B del Ejemplo 17) (0,47 g, 2,0 mmol) a temperatura ambiente. La reacción se agitó a 70 °C durante 2 horas. La reacción se enfrió hasta temperatura ambiente y se concentró a vacío. La urea bruta se purificó por cromatografía (Biotage: 85% de $CHCl_3$, 14% de MeOH, 1% de NH_4OH). El producto se trató entonces con N,N-dimetilformamida (20 ml) y N,N'-diisopropilcarbodiimida (0,94 ml, 6,0 mmol). La reacción se calentó hasta 70°C durante 2 horas. La reacción se

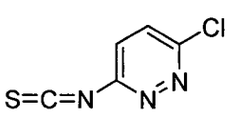
enfrió hasta temperatura ambiente y se concentró proporcionando el producto bruto. El producto bruto se purificó por cromatografía (Biotage: 85% de $CHCl_3$, 14% de MeOH, 1% de NH_4OH) proporcionando (R)-N-(5-cloro-4-metilpiridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,19 g, 0,61 mmol, 30,3 % de rendimiento) como un polvo blanco. RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 8,79 (s, 1 H), 8,08 - 8,15 (m, 2 H), 6,78 (s, 1 H), 3,82 (d, *J*=8,55 Hz, 2 H), 3,55 (d, *J*=10,38 Hz, 2 H), 2,93 - 3,02 (m, 5 H), 2,71 - 2,80 (m, 5 H), 2,66 (t, *J*=7,63 Hz, 4 H), 2,23 - 2,29 (m, 7 H), 1,94 - 2,02 (m, 2 H), 1,92 (s, 1 H), 1,86 (s, 2 H), 1,53 - 1,62 (m, 5 H), 1,41 - 1,49 (m, *J*=12,55, 9,88, 7,02, 2,29 Hz, 2 H). MS (LC/MS) T. R. = 0,72; $[M+H]^+$ = 307,1.

EJEMPLO 254

(R)-N-(6-Cloropiridazin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



Etapa A: 3-Cloro-6-isotiocianatopiridazina

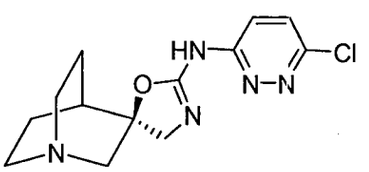


3-Cloro-6-isotiocianatopiridazina se sintetizó por el procedimiento del Ejemplo 218, Etapa D. La cromatografía ultrarrápida en un cartucho de gel de

sílice de 120 g con 0 a 25% de EtOAc en hexano, 25 min, a 35 ml/min proporcionó 213 mg (31 % de rendimiento).

LCMS: TR = 1,25 min, MH+ = 172,00.

Etapa B: (R)-N-(6-Cloropiridazin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



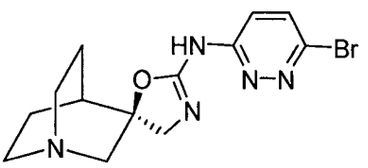
(R)-N-(6-Cloropiridazin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina se sintetizó por el procedimiento del Ejemplo 218, Etapa E. La cromatografía ultrarrápida en un cartucho de gel de sílice de 160 g con 1-3 % de [MeOH 9:1/NH_4OH] en $CHCl_3$, 50 min, a 40 ml/min proporcionó 29 mg (8 % de rendimiento).

RMN de ^{1}H (400 MHz, *$CDCl_3$*) δ ppm 9,27 (1 H, s ancho), 7,28 (1 H, d, *J*=9,07 Hz), 7,10 (1 H, d, *J*=9,07 Hz), 3,95 (1 H, d, *J*=9,57 Hz), 3,62 (1 H, d, *J*=9,57 Hz), 3,34 (1 H, dd, *J*=14,98, 1,64 Hz), 2,67 - 3,04 (5 H, m), 2,14 - 2,21 (1 H, m), 2,12 (1 H, s ancho), 1,65 - 1,79 (1 H, m), 1,45 - 1,61 (2 H, m).

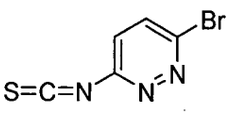
LCMS: TR = 0,62 min, MH- = 292,1, MH+ = 294,1.

EJEMPLO 255

(R)-N-(6-Bromopiridazin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



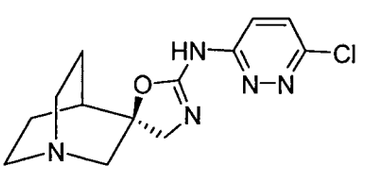
Etapa A: 3-Bromo-6-isotiocianatopiridazina



3-Bromo-6-isotiocianatopiridazina se sintetizó por el procedimiento del Ejemplo 218, Etapa D. La cromatografía ultrarrápida en un cartucho de gel de sílice de 120 g con 0 a 25% de EtOAc en hexano, 25 min, a 35 ml/min proporcionó 364 mg (42 % de rendimiento).

LCMS: TR = 1,34 min, MH+ = 215,92.

Etapa B : (R)-N-(6-Bromopiridazin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



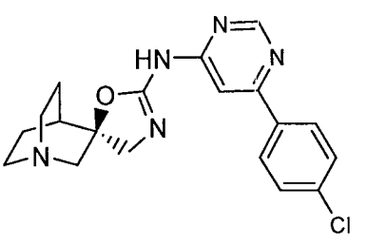
(R)-N-(6-Bromopiridazin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina se sintetizó por el procedimiento del Ejemplo **218**, Etapa E. La cromatografía ultrarrápida en un cartucho de gel de sílice de 160 g con 1-3 % de [MeOH/NH_4OH 9:1] en $CHCl_3$, 50 min, a 40 ml/min proporcionó 211 mg (37 % de rendimiento).

RMN de ^1H (400 MHz, *$CDCl_3$*) δ ppm 9,23 (1 H, s ancho), 7,37 (1 H, d, *J*=9,07 Hz), 6,97 (1 H, d, *J*=9,07 Hz), 3,92 (1 H, d, *J*=9,57 Hz), 3,59 (1 H, d, *J*=9,82 Hz), 3,29 (1 H, dd, *J*=14,98, 1,64 Hz), 2,63 - 2,99 (5 H, m), 2,04 - 2,19 (2 H, m), 1,59 - 1,74 (1 H, m), 1,39 - 1,58 (2 H, m)

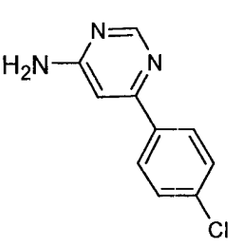
LCMS: RT= 0,64 min., MH- 336,1, MH+ 338,0.

EJEMPLO 256

(R)-N-(6-(4-Clorofenil)pirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

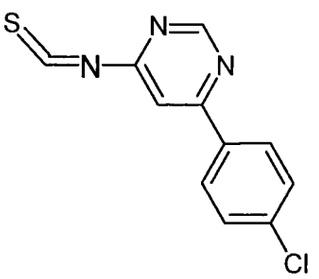


Etapa A: 6-(Piridin-4-il)pirimidin-4-amina



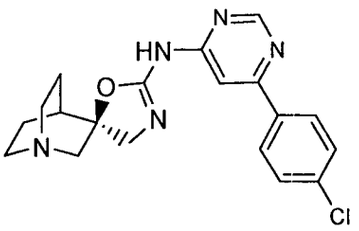
Una mezcla de 6-cloropirimidin-4-amina (0,324 g, 2,5 mmol), ácido 4-clorofenilborónico (0,489 g, 3,13 mmol), Na_2CO_3 (0,795 g, 7,50 mmol) y cloruro de bis(trifenilfosfina)paladio(II) (0,035 g, 0,050 mmol) se suspendió en una mezcla de DME/EtOH/agua (15:2:3 ml). La mezcla se calentó en el sintetizador de microondas a 125 °C durante 20 min y se concentró. El residuo se purificó por cromatografía sobre gel de sílice (2-15 % de metanol:hidróxido amónico 9:1-acetato de etilo) proporcionando 6-(piridin-3-il)pirimidin-4-amina (0,3 g, 0,871 mmol, 58,4 % de rendimiento) como un sólido blanquecino. LCMS T. R. = 1,42; $[M+2H]^+$ = 207,91.

Etapa B: 4-(4-Clorofenil)-6-isotiocianatopirimidina



A una solución naranja brillante de 1,1'-tiocarbonildipiridin-2(1H)-ona (0,666 g, 2,87 mmol) diclorometano/ N,N-dimetilformamida a temperatura ambiente se añadió 6-(4-clorofenil)pirimidin-4-amina (0,59 g, 2,87 mmol). La mezcla naranja se calentó a 60 °C durante 18 horas. La LC/MS mostró el pico del producto deseado como un pico principal. La mezcla naranja intenso se purificó por cromatografía sobre gel de sílice (acetato de etilo del 0-40%-hexanos) proporcionando 4-(4-clorofenil)-6-isotiocianatopirimidina (0,322 g, 1,300 mmol, 45 % de rendimiento) como un aceite naranja. LCMS T. R. = 2,82; $[M]^+$ = 248,03.

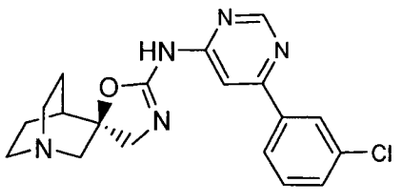
Etapa C: (R)-N-(6-(4-Clorofenil)pirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



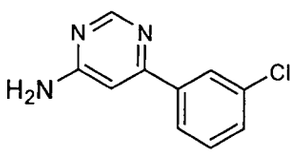
A diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (0,298 g, 1,300 mmol) en N,N-dimetilformamida (15 ml) se añadió Cs_2CO_3 (1,059 g, 3,25 mmol) y 4-(4-clorofenil)-6-isotiocianatopirimidina (0,322 g, 1,300 mmol). La suspensión se agitó a temperatura ambiente durante 30 minutos. Se añadió entonces N,N'-diisopropilcarbodiimida (0,608 ml, 3,90 mmol) y la mezcla se agitó a temperatura ambiente durante 18 horas. La mezcla se concentró y se purificó por cromatografía sobre gel de sílice (5-25 % de metanol:hidróxido amónico 9:1-acetato de etilo) proporcionando (R)-N-(6-(piridin-4-il)pirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,104 g, 0,276 mmol, 21 % de rendimiento) como un sólido amarillo. RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 9,54 (1 H, s ancho), 8,83 (1 H, d), 7,89 - 8,04 (2 H, m), 7,41 - 7,54 (2 H, m), 7,33 (1 H, s ancho), 4,02 (1 H, d), 3,71 (1 H, d), 3,42 (1 H, d), 2,73 - 3,15 (5 H, m), 2,10 - 2,31 (2 H, m), 1,46 - 1,89 (3 H, m). LCMS T. R. = 1,92; $[M]^+$ = 370,35.

EJEMPLO 257

(R)-N-(6-(3-Clorofenil)pirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

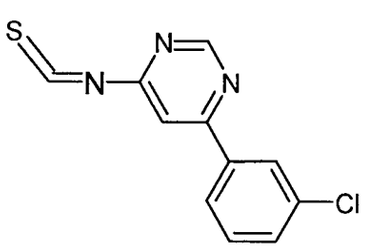


Etapa A: 6-(3-Clorofenil)pirimidin-4-amina



Se suspendió una mezcla de 6-cloropirimidin-4-amina (0,324 g, 2,5 mmol), ácido 3-clorofenilborónico (0,489 g, 3,13 mmol), Na_2CO_3 (0,795 g, 7,50 mmol) y cloruro de bis(trifenilfosfina)paladio(II) (0,035 g, 0,050 mmol) en una mezcla de DME/EtOH/agua (15:2:3 ml). La mezcla se calentó en el sintetizador de microondas a 125 °C durante 20 min y se concentró. El residuo se purificó por cromatografía sobre gel de sílice (acetato de etilo del 30-70 % en hexanos) proporcionando 6-(3-clorofenil)pirimidin-4-amina (0,47g, 2,286 mmol, 91 % de rendimiento) como un sólido amarillo. LCMS T. R. = 1,45; $[M+2H]^+$ = 208,05.

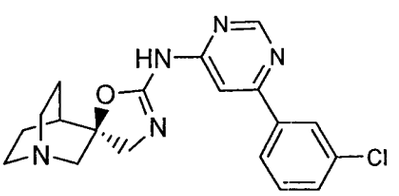
Etapa B: 4-(3-Clorofenil)-6-isotiocianatopirimidina



A una solución naranja brillante de 1,1'-tiocarbonildipiridin-2(1H)-ona(0,486 g, 2,091 mmol) en diclorometano/ N,N-dimetilformamida a temperatura ambiente se añadió 6-(3-clorofenil)pirimidin-4-amina (0,43 g, 2,091

mmol). La mezcla naranja se calentó a 60 °C durante 18 horas. La LC/MS mostró el pico del producto deseado como un pico principal. La mezcla naranja intenso se purificó por cromatografía sobre gel de sílice (acetato de etilo del 0-40%-hexanos) proporcionando 4-(3-clorofenil)-6-isotiocianatopirimidina (0,12 g, 0,484 mmol, 23 % de rendimiento) como un aceite naranja. LCMS T. R. = 2,15; $[M]^+$ = 248,31.

Etapa C: (R)-N-(6-(3-Clorofenil)pirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

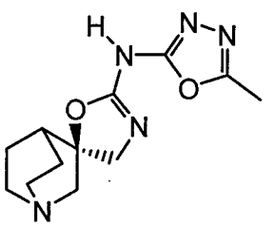


A diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (0,111 g, 0,484 mmol) en N,N-dimetilformamida (15 ml) se añadió Cs_2CO_3 (0,395 g, 1,211 mmol) y 4-(3-clorofenil)-6-isotiocianatopirimidina (0,12 g, 0,484 mmol). La suspensión se agitó a temperatura ambiente durante 30 minutos. Se añadió entonces N,N'-diisopropilcarbodiimida (0,226 ml, 1,453 mmol) y se continuó agitando la mezcla a temperatura ambiente durante 18 horas. La mezcla se concentró y se purificó por cromatografía sobre gel de sílice (5-25 %, luego, 2-10 % de metanol:hidróxido amónico 9:1-acetato de etilo) proporcionando (R)-N-(6-(3-clorofenil)pirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,086 g, 0,221 mmol, 46 % de rendimiento) como un sólido amarillo. RMN de ^1H (400 MHz, MeOD) δ ppm 8,82 (1 H, d), 8,05 (1 H, d), 7,93 (1 H, ddd), 7,43 - 7,52 (2 H, m), 7,35 (1 H, s ancho), 4,13 (1 H, d), 3,93 (1 H, d), 3,63 - 3,81 (2 H, m), 3,42 - 3,53 (1 H, m), 3,30 - 3,40 (3 H, m), 2,46 (1 H, d), 2,26 -

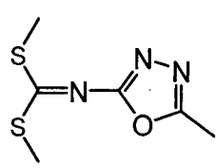
2,40 (1 H, m), 1,88 - 2,16 (3 H, m). LCMS T. R. = 1,90; $[M]^+$ = 370,28.

EJEMPLO 258

(R)-N-(5-Metil-1,3,4-oxadiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

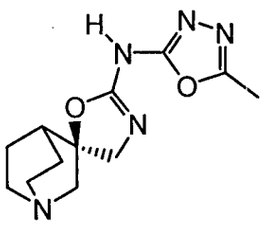


Etapa A: 5-Metil-1,3,4-oxadiazol-2-ilcarbonimidoditioato de dimetilo



A una solución de 5-metil-1,3,4-oxadiazol-2-amina (1,92g, 20 mmol) en DMF (10ml) se añadió NaOH (20M, 2 ml), CS_2 (3 ml), NaOH (20M, 2 ml) y yodometano (3ml) lentamente durante 10 minutos. La mezcla se agitó a temperatura ambiente durante 1 h y se vertió en 20 ml de agua. El sólido precipitado se filtró, se lavó con agua y se secó obteniendo el producto deseado 5-metil-1,3,4-oxadiazol-2-ilcarbonimidoditioato de dimetilo como un sólido blanco (1,45g, 35,7%). RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 2,63 (s, 6H), 2,50 (s, 3H). LCMS T.R. 1,66 min; [M+H] = 203,91.

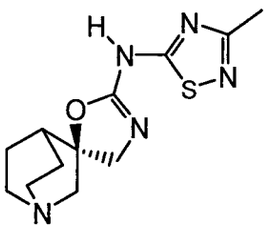
Etapa B: (R)-N-(5-Metil-1,3,4-oxadiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



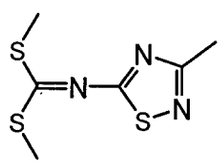
Una mezcla de 5-metil-1,3,4-oxadiazol-2-ilcarbonimidoditioato de dimetilo (260 mg, 1,28 mmol), diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (200 mg, 1,28 mmol) y carbonato de cesio (876 mg, 2,69 mmol) en DMF (5ml) se agitó durante la noche a temperatura ambiente. La mezcla se concentró y se purificó en una columna de gel de sílice Biotage (acetato de etilo al 100%, luego metanol del 10-35%:hidróxido amónico 9:1-cloroformo) obteniendo el producto deseado, (R)-N-(5-metil-1,3,4-oxadiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (192 mg, 54,1%). RMN de ^{1}H (500 MHz, MeOD) δ ppm 4,05 (d, 1H), 3,74 (d, 1H), 3,25 (d, 1H), 3,15 (d, 1H), 2,94 (m, 2H), 2,85 (m, 2H), 2,43 (s, 3H), 2,19(m, 1H), 2,10 (m, 1H), 1,6-1,8 (m, 3H). MS (LCMS) [M+H] = 264,05. T. R. 0,16 min.

EJEMPLO 259

(R)-N-(3-Metil-1,2,4-tiadiazol-5-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

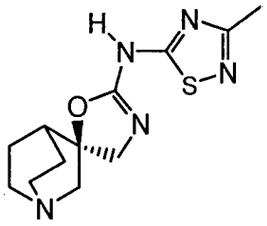


Etapa A: 3-Metil-1,2,4-tiadiazol-5-ilcarbonimidoditioato de dimetilo



A una solución de 3-metil-1, 2, 4-tiadiazol-5-amina (2,3g, 20 mmol) en DMF (10ml) se añadió NaOH (20M, 2ml), CS_2 (3ml), NaOH (20M, 2ml) y yodometano (3ml) lentamente durante 10 minutos. La mezcla se agitó a temperatura ambiente durante 1 h y se vertió en 20 ml de agua. El sólido precipitado se filtró y se lavó con agua, y se secó obteniendo 3-metil-1,2,4-tiadiazol-5-ilcarbonimidoditioato de dimetilo impuro, un sólido amarillo (2,3 g, 52,5%). RMN de ^1H (500 MHz, CDCl3) δ ppm 2,67 (s), 2,62 (s). MS [M+H] = 219,85.

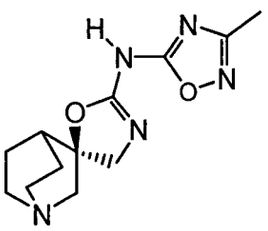
Etapa B: (R)-N-(3-Metil-1,2,4-tiadiazol-5-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



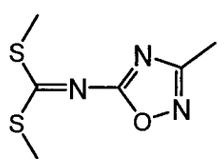
Se agitó a temperatura ambiente durante la noche una mezcla de 3-metil-1,2,4-tiadiazol-5-ilcarbonimidoditioato de dimetilo (281 mg, 1,28 mmol), diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (200 mg, 1,28 mmol) y carbonato de cesio (876 mg, 2,69 mmol) en DMF (5 ml). La mezcla se concentró y se purificó en una columna de gel de sílice Biotage (acetato de etilo al 100%, luego metanol al 10-35%:hidróxido amónico 9:1-cloroformo) obteniendo el producto deseado, (R)-N-(3-metil-1,2,4-tiadiazol-5-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (147,8 mg, 40,5%). RMN de ^{1}H (500 MHz, MeOD) δ ppm 4,01-3,99 (d, 1H), 3,72-3,70 (d, 1H), 3,27 (d, 1H), 3,16 (d, 1H), 3,01-2,9 (m, 2H), 2,86-2,83 (m, 2H), 2,43 (s, 3H), 2,21-2,0(m, 2H), 1,81-1,75(m, 1H), 1,75-1,70 (m, 2H). MS (LCMS) [M+H] = 279,99; T. R. = 0,2 min.

EJEMPLO 260

(R)-N-(3-Metil-1,2,4-oxadiazol-5-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

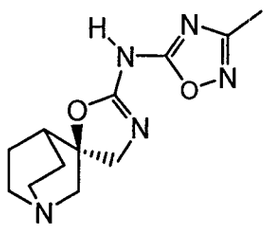


Etapa A: 3-Metil-1,2,4-oxadiazol-5-ilcarbonimidoditioato de dimetilo



A una solución de 3-metil-1, 2, 4-oxadiazol-5-amina (490 mg, 4,94mmol) en DMF (5ml) se añadió NaOH (20M, 0,5ml), CS_2 (1ml), NaOH (20M, 0,5ml) y yodometano (1ml) lentamente durante 10 minutos. La mezcla se agitó a temperatura ambiente durante 1 hora. La mezcla se volvió muy densa y se añadieron 20 ml de agua. Se separó el sólido por filtración, se lavó con agua y se secó obteniendo 3-metil-1,2,4-oxadiazol-5-ilcarbonimidoditioato de dimetilo impuro, un sólido amarillo (770 mg, 77%). MS (LCMS) [M+H] = 203,91; T. R. = 1,84 min. El producto se usó directamente en la etapa siguiente.

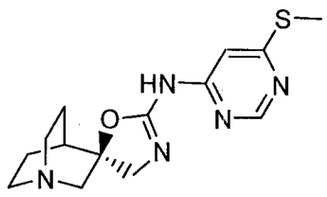
Etapa B: (R)-N-(3-Metil-1,2,4-oxadiazol-5-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



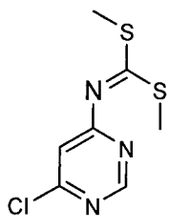
Se agitó a temperatura ambiente durante la noche una mezcla de 3-metil-1,2,4-oxadiazol-5-ilcarbonimidoditioato de dimetilo (280 mg, 1,37 mmol), diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (215 mg, 1,37 mmol) y carbonato de cesio (942 mg, 2,89 mmol) en DMF (5ml). La mezcla se concentró y se purificó en una columna de gel de sílice Biotage (acetato de etilo al 100%, luego metanol al 10-35%:hidróxido amónico 9:1-cloroformo) obteniendo el producto deseado, (R)-N-(3-metil-1,2,4-oxadiazol-5-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (198 mg, 51,9%). RMN de ^{1}H (500 MHz, MeOD) δ ppm 4,1-4,0 (d, 1H), 3,8-3,7 (d, 1H), 3,4-3,2 (d, 1H), 3,2-3,1 (d, 1H), 3,0-2,9 (m, 2H), 2,9-2,8 (m, 2H), 2,27 (s, 3H), 2,2 (m, 1H), 2,2-2,0 (m, 1H), 1,9-1,6 (m, 3H). MS (LCMS) [M+H] = 264,05; T. R. = 0,26 min.

EJEMPLO 261

(R)-N-(6-(Metiltio)pirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

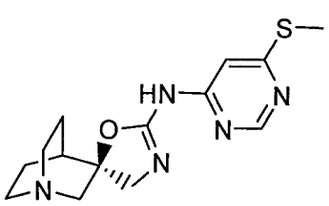


Etapa A: 6-Cloropirimidin-4-ilcarbonimidoditioato de dimetilo



A una solución de 6-cloropirimidin-4-amina (1,295 g, 10 mmol) en N,N-dimetilformamida (12 ml) se añadió gota a gota NaOH (1 ml, 20,00 mmol, 20 M), CS_2 (1,5 ml, 24,88 mmol), NaOH (1 ml, 20,00 mmol, 20 M) y yodometano (1,5 ml, 23,99 mmol) a intervalos de 15 min. Se continuó agitando durante 1,5 h y la mezcla se vertió en agua. Se lavó el sólido naranja separado con agua, se secó y recristalizó en metanol proporcionando 6-cloropirimidin-4-ilcarbonimidoditioato de dimetilo (0,966 g, 4,13 mmol, 41,3 % de rendimiento) como un sólido amarillo. LCMS T. R. = 2,39; $[M+H]^+$ = 234,08.

Etapa B: (R)-N-(6-(Metiltio)pirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

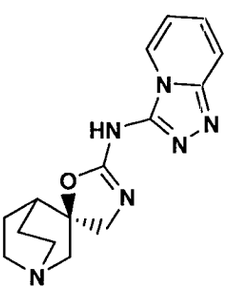


A diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (0,9 g, 3,93 mmol) en N,N-dimetilformamida (20 ml) se añadió Cs_2CO_3 (2,69 g, 8,25 mmol) y 6-cloropirimidin-4-ilcarbonimidoditioato de dimetilo (0,964 g, 4,12 mmol). La suspensión se agitó a temperatura ambiente durante 18 horas, luego se calentó a 100 ºC durante 3 horas. La mezcla se concentró y se purificó por cromatografía sobre gel de sílice (5-15 % de metanol:hidróxido amónico 9:1-

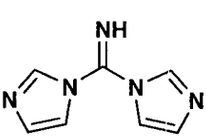
acetato de etilo) proporcionando (R)-N-(6-(metiltio)pirimidin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,21 g, 0,72 mmol, 48,2% de rendimiento) como un sólido amarillo pálido. RMN de ^{1}H (400 MHz, $CDCl_3$) δ ppm 9,43 (1 H, s ancho), 8,55 (1 H, d), 6,78 (1 H, s ancho), 3,98 (1 H, d), 3,64 (1 H, d), 3,37 (1 H, dd), 2,72 - 3,06 (5 H, m), 2,51 (3 H, s), 2,08 - 2,24 (2 H, m), 1,69 - 1,81 (1 H, m), 1,41 - 1,64 (2 H, m). LCMS T. R. = 0,93; $[M+H]^+$ = 306,29.

EJEMPLO 262

(R)-N-([1,2,4]Triazol[4,3-a]piridin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



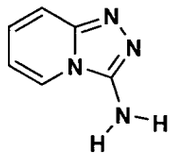
Etapa A: Di(1H-imidazol-1-il)metanimina



A una solución de 1H-imidazol (42g, 617mmol) en diclorometano (1L) se añadió bromuro de cianógeno (22,5, 212 mmol) y la mezcla se calentó hasta reflujo durante 30 minutos, se dejó enfriar hasta temperatura ambiente y se separó el sólido blanco por filtración. El filtrado se concentró hasta 10 0ml y se

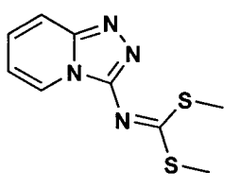
almacenó en el refrigerador durante 3 días. Se separó el sólido precipitado por filtración obteniendo 8 g de di(1H-imidazol-1-il)metanimina (49,6mmol, 8%). RMN de ^{1}H (500 MHz, DMSO) δ ppm 8,09 (s, 1H), 7,55 (s, 1H), 7,13 (s, 1H).

Etapa B: [1, 2, 4]Triazolo[4,3-a]piridin-3-amina



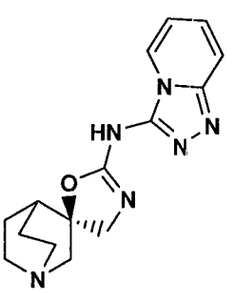
A una solución de 2-hidrazinilpiridina (5,2g, 47,6 mmol) en THF (70ml) se añadió di(1H-imidazol-1-il)metanimina (7,8g, 48,4mmol). La mezcla se calentó hasta reflujo durante la noche. La mezcla bruta se evaporó y se purificó en una columna de gel de sílice Biotage (0-25%, metanol-cloruro de metileno) recogiendo la mancha de color púrpura, [1, 2, 4]triazolo[4,3-a]piridin-3-amina (4,7g, 35mmol, 73,5%). RMN de ^{1}H (500 MHz, DMSO) δ ppm 8,05-8,0 (m, 1H), 7,44-7,40 (m, 1H), 7,08-7,0 (m, 1H), 6,74-6,70 (m, 1H), 6,35 (s, 2H). MS (LCMS) [M+H] = 134,98; T. R. = 0,1 min.

Etapa C: [1, 2, 4]Triazol[4,3-a]piridin-3-ilcarbonimidoditioato de dimetilo



A una solución de [1,2,4]triazolo[4,3-a]piridin-3-amina (300 mg, 2,24mmol) en DMF (5ml) se añadió NaOH (20M, 0,25ml), CS_2 (0,5ml), NaOH (20M, 0,25ml) y yodometano (0,5ml) lentamente durante 10 minutos. La mezcla se agitó a temperatura ambiente durante 1 h y se añadieron a la mezcla de reacción 10 ml de agua. El sólido precipitado se separó por filtración, se lavó con agua (100ml), y se secó obteniendo 230 mg [1, 2, 4]triazol[4,3-a]piridin-3-ilcarbonimidoditioato de dimetilo (0,96 mmol, 43,1%), un sólido blanco. RMN de ^{1}H (500 MHz, CDCl3) δ ppm 8,17 (d, 1H), 7,7 (d, 1H), 7,24-7,22 (t, 1H), 6,84-6,80 (t, 1H), 2,71-2,68 (d, 6H). MS (LCMS) [M+H] = 238,94; T. R. = 1,26 min.

Etapa D: (R)-N-([1,2,4]Triazol[4,3-a]piridin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

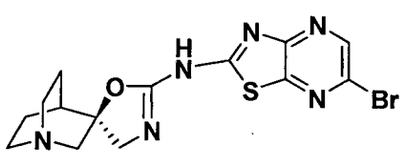


Se calentó a 70 °C durante 6 horas una mezcla de [1,2,4]triazol[4,3-a]piridin-3-ilcarbonimidotioato de dimetilo (120 mg, 0,50 mmol), diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (120 mg, 0,76 mmol) y carbonato de cesio (492 mg, 1,5 mmol) en DMF (5ml). La mezcla se concentró y se purificó en una columna de gel de sílice Biotage (acetato de etilo al 100%, luego metanol al 10-

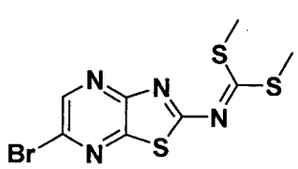
35%:hidróxido amónico 9:1-cloroformo) obteniendo el producto deseado, (R)-N-([1,2,4]triazol[4,3-a]piridin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (97,2 mg, 61,5%). RMN de ^{1}H (500 MHz, CDCl3) δ ppm 8,2-8,1 (d, 1H), 7,6-7,5 (d, 1H), 7,2-7,1 (t, 1H), 6,7-6,6 (t, 1H), 4,1-4,0 (d, 1H), 3,7-3,6 (d, 1H), 3,5-3,4 (m, 1H), 3,1-2,7 (m, 5H), 2,4-2,2 (m, 2H), 1,8-1,7 (m, 1H), 1,7-1,5(m, 2H). MS (LCMS) [M+H] = 299,3; T. R. = 1,22 min.

EJEMPLO 263

(R)-N-(6-bromotiazolo[5,4-b]pirazin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



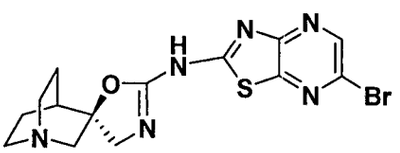
Etapa A: 6-Bromotiazolo[5,4-b]pirazin-2-ilcarbonimidoditioato de dimetilo



A una suspensión de 6-bromotiazolo[5,4-b]pirazin-2-amina (700 mg, 3,03 mmol) en DMF (3 ml) se añadió hidróxido sódico 16,0M (400 µl, 6,40 mmol). La mezcla se dejó agitar 10 min a temperatura ambiente momento en el que se añadió disulfuro de carbono (450 µl, 7,57 mmol) y la mezcla marrón rojizo resultante se agitó durante 10 minutos. Se añadió una porción adicional de hidróxido sódico 16,0M (400 µl, 6,40 mmol) y la mezcla se agitó de nuevo durante 10 minutos. Finalmente, se añadió yodometano (450 µl, 7,27 mmol)

gota a gota. La mezcla se agitó durante 5 minutos, momento en el que se formó un precipitado amarillo voluminoso. La mezcla se vertió en agua y los sólidos se recogieron por filtración proporcionando 6-bromotiazolo[5,4-b]pirazin-2-ilcarbonimidoditioato de dimetilo (680 mg, 67% de rendimiento) como un sólido amarillo de pureza suficiente para usar sin purificación posterior. RMN de ^{1}H (400 MHz, $CDCl_3$) δ ppm 8,63 (s, 1 H) 2,68 (s, 6 H).

Etapa B: (R)-N-(6-bromotiazolo[5,4-b]pirazin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



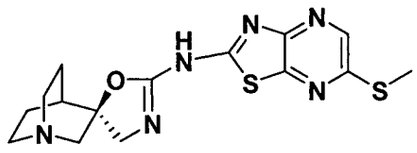
Una mezcla de 6-bromotiazolo[5,4-b]pirazin-2-ilcarbonimidoditioato de dimetilo (300 mg, 0,895 mmol), diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (210 mg, 0,895 mmol) y carbonato de cesio (600 mg, 1,79 mmol) en acetonitrilo (25 ml) se calentó en un baño de aceite a 100 °C durante 2 horas en un matraz abierto, con burbujeo de nitrógeno a través de la solución todo el tiempo para ayudar a la eliminación del metanotiol. Después de 2 horas, la TLC mostró que la reacción se había completado, de modo que la mezcla se enfrió hasta temperatura ambiente, se diluyó con agua y se concentró a vacío. La mezcla se extrajo con cloroformo (4x). Los orgánicos reunidos se lavaron con salmuera, se secó sobre sulfato sódico, se filtraron, se concentraron a vacío y el residuo bruto se purificó por cromatografía sobre gel de sílice (2-40 % de

metanol:hidróxido amónico 9:1-cloroformo). Las fracciones de producto se reunieron y concentraron a vacío proporcionando (R)-N-(6-bromotiazolo[5,4-b]pirazin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (200 mg, 57% de rendimiento).

RMN de ^{1}H (400 MHz, $CDCl_3$) δ ppm 9,39 (s ancho, 1 H) 8,48 (s, 1 H) 4,05 (d, *J*=9,79 Hz, 1 H) 3,72 (d, *J*=9,79 Hz, 1 H) 3,42 (dd, *J*=15,06, 1,76 Hz, 1 H) 2,73 - 3,08 (m, 5 H) 2,10 - 2,22 (m, 2 H) 1,73 - 1,84 (m, *J*=14,09, 9,94, 4,17, 4,17 Hz, 1 H) 1,52 - 1,65 (m, 2 H). MS (LC/MS) T. R. = 1,29; $[M+H]^+$ = 394,99.

EJEMPLO 264

(R)-N-(6-(metiltio)tiazolo[5,4-b]pirazin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

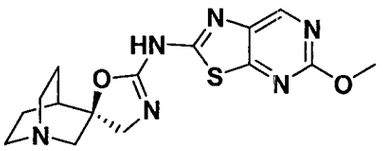


Una mezcla de 6-bromotiazolo[5,4-b]pirazin-2-ilcarbonimidoditioato de dimetilo de la **Etapa A del Ejemplo 263** (100 mg, 0,298 mmol), diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (68 mg, 0,298 mmol) y carbonato de cesio (100 mg, 0,60 mmol) en DMF (1,5 ml) se colocaron en un vial de 1 dram y se calentó en un baño de aceite a 100 °C durante 1 hora, momento en el que, se añadió tiometóxido sódico (100 mg, 1,43 mmol) y la mezcla se calentó durante la noche. La mezcla se enfrió hasta temperatura ambiente y se vertió en agua (20 ml) y los sólidos resultantes se recogieron por filtración y luego se purificó por cromatografía sobre gel de sílice (2-40 % de metanol:hidróxido amónico

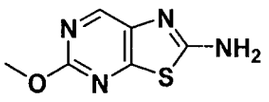
9:1-cloroformo). Las fracciones de producto se reunieron y concentraron a vacío proporcionando (R)-N-(6-(metiltio)tiazolo[5,4-b]pirazin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (52 mg, 46% de rendimiento). RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 9,39 (s ancho, 1 H) 8,31 (s, 1 H) 4,03 (d, *J*=9,77 Hz, 1 H) 3,70 (d, *J*=9,77 Hz, 1 H) 3,41 (dd, *J*=14,95, 1,83 Hz, 1 H) 2,73 - 3,10 (m, 5 H) 2,63 (s, 3 H) 2,10 - 2,25 (m, 2 H) 1,47 - 1,86 (m, 3 H). MS (LC/MS) T. R. = 1,04; $[M+H]^+$ = 363,04.

EJEMPLO 265

(R)-N-(5-Metoxitiazolo[5,4-d]pirimidin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



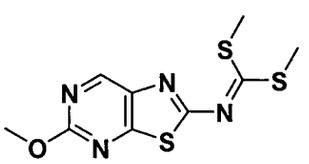
Etapa A: 5-Metoxitiazolo[5,4-d]pirimidin-2-amina



Se suspendió 5-clorotiazolo[5,4-d]pirimidin-2-ilcarbamato de etilo (250 mg, 0,966 mmol) en MeOH (10 ml) y se añadió una solución al 25% (p/p) de metóxido sódico en metanol (10 ml, 46,3 mmol). La solución resultante se llevó a reflujo durante la noche, se enfrió hasta temperatura ambiente, se vertió en un volumen igual de agua y se extrajo con cloroformo (4x). Todavía había

presente una cantidad significativa de compuesto en la fase acuosa por lo que ésta se concentró hasta residuo y luego se disolvió en una pequeña cantidad de HCl 1N (no suficiente para hacer la solución resultante ácida) y se extrajo de nuevo con EtOAc (5x). Los orgánicos reunidos se lavaron con salmuera, se secaron sobre sulfato sódico, se filtraron y concentraron a vacío. Se obtuvo así 5-metoxitiazolo[5,4-d]pirimidin-2-amina (144mg, 0,790 mmol, 82 % de rendimiento) como un sólido blanco. RMN de ^{1}H (400 MHz, DMSO-d_6) δ ppm 8,43 (s, 1 H) 7,81 (s, 2 H) 3,90 (s, 3 H). MS (LC/MS) T. R. = 0,73; $[M+H]^+$ = 183,03.

Etapa B: 5-Metoxitiazolo[5,4-d]pirimidin-2-ilcarbonimidoditioato de dimetilo

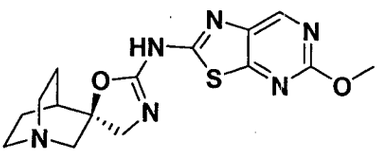


A una suspensión de 5-metoxitiazolo[5,4-d]pirimidin-2-amina (911 mg, 5,00 mmol) en DMF (5 ml) se añadió hidróxido sódico 20,0M (500 µl, 10,00 mmol). La mezcla se dejó agitar 10 min a temperatura ambiente momento en el que se añadió disulfuro de carbono (750 µl, 12,50 mmol) y la mezcla marrón rojiza resultante se agitó durante 10 minutos. Se añadió una porción adicional de hidróxido sódico 20,0M (500 µl, 10,00 mmol) y la mezcla se agitó de nuevo durante 10 minutos. Finalmente, se añadió gota a gota yodometano (750 µl, 12,00 mmol). La mezcla se agitó durante 5 minutos, momento en el que se formó un precipitado amarillo voluminoso. La mezcla se vertió en agua y los sólidos se recogieron por filtración proporcionando un sólido amarillo que se

purificó adicionalmente por cromatografía sobre gel de sílice (EtOAc al 2-20%/$CHCl_3$) proporcionando 5-metoxitiazolo[5,4-d]pirimidin-2-ilcarbonimidoditioato de dimetilo (380 mg, 27% de rendimiento).

RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 8,90 (s, 1 H) 4,09 (s, 3 H) 2,66 (s, 6 H).

Etapa C: (R)-N-(5-metoxitiazolo[5,4-d]pirimidin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

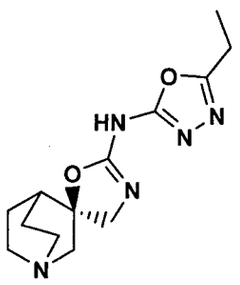


Una mezcla de 5-metoxitiazolo[5,4-d]pirimidin-2-ilcarbonimidoditioato de dimetilo (100 mg, 0,349 mmol), diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (80 mg, 0,349 mmol) y carbonato de cesio (228 mg, 0,698 mmol) en DMF (1,7 ml) se calentó hasta 100 °C durante 2 horas. La mezcla de reacción se enfrió hasta temperatura ambiente, se vertió en agua y los sólidos se recogieron por filtración proporcionando (R)-N-(5-metoxitiazolo[5,4-d]pirimidin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (78 mg, 64% de rendimiento). RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 9,12 (s ancho, 1 H) 8,63 (s, 1 H) 3,95 - 4,18 (m, 4 H) 3,71 (d, *J*=9,77 Hz, 1 H) 3,41 (d, *J*=15,26 Hz, 1 H) 2,74 - 3,10 (m, 5 H) 2,11 - 2,27 (m, 2 H) 1,71 - 1,86 (m, 1 H) 1,50 - 1,70 (m, 2 H). MS (LC/MS) T. R. = 1,66; $[M+H]^+$ = 347,0.

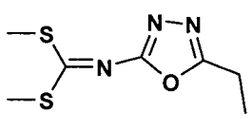
EJEMPLO 266

(R)-N-(5-Etil-1,3,4-oxadiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-

2-amina

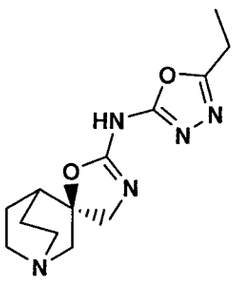


Etapa A: 5-Etil-1,3,4-oxadiazol-2-ilcarbonimidoditioato de dimetilo



A una solución de 5-etil-1,3,4-oxadiazol-2-amina (2,26g, 20 mmol) en DMF (10ml) se añadió NaOH (20M, 2ml), CS_2 (3ml), NaOH (20M, 2ml) y yodometano (3ml) lentamente durante 10 minutos. La mezcla se agitó a temperatura ambiente durante 2 h y se vertió en 30 ml de agua. El sólido amarillo precipitado se separó por filtración, se lavó con agua, y se secó obteniendo el producto deseado, 5-etil-1,3,4-oxadiazol-2-ilcarbonimidoditioato de dimetilo, un sólido blanco (2,6 g, 59,8%). RMN de ^1H (500 MHz, CDCl3) δ ppm 2,86-2,83 (c, 2H), 2,63 (s, 6H), 1,3901,35 (t, 3H). MS (LCMS) [M+H] = 217,95; T. R. = 1,93 min.

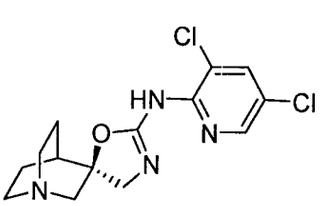
Etapa B: (R)-N-(5-Etil-1,3,4-oxadiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



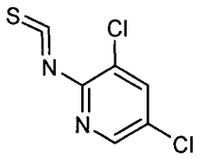
Una mezcla de 5-etil-1,3,4-oxadiazol-2-ilcarbonimidoditioato de dimetilo (327 mg, 1,5 mmol), diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (235 mg, 1,5 mmol) y carbonato de cesio (1000 mg, 3,16 mmol) en DMF (10 ml) se agitó durante la noche a temperatura ambiente. La mezcla se concentró y se purificó en una columna de gel de sílice Biotage (acetato de etilo al 100%, luego metanol al 10-35%:hidróxido amónico 9:1-cloroformo) obteniendo el producto deseado, (R)-N-(5-etil-1,3,4-oxadiazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (290mg, 66%). RMN de ^{1}H (500 MHz, MeOD) δ ppm 4,05 (d, 1H), 3,74 (d, 1H), 3,3-3,2 (d, 1H), 3,2-3,1(d, 1H), 3,0-2,9(m, 2H), 2,9-2,8 (m, 5H), 2,2 (s, 1H), 2,15-2,0 (m, 1H), 1,9-1,6 (m, 3H), 1,4-1,3 (t, 3H). (m, 2H). MS (LCMS) [M+H] = 278,09; T. R. = 0,48 min.

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(R)-N-(3,5-Dicloropiridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

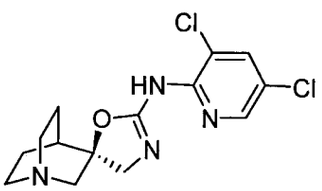


Etapa A: 3,5-Dicloro-2-isotiocianatopiridina



A 3,5-dicloropiridin-2-amina (0,36 g, 2,209 mmol) en diclorometano (25 ml) se añadió 1,1'-tiocarbonildipiridin-2(1H)-ona (0,523 g, 2,253 mmol). La reacción se agitó a 40 °C durante 3 horas. La reacción se enfrió hasta temperatura ambiente y el bruto se purificó por cromatografía (Biotage: acetato de etilo del 25-100%/hexano) proporcionando 3,5-dicloro-2-isotiocianatopiridina (0,4 g, 1,951 mmol, 88 % de rendimiento). RMN de ^{1}H (500 MHz, *DMSO-D6*) δ ppm 8,50 (t, *J*=2,59 Hz, 1 H), 8,45 (t, *J*=2,59 Hz, 1 H). MS (LC/MS) T. R. = 2,07; $[M+H]^+$ = 204,8.

Etapa B: (R)-N-(3,5-Dicloropiridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

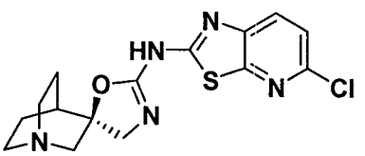


A 3,5-dicloro-2-isotiocianatopiridina (0,11 g, 0,55 mmol) en N,N-dimetilformamida (10 ml) se añadió Et_3N (0,17 ml, 1,21 mmol) y diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (0,13 g, 0,56 mmol) a temperatura ambiente. La reacción se agitó a 70 °C durante 2 horas. La reacción se enfrió hasta temperatura ambiente y se concentró a vacío. La urea bruta se purificó por cromatografía (Biotage: 85% de $CHCl_3$, 14% de MeOH, 1% de NH_4OH). El

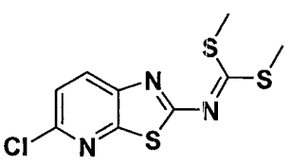
producto se trató entonces con N,N-dimetilformamida (10 ml) y N, N'-diisopropilcarbodiimida (0,26 ml, 1,65 mmol). La reacción se calentó hasta 70°C durante 2 horas. La reacción se enfrió hasta temperatura ambiente y se concentró a vacío proporcionando el producto bruto. El producto bruto se purificó por cromatografía (Biotage: 85% de $CHCl_3$, 14% de MeOH, 1% de NH_4OH) proporcionando (R)-N-(3, 5-dicloropiridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,08 g, 0,24 mmol, 44 % de rendimiento) como un polvo blanco. RMN de ^1H (500 MHz, *DMSO-D6*) δ ppm 8,91 (s, 1 H), 8,11 - 8,17 (m, 1 H), 7,97 (d, *J*=2,44 Hz, 1 H), 3,84 (d, *J*=9,77 Hz, 1 H), 3,59 (d, *J*=9,77 Hz, 1 H), 2,95 - 3,04 (m, 2 H), 2,72 - 2,81 (m, 2 H), 2,66 (t, *J*=7,63 Hz, 2 H), 2,01 (s, 1 H), 1,89 (s, 1 H), 1,54 - 1,62 (m, 2 H), 1,42 - 1,50 (m, 1 H). MS (LC/MS) T. R. = 0,78; $[M+]^+$ = 326,1.

EJEMPLO 268

(R)-N-(5-Clorotiazolo[5,4-b]piridin-2-il)-4H-1'-azaspiro[oxazol-5,3' biciclo[2.2.2]octan]-2-amina

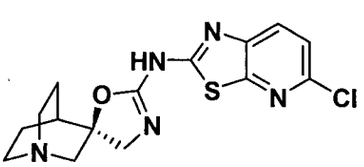


Etapa A: 5-Clorotiazolo[5,4-b]piridin-2-ilcarbonimidoditioato de dimetilo



A una suspensión de 5-clorotiazolo[5,4-b]piridin-2-amina (930 mg, 5,00 mmol) en DMF (5 ml) se añadió hidróxido sódico 20,0M (500 µl, 10,00 mmol). La mezcla se dejó agitar 10 min a temperatura ambiente momento en el que se añadió disulfuro de carbono (750 µl, 12,50 mmol) y la mezcla se agitó durante 10 minutos. Se añadió una porción adicional de hidróxido sódico 20,0M (500 µl, 10,0 mmol) y la mezcla se agitó de nuevo durante 10 minutos. Finalmente se añadió yodometano (750 µl, 12,00 mmol) gota a gota. Durante esta adición se apreció una exotermia. La mezcla se agitó durante 15 minutos, momento en el que se había formado un precipitado voluminoso. La mezcla se vertió en agua y los sólidos se recogieron por filtración. La mayoría de los sólidos recogidos eran amarillo pálido y cristalinos. También había presentes unos pocos aglutinados pequeños de sólido naranja gomoso ligeramente más oscuro y estos se separaron manualmente y desecharon. El resto era el compuesto del epígrafe, 5-clorotiazolo[5,4-b]piridin-2-ilcarbonimidoditioato de dimetilo (1,00g, 69% de rendimiento). RMN de ^{1}H (400 MHz, $CDCl_3$) δ ppm 8,04 (d, *J*=8,53 Hz, 1 H) 7,38 (d, *J*=8,53 Hz, 1 H) 2,66 (s, 6 H).

Etapa B: (R)-N-(5-clorotiazolo[5,4-b]piridin-2-il)-4H-1'-azaspiro[oxazol-5,3' biciclo[2.2.2]octan]-2-amina

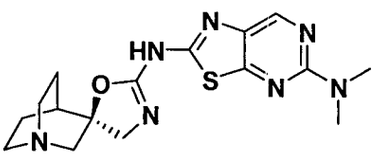


Una mezcla de 5-clorotiazolo[5,4-b]piridin-2-ilcarbonimidoditioato de dimetilo (100 mg, 0,35 mmol), diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol

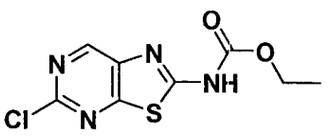
(79 mg, 0,35mmol) y carbonato de cesio (225 mg, 0,69 mmol) en DMF (1,7 ml) se calentó hasta 100 ºC durante 2 horas. La mezcla de reacción se enfrió hasta temperatura ambiente, se vertió en agua y los sólidos se recogieron por filtración. Los sólidos brutos se purificaron por cromatografía sobre gel de sílice (2-40 % de metanol:hidróxido amónico 9:1-cloroformo) proporcionando (R)-N-(5-clorotiazolo[5,4-b]piridin-2-il)-4H-1'-azaspiro[oxazol-5,3' biciclo[2.2.2]octan]-2-amina (62mg, 51% de rendimiento). RMN de ^{1}H (400 MHz, DMSO-d_6) δ ppm 9,13 (s ancho, 1 H) 7,93 (d, *J*=8,53 Hz, 1 H) 7,45 (d, *J*=8,28 Hz, 1 H) 3,92 (d, *J*=10,29 Hz, 1 H) 3,67 (d, *J*=10,29 Hz, 1 H) 3,00 - 3,14 (m, 2 H) 2,77 - 2,93 (m, 2 H) 2,69 (t, *J*=7,65 Hz, 2 H) 2,12 (s ancho, 1 H) 1,95 (s ancho, 1 H) 1,43 - 1,72 (m, 3 H). MS (LC/MS) T. R. = 1,10; $[M+H]^+$ = 350,10.

EJEMPLO 269

(R)-N^5,N^5-dimetil-N^2-(4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octano]-2-il)tiazolo[5,4-d]pirimidina-2,5-diamina



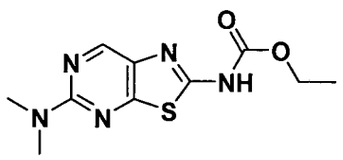
Etapa A: 5-Clorotiazolo[5,4-d]pirimidin-2-ilcarbamato de etilo



Se mezclaron isotiocianato de etoxicarbonilo (4,32 ml, 36,6mmol) y 2,4-

dicloro-pirimidin-5-ilamina (3,00 g, 18,29 mmol) puros y se sometieron a ultrasonidos durante 5 minutos para ayudar a disolver. La mezcla se agitó a temperatura ambiente durante 10 minutos, momento en el que se había solidificado toda la mezcla. Se añadió metanol (100 ml) y la mezcla se llevó a reflujo durante 30 minutos, se enfrió hasta temperatura ambiente y los sólidos se recogieron por filtración proporcionando 5-clorotiazolo[5,4-d]pirimidin-2-ilcarbamato de etilo (3,8 g, 80% de rendimiento). RMN de ^{1}H (400 MHz, DMSO-d_6) δ ppm 12,64 (s, 1 H) 9,05 (s, 1 H) 4,31 (c, *J*=7,19 Hz, 2 H) 1,32 (t, *J*=7,15 Hz, 3 H).

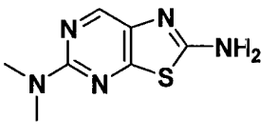
Etapa B: 5-(Dimetilamino)tiazolo[5,4-d]pirimidin-2-ilcarbamato de etilo



Se suspendió 5-clorotiazolo[5,4-d]pirimidin-2-ilcarbamato de etilo (300 mg, 1,16 mmol) en una solución 2,0 M de dimetilamina en metanol (5,0 ml, 10,00 mmol) en un recipiente a presión que se selló y calentó durante la noche en un baño de aceite a 75 °C. La mezcla se enfrió hasta temperatura ambiente, se evaporó el disolvente y el residuo se repartió entre bicarbonato acuoso y cloroformo y se extrajo 3 veces. Los orgánicos reunidos se lavaron con salmuera, se secaron sobre sulfato sódico, se filtraron y concentraron a vacío proporcionando 5-(dimetilamino)tiazolo[5,4-d]pirimidin-2-ilcarbamato de etilo (236 mg, 99% de rendimiento). RMN de ^{1}H (400 MHz, DMSO-d_6) δ ppm 11,97 (s, 1 H) 8,67 (s, 1 H) 4,26 (c, *J*=7,03 Hz, 2 H) 3,17 (s, 6 H) 1,16 - 1,40 (m, 3 H).

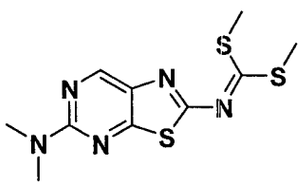
MS (LC/MS) T. R. = 1,88; $[M+H]^+$ = 268,09.

Etapa C: Etil N^5,N^5-dimetiltiazolo[5,4-d]pirimidina-2,5-diamina



Se suspendió 5-(dimetilamino)tiazolo[5,4-d]pirimidin-2-ilcarbamato de etilo (236 mg, 0,88 mmol) en una solución al 25% (p/p) metóxido sódico en metanol (5 ml, 23,0 mmol) y la mezcla se calentó hasta reflujo durante la noche. La mezcla de reacción se evaporó hasta sequedad y el residuo se repartió entre agua y cloroformo y se extrajo 3 veces. Los orgánicos reunidos se lavaron con salmuera, se secaron sobre sulfato sódico, se filtraron y concentraron a vacío proporcionando etil N^5,N^5-dimetiltiazolo[5,4-d]pirimidina-2,5-diamina (170 mg, 99% de rendimiento) como un sólido blanco. RMN de ^{1}H (400 MHz, DMSO-d_6) δ ppm 8,27 (s, 1 H) 7,44 (s, 2 H) 3,10 (s, 6 H).

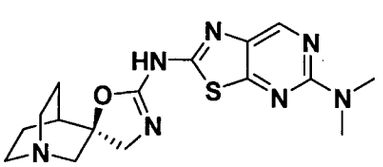
Etapa D: 5-(Dimetilamino)tiazolo[5,4-d]pirimidin-2-ilcarbonimidoditioato de dimetilo



A una suspensión de etil N^5,N^5-dimetiltiazolo[5,4-d]pirimidina-2,5-diamina (160 mg, 0,819 mmol) en DMF (1 ml) se añadió hidróxido sódico 20,0 M (100

µl, 2,00 mmol). La mezcla se dejó agitar 10 min a temperatura ambiente momento en el que se añadió disulfuro de carbono (120 µl, 2 mmol) y la mezcla marrón rojizo resultante se agitó durante 10 minutos. Se añadió una porción adicional de hidróxido sódico 20,0 M (100 µl, 2,0 mmol) y la mezcla se agitó de nuevo durante 10 minutos. Finalmente se añadió yodometano (120 µl, 1,9 mmol) gota a gota. La mezcla se agitó durante 5 minutos, momento en el que se había formado un precipitado amarillo voluminoso. La mezcla se vertió en agua y los sólidos se recogieron por filtración proporcionando 5-(dimetilamino)tiazolo[5,4-d]pirimidin-2-ilcarbonimidoditioato de dimetilo (194 mg, 79% de rendimiento). RMN de ^{1}H (400 MHz, $CDCl_3$) δ ppm 8,75 (s, 1 H) 3,26 (s, 6 H) 2,64 (s, 6 H).

Etapa E: (R)-N^5,N^5-dimetil-N^2-(4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octano]-2-il)tiazolo[5,4-d]pirimidina-2,5-diamina

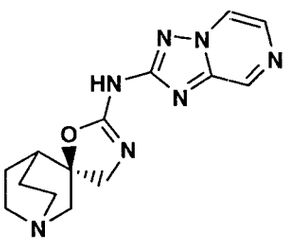


Una mezcla de 5-(dimetilamino)tiazolo[5,4-d]pirimidin-2-ilcarbonimidoditioato de dimetilo (90 mg, 0,301 mmol), diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (83 mg, 0,361 mmol) y carbonato de cesio (196 mg, 0,60 mmol) en DMF (1,0 ml) se calentó hasta 100 °C durante 1,5 horas. La mezcla de reacción se enfrió hasta temperatura ambiente, se vertió en agua y se extrajo con cloroformo (4x). Los orgánicos reunidos se lavaron con

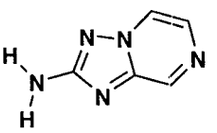
salmuera, se secaron sobre sulfato sódico, se filtraron y concentraron a vacío y el residuo bruto se purificó por cromatografía sobre gel de sílice (2-40 % de metanol:hidróxido amónico 9:1-cloroformo) proporcionando (R)-N^5,N^5-dimetil-N^2-(4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octano]-2-il)tiazolo[5,4-d]pirimidina-2,5-diamina (81 mg, 71% de rendimiento) como un sólido color castaño. RMN de ^{1}H (400 MHz, $CDCl_3$) δ ppm 9,07 (s ancho, 1 H) 8,50 (s, 1 H) 4,01 (d, *J*=9,54 Hz, 1 H) 3,67 (d, *J*=9,54 Hz, 1 H) 3,39 (dd, *J*=14,93, 1,63 Hz, 1 H) 3,23 (s, 6 H) 2,71 - 3,10 (m, 5 H) 2,10 - 2,24 (m, 2 H) 1,68 - 1,84 (m, 1 H) 1,46 - 1,68 (m, 2 H). MS (LC/MS) T. R. = 0,87; $[M+H]^+$ = 360,23.

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(R)-N-([1,2,4]Triazol[1,5-a]pirazin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

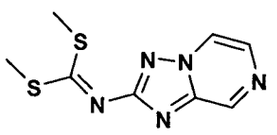


Etapa A: [1, 2, 4]Triazolo[1,5-a]pirazin-2-amina



A una solución de pirazin-2-amina (25 g, 260 mmol) en dioxano (300 ml) a temperatura ambiente se añadió isotiocianato de etoxicarbonilo (37. 9g, 289 mmol) lentamente. La mezcla se agitó durante 18 horas y el disolvente se evaporó a vacío. El sólido residual se disolvió en una mezcla de metanol (150 ml) y etanol (150 ml). A esta solución se añadió TEA (109 ml, 780 mmol) y clorhidrato de hidroxilamina (72,5g, 1040 mmol). La mezcla se agitó a temperatura ambiente durante 2 horas y se calentó hasta reflujo durante 4 horas. La mezcla bruta se enfrió hasta temperatura ambiente y se evaporó el disolvente. El sólido residual se purificó por cromatografía en columna (0-20% de metanol/CH_2Cl_2) obteniendo un sólido blanco (60g). El sólido se llevó a EtOAc y agua. La fase acuosa se extrajo con EtOAc dos veces. La fase orgánica reunida se lavó con salmuera y se secó sobre sulfato sódico obteniendo [1, 2, 4]triazolo[1,5-a]pirazin-2-amina como un sólido blanco (12g, 88 mmol, 33%). MS (LCMS) [M+H] = 135,96; T. R. = 0,21 min.

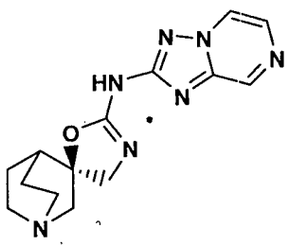
Etapa B: [1,2,4]Triazol[1,5-a]pirazin-2-ilcarbonimidoditioato de dimetilo



A una solución de [1, 2, 4]triazolo[1,5-a]pirazin-2-amina (676 mg, 5 mmol) en DMF (10 ml) se añadió NaOH (20 M, 0,5 ml), CS_2 (1 ml), NaOH (20 M, 0,5 ml) y yodometano (1 ml) lentamente durante 10 minutos. La mezcla se agitó a temperatura ambiente durante 1 h y 10 ml agua se añadió a la mezcla de reacción, que se enturbió. La mezcla se extrajo con EtOAc (100ml x 3). Las

fases orgánicas reunidas se lavaron con salmuera, se secaron sobre sulfato sódico, se filtraron y evaporaron. El residuo se purificó en una columna de gel de sílice Biotage (acetato de etilo-hexano 10-30%) obteniendo [1, 2, 4]triazol[1,5-a]pirazin-2-ilcarbonimidoditioato de dimetilo como un sólido amarillo (720 mg, 3 mmol, 60%). RMN de ^{1}H (500 MHz, CDCl3) δ ppm 9,2 (2, 1H), 8,5 (d, 1H), 8,2 (d, 1H), 2,67 (s, 6H). MS (LCMS) [M+H] = 239,92. [M+Na] = 261,89; T. R. = 1,55 min.

Etapa C: (R)-N-([1,2,4]Triazol[1,5-a]pirazin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



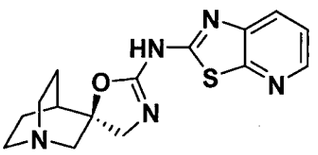
Una mezcla de [1, 2, 4]triazol[1,5-a]pirazin-2-ilcarbonimidoditioato de dimetilo (120 mg, 0,50 mmol), diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (120 mg, 0,76 mmol) y carbonato de cesio (492 mg, 1,5 mmol) en DMF (5 ml) se calentó a 70 ºC durante 6 horas. La mezcla se concentró y se purificó en una columna de gel de sílice Biotage (acetato de etilo al 100%, luego metanol al 10-35%:hidróxido amónico 9:1-cloroformo) obteniendo el producto deseado, (R)-N-([1,2,4]triazol[1,5-a]pirazin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (85mg, 26,7%) como un sólido blanco. RMN de ^{1}H

(500 MHz, MeOD) δ ppm 9,0 (m, 1H), 8,71-8,70 (m, 1H), 8,15-8,10 (m, 1H), 4,15-4,0 (d, 1H), 3,85-3,8 (d, 1H), 3,6-3,5 (d, 1H), 3,4-3,3 (d, 1H), 3,3-3,0 (m, 4H), 2,4-2,2 (m, 2H), 2,0-1,8 (m, 3H).

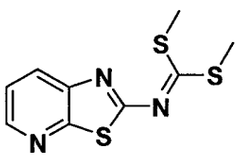
MS (LCMS) [M+H] = 300,06; T. R. = 0,2 min.

Ejemplo 271

(R)-N-(Tiazolo[5,4-b]piridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



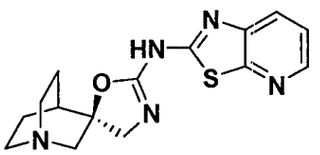
Etapa A: Dimetilo tiazolo[5,4-b]piridin-2-ilcarbonimidoditioato



A una suspensión de tiazolo[5,4-b]piridin-2-amina (300 mg, 1,98 mmol) en DMF (2 ml) se añadió hidróxido sódico 20,0M (200 µl, 4,0 mmol). La mezcla se dejó agitar 10 min a temperatura ambiente momento en el que se añadió disulfuro de carbono (300 µl, 4,96 mmol) y la mezcla marrón rojizo resultante se agitó durante 10 minutos. Se añadió una porción adicional de hidróxido sódico 20,0M (200 µl, 4,0 mmol) y la mezcla se agitó de nuevo durante 10 minutos. Finalmente se añadió yodometano (300 µl, 4,76 mmol) gota a gota. La mezcla

se agitó durante 5 minutos, momento en el que se había formado un precipitado amarillo voluminoso. La mezcla se vertió en agua y los sólidos se recogieron por filtración proporcionando tiazolo[5,4-b]piridin-2-ilcarbonimidoditioato de dimetilo (190 mg, 38% de rendimiento) como un sólido amarillo de pureza suficiente para usar sin purificación posterior. RMN de ^{1}H (500 MHz, *CDCl$_3$*) δ ppm 8,47 (d, *J*=4,58 Hz, 1 H) 8,11 (dd, *J*=8,24, 1,53 Hz, 1 H) 7,37 (dd, *J*=8,24, 4,88 Hz, 1 H) 2,66 (s, 6 H).

Etapa B: (R)-N-(Tiazolo[5,4-b]piridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

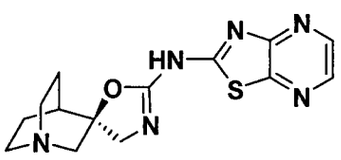


Una mezcla de tiazolo[5,4-b]piridin-2-ilcarbonimidoditioato de dimetilo (90 mg, 0,35 mmol), diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (97mg, 0,42 mmol) y carbonato de cesio (230 mg, 0,71 mmol) en DMF (1 ml) se calentó hasta 100 ºC durante 2 horas. La mezcla de reacción se enfrió hasta temperatura ambiente, se vertió en agua y se extrajo con cloroformo (4x). Los orgánicos reunidos se lavaron con salmuera, se secaron sobre sulfato sódico, se filtraron y concentraron a vacío. La mezcla se purificó por cromatografía sobre gel de sílice (2-40 % de metanol:hidróxido amónico 9:1-cloroformo). Las fracciones de producto se reunieron y concentraron a vacío proporcionando (R)-N-(tiazolo[5,4-b]piridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (84 mg, 76% de rendimiento). RMN de ^{1}H (400 MHz, *CDCl$_3$*) δ ppm 9,30

(s ancho, 1 H) 8,37 (dd, *J*=4,77, 1,51 Hz, 1 H) 7,82 (dd, *J*=8,03, 1,51 Hz, 1 H) 7,28 (dd, *J*=8,03, 4,77 Hz, 1 H) 4,05 (d, *J*=9,54 Hz, 1 H) 3,70 (d, *J*=9,54 Hz, 1 H) 3,42 (dd, *J*=15,06, 1,76 Hz, 1 H) 2,75 - 3,07 (m, 5 H) 2,14 - 2,26 (m, 2 H) 1,71 - 1,84 (m, *J*=13,99, 9,79, 4,17, 4,17 Hz, 1 H) 1,48 - 1,68 (m, 2 H). MS (LC/MS) T. R. = 0,64; $[M+H]^+$ = 316,15.

Ejemplo 272

(R)-N-(Tiazolo[5,4-b]pirazin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

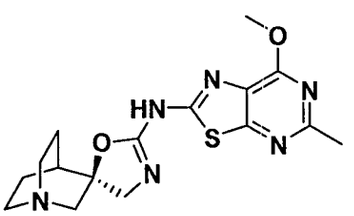


Se suspendió (R)-N-(6-bromotiazolo[5,4-b]pirazin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (44 mg, 0,111 mmol) en MeOH (50 ml) y se añadió HCl 3N hasta que se habían disuelto todos los sólidos (~10ml). El matraz de reacción se cubrió con nitrógeno y luego se añadió paladio al 10% sobre carbón (35 mg) y se equipó el matraz con un balón de hidrógeno. Se dejó reaccionar la mezcla durante la noche, momento en el que la TLC mostró consumo del material de partida. El matraz cubrió con nitrógeno, se filtró a través de celite y se lavó con metanol. Los filtrados reunidos se concentraron hasta ~90% para eliminar la mayor parte del metanol y se basificó la solución mediante la adición de una solución saturada de bicarbonato sódico. La fase acuosa básica se extrajo con cloroformo (4x). Los orgánicos reunidos se lavaron con salmuera, se secaron sobre sulfato sódico,

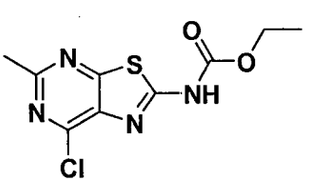
se filtraron y concentraron a vacío. La mezcla se purificó por cromatografía sobre gel de sílice (2-40 % [metanol:hidróxido amónico 9:1]-cloroformo). Las fracciones de producto se reunieron y concentraron a vacío proporcionando (R)-N-(tiazolo[5,4-b]pirazin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (24 mg, 0,075 mmol, 67,5 % de rendimiento). RMN de ^{1}H (400 MHz, *CDCl$_3$*) δ ppm 9,50 (s ancho, 1 H) 8,41 (d, *J*=2,76 Hz, 1 H) 8,27 (d, *J*=2,76 Hz, 1 H) 4,06 (d, *J*=9,79 Hz, 1 H) 3,72 (d, *J*=9,79 Hz, 1 H) 3,43 (dd, *J*=15,06, 1,76 Hz, 1 H) 2,74 - 3,09 (m, 5 H) 2,12 - 2,25 (m, 2 H) 1,71 - 1,86 (m, 1 H) 1,49 - 1,67 (m, 2 H). MS (LC/MS) T. R. = 0,75; $[M+H]^+$ = 317,13.

Ejemplo 273

(R)-N-(7-Metoxi-5-metiltiazolo[5,4-d]pirimidin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



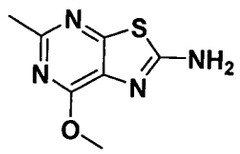
Etapa A: 7-Cloro-5-metiltiazolo[5,4-d]pirimidin-2-ilcarbamato de etilo



A una mezcla de 4,6-dicloro-2-metilpirimidin-5-amina (1 g, 5,62 mmol) y

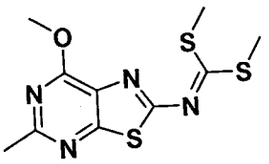
de carbonisotiocianatidato de O-etilo (0,66 ml, 5,62 mmol) se añadió tolueno (2 ml) hasta humedecer los sólidos totalmente. La mezcla se colocó en un baño de aceite a 100 ºC durante 1,5 horas, momento en el que se había detenido dando una masa sólida. Los sólidos se enfriaron hasta temperatura ambiente y se trituraron con éter, luego los sólidos resultantes se recogieron por filtración dando 7-cloro-5-metiltiazolo[5,4-d]pirimidin-2-ilcarbamato de etilo (1,08 g, 3,96 mmol, 70,5 % de rendimiento). RMN de ^{1}H (400 MHz, DMSO-d_6) δ ppm 12,70 (s ancho, 1 H) 4,30 (c, *J*=7,19 Hz, 2 H) 2,69 (s, 3 H) 1,30 (t, *J*=7,15 Hz, 3 H).

Etapa B: 7-Metoxi-5-metiltiazolo[5,4-d]pirimidin-2-amina



Se suspendió 7-cloro-5-metiltiazolo[5,4-d]pirimidin-2-ilcarbamato de etilo (300 mg, 1,100 mmol) en una solución al 25% p/p de metóxido sódico en metanol (5 ml, 23,14 mmol) y la mezcla se llevó a reflujo durante la noche. La mezcla se enfrió hasta temperatura ambiente, se diluyó con agua y se extrajo con cloroformo (4x). Los orgánicos reunidos se lavaron con salmuera, se secaron sobre sulfato sódico, se filtraron y concentraron a vacío proporcionando 7-metoxi-5-metiltiazolo[5,4-d]pirimidin-2-amina (120 mg, 0,612 mmol, 55,6 % de rendimiento). RMN de ^{1}H (400 MHz, DMSO-d_6) δ ppm 7,71 (s, 2 H) 3,98 (s, 3 H) 2,52 (s, 3 H).

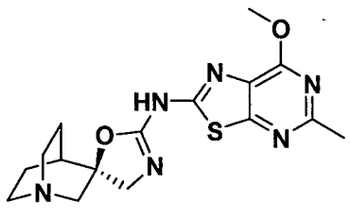
Etapa C: 7-Metoxi-5-metiltiazolo[5,4-d]pirimidin-2-ilcarbonimidoditioato de dimetilo



A una suspensión de 7-metoxi-5-metiltiazolo[5,4-d]pirimidin-2-amina (100 mg, 0,51 mmol) en DMF (0,5 ml) se añadió hidróxido sódico 16,0M (75 µl, 1,2 mmol). La mezcla se dejó agitar 10 min a temperatura ambiente momento en el que se añadió disulfuro de carbono (80 µl, 1,27 mmol) y la mezcla marrón rojizo resultante se agitó durante 10 minutos. Se añadió una porción adicional de hidróxido sódico 16,0M (75 µl, 1,2 mmol) y la mezcla se agitó de nuevo durante 10 minutos. Finalmente se añadió yodometano (80 µl, 1,29 mmol) gota a gota. La mezcla se agitó durante 5 minutos, momento en el que se había formado un precipitado amarillo voluminoso. La mezcla se vertió en agua y los sólidos se recogieron por filtración proporcionando un sólido amarillo bruto que se purificó posteriormente por cromatografía sobre gel de sílice (acetato de etilo al 2-20%-cloroformo). Las fracciones de producto se reunieron y concentraron a vacío proporcionando 7-metoxi-5-metiltiazolo[5,4-d]pirimidin-2-ilcarbonimidoditioato de dimetilo (90 mg, 59% de rendimiento) como un sólido amarillo. RMN de ^{1}H (400 MHz, *CDCl$_3$*) δ ppm 4,17 (s, 3 H) 2,71 (s, 3 H) 2,64 (s, 6 H).

Etapa D: (R)-N-(7-Metoxi-5-metiltiazolo[5,4-d]pirimidin-2-il)-4H-1'-

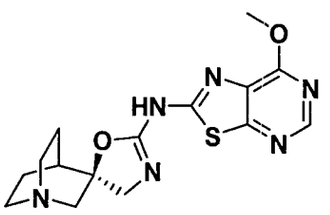
azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



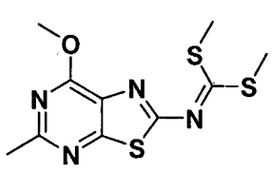
Se calentó una mezcla de 7-metoxi-5-metiltiazolo[5,4-d]pirimidin-2-ilcarbonimidoditioato de dimetilo (56 mg, 0,19 mmol), diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (51mg, 0,22 mmol) y carbonato de cesio (175 mg, 0,54 mmol) en DMF (0,5 ml) hasta 100 ºC durante 2 horas. La mezcla de reacción se enfrió hasta temperatura ambiente, se vertió en agua y se extrajo con cloroformo (4x). Los orgánicos reunidos se lavaron con salmuera, se secaron sobre sulfato sódico, se filtraron y concentraron a vacío. La mezcla se purificó por cromatografía sobre gel de sílice (2-40 % [metanol:hidróxido amónico 9:1]-cloroformo). Las fracciones de producto se reunieron y concentraron a vacío proporcionando (R)-N-(7-metoxi-5-metiltiazolo[5,4-d]pirimidin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (34 mg, 50% de rendimiento). RMN de ^{1}H (400 MHz, *CDCl$_3$*) δ ppm 9,10 (s ancho, 1 H) 4,14 (s, 3 H) 4,03 (d, *J*=9,54 Hz, 1 H) 3,68 (d, *J*=9,54 Hz, 1 H) 3,39 (dd, *J*=14,93, 1,63 Hz, 1 H) 2,74 - 3,07 (m, 5 H) 2,68 (s, 3 H) 2,04 - 2,28 (m, 2 H) 1,70 - 1,86 (m, 1 H) 1,44 - 1,67 (m, 2 H). MS (LC/MS) T. R. = 1,10; $[M+H]^+$ = 361,32.

Ejemplo 274

(R)-N-(7-Metoxitiazolo[5,4-d]pirimidin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



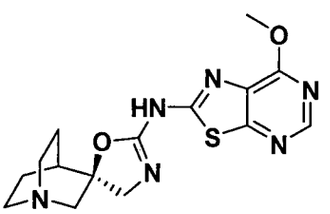
Etapa A: 7-Metoxi-5-metiltiazolo[5,4-d]pirimidin-2-ilcarbonimidoditioato de dimetilo



A una suspensión de 7-metoxitiazolo[5,4-d]pirimidin-2-amina (300 mg, 1,67 mmol) en DMF (1,5 ml) se añadió hidróxido sódico 16,0M (210 µl, 3,4 mmol). La mezcla se dejó agitar 10 min a temperatura ambiente momento en el que se añadió disulfuro de carbono (250 µl, 4,15 mmol) y la mezcla marrón rojizo resultante se agitó durante 10 minutos. Se añadió una porción adicional de hidróxido sódico 16,0M (210 µl, 3,4 mmol) y la mezcla se agitó de nuevo durante 10 minutos. Finalmente se añadió yodometano (250 µl, 4,00 mmol) gota a gota. La mezcla se agitó durante 10 minutos, momento en el que se había formado un precipitado amarillo voluminoso. La mezcla se vertió en agua y los sólidos se recogieron por filtración proporcionando 7-metoxi-5-metiltiazolo[5,4-d]pirimidin-2-ilcarbonimidoditioato de dimetilo (324 mg, 69% de rendimiento) como un sólido amarillo. RMN de ^{1}H (400 MHz, *CDCl$_3$*) δ ppm 8,60

(s, 1 H) 4,20 (s, 3 H) 2,65 (s, 6 H).

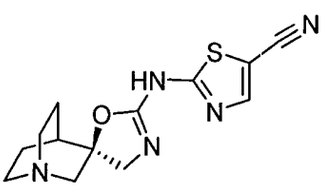
Etapa B: (R)-N-(7-Metoxitiazolo[5,4-d]pirimidin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



Se calentó una mezcla de 7-metoxitiazolo[5,4-d]pirimidin-2-ilcarbonimidoditioato de dimetilo (150 mg, 0,52 mmol), diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (132mg, 0,58 mmol) y carbonato de cesio (427 mg, 1,31 mmol) en DMF (3 ml) hasta 100 °C durante 2 horas. La mezcla de reacción se enfrió hasta temperatura ambiente, se vertió en agua y se extrajo con cloroformo (4x). Los orgánicos reunidos se lavaron con salmuera, se secaron sobre sulfato sódico, se filtraron y concentraron a vacío. La mezcla se purificó por cromatografía sobre gel de sílice (2-40 % [metanol:hidróxido amónico 9:1]-cloroformo). Las fracciones de producto se reunieron y concentraron a vacío proporcionando (R)-N-(7-metoxitiazolo[5,4-d]pirimidin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (95 mg, 51% de rendimiento). RMN de ^{1}H (400 MHz, *CDCl$_3$*) δ ppm 9,12 (s ancho, 1 H) 8,52 (s, 1 H) 4,16 (s, 3 H) 4,05 (d, *J*=9,54 Hz, 1 H) 3,70 (d, *J*=9,54 Hz, 1 H) 3,40 (dd, *J*=14,93, 1,88 Hz, 1 H) 2,70 - 3,07 (m, 5 H) 2,08 - 2,27 (m, 2 H) 1,68 - 1,85 (m, 1 H) 1,48 - 1,66 (m, 2 H). MS (LC/MS) T. R. = 0,90; $[M+H]^+$ = 347,34.

EJEMPLO 275

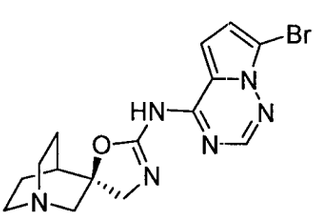
(R)-2-(4H-1'-Azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-ilamino)tiazol-5-carbonitrilo



(R)-2-(4H-1'-Azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-ilamino)tiazol-5-carbonitrilo se sintetizó por el procedimiento del Ejemplo 274, partiendo de 2-amino-5-cianotiazol. RMN de ^{1}H (500 MHz, *DMSO-D6*) δ ppm 9,05 (s, 1 H), 8,13 (s, 1 H), 3,86 (d, *J*=10,38 Hz, 1 H), 3,61 (d, *J*=10,38 Hz, 1 H), 3,01 - 3,10 (m, 2 H), 2,83 (t, *J*=7,63 Hz, 2 H), 2,62 - 2,71 (m, 2 H), 2,09 (s, 1 H), 1,90 - 1,97 (m, 2 H), 1,54 - 1,62 (m, 3 H). MS (LC/MS) T. R. = 0,52; $[M+H]^+$ = 290,0.

EJEMPLO 276

(R)-N-(7-Bromopirrolo[1,2-f][1,2,4]triazin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

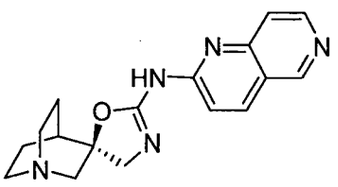


Se sintetizó (R)-N-(7-bromopirrolo[1,2-f][1,2,4]triazin-4-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina por el procedimiento del Ejemplo 274 partiendo de 7-bromopirrolo[1,2-f][1,2,4]triazin-4-amina. RMN de

^{1}H (400 MHz, *MeOD*) δ ppm 8,13 (1 H, s), 7,04 (1 H, d, *J*=4,53 Hz), 6,77 (1 H, d, *J*=4,53 Hz), 4,09 (1 H, d, *J*=10,32 Hz), 3,79 (1 H, d, *J*=10,58 Hz), 3,24 (1 H, d), 3,12 (1 H, d), 2,70 - 3,00 (4 H, m), 2,06 - 2,25 (2 H, m), 1,52 - 1,86 (3 H, m) MS (LC/MS) T. R. = 1,62; $[M+H]^+$ = 377,2.

EJEMPLO 277

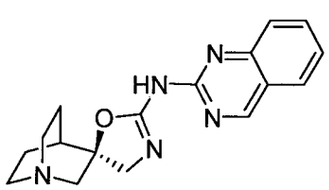
(R)-N-(1,6-Naftiridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



Se sintetizó (R)-N-(1,6-Naftiridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina por el procedimiento del Ejemplo 274 partiendo de 1,6-naftiridin-2-amina. RMN de ^{1}H (400 MHz, *MeOD*) δ ppm 8,99 (1 H, s), 8,48 (1 H, d, *J*=6,04 Hz), 8,20 (1 H, d, *J*=8,56 Hz), 7,77 (1 H, d, *J*=6,04 Hz), 7,12 (1 H, d, *J*=8,81 Hz), 4,12 (1 H, d, *J*=10,32 Hz), 3,82 (1 H, d, *J*=10,32 Hz), 3,36 (1 H, d), 3,21 (1 H, d), 2,79 - 3,09 (4 H, m), 2,08 - 2,30 (2 H, m), 1,56 - 1,95 (3 H, m). (LC/MS) T. R. = 0,38; $[M+H]^+$ = 310,3.

EJEMPLO 278

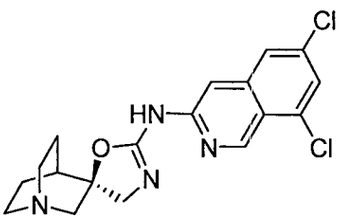
(R)-N-(Quinazolin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



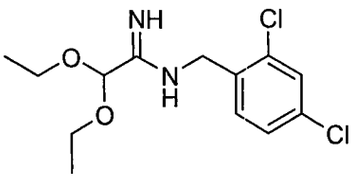
Se sintetizó (R)-N-(Quinazolin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan] -2-amina por el procedimiento del Ejemplo 274 partiendo de 2-aminoquinazolina. RMN de ^{1}H (400 MHz, *MeOD*) δ ppm 9,27 (1 H, s), 7,72 - 7,99 (3 H, m), 7,47 (1 H, dd, *J*=7,55, 3,78 Hz), 4,07 (1 H, d, *J*=10,07 Hz), 3,76 (1 H, d, *J*=10,07 Hz), 3,26 (1 H, s ancho), 3,13 (1 H, d), 2,70 - 3,03 (4 H, m), 2,17 (2 H, s ancho), 1,50 - 1,88 (3 H, m). (LC/MS) T. R. = 1,11; $[M+H]^+$ = 310,3.

EJEMPLO 279

(R)-N-(6,8-Dicloroisoquinolin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



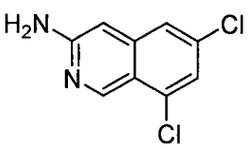
Etapa A: N-(2,4-Diclorobencil)-2,2-dietoxiacetimidamida



Se añadió (2,4-diclorofenil)metanamina (2 g, 11,4 mmol) a una solución de 2,2-dietoxiacetimidato de metilo (2,04 g, 12,6 mmol) en metanol (10 ml). La mezcla se calentó a 70°C durante 1 h. La mezcla se purificó por cromatografía (Biotage: 100% acetato de etilo). Las fracciones deseadas se concentraron proporcionando N-(2,4-diclorobencil)-2,2-dietoxiacetimidamida (2,8 g, 9,2 mmol,

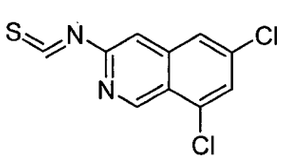
72,7 % de rendimiento) como un aceite viscoso incoloro. RMN de ^{1}H (500 MHz, *DMSO-D$_6$*) δ ppm 7,27 - 7,70 (m, 3 H), 4,77 (s, 1 H), 4,14 - 4,35 (m, 2 H), 3,45 - 3,68 (m, 4 H), 1,09 - 1,29 (m, 6 H). LC/MS RT=2,03; $[M+H]^+$ = 304,9.

Etapa B: 6,8-Dicloroisoquinolin-3-amina



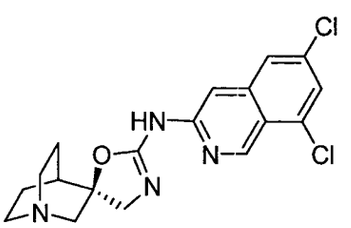
A ácido sulfúrico (4 ml, 75 mmol) se añadió N-(2,4-diclorobencil)-2,2-dietoxiacetimidamida (2 g, 6,6 mmol) a temperatura ambiente. La reacción se calentó hasta 40°C durante 18 horas. TLC y LC/MS indicaron la presencia de producto. La reacción se enfrió hasta temperatura ambiente y se inactivó con NaOH acuoso (~15 M) hasta que la mezcla de reacción tenía ~pH 7. El producto bruto se extrajo con acetato de etilo (2 x 50 ml) y los orgánicos se secaron con $MgSO_4$, se filtraron y concentraron a vacío proporcionando el producto. El producto bruto se purificó por cromatografía (Biotage:10-80% acetato de etilo/ hexanos) proporcionando 5,7-dicloroisoquinolin-1-amina (0,32 g, 1,50 mmol, 22,9 % de rendimiento) como un polvo amarillo oscuro. RMN de ^{1}H (400 MHz, *DMSO-D$_6$*) δ ppm 8,99 (s, 1 H), 7,64 - 7,73 (m, 1 H), 7,30 (d, *J*=2,01 Hz, 1 H), 6,61 (s, 1 H), 6,43 (s, 2 H). MS (LC/MS) T. R. = 1,40; $[M+H]^+$ = 213,1.

Etapa C: 6,8-Dicloro-3-isotiocianatoisoquinolina



A 6,8-dicloroisoquinolin-3-amina (0,27 g, 1,28 mmol) en diclorometano (20 ml) se añadió 1,1'-tiocarbonildipiridin-2(1H)-ona (0,30 g, 1,29 mmol) y la mezcla de reacción se agitó a 40°C durante 4 horas. La reacción se enfrió hasta temperatura ambiente y se sometió a cromatografía (Biotage: acetato de etilo al 10-100%/hexanos) proporcionando 6,8-dicloro-3-isotiocianatoisoquinolina (0,2 g, 0,78 mmol, 61,9 % de rendimiento) como un polvo. RMN de ^{1}H (500 MHz, *DMSO-D$_6$*) δ ppm 9,42 (s, 1 H), 8,16 (d, *J*=1,83 Hz, 1 H), 8,02 (d, *J*=2,14 Hz, 1 H), 7,92 (s, 1 H). MS (LC/MS) T. R. = 3,63; $[M+H]^+$ = 255,0.

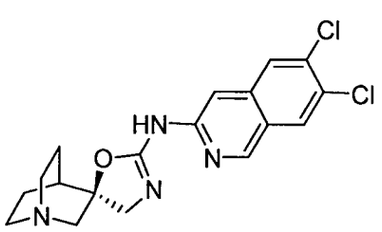
Etapa D: (R)-N-(6,8-Dicloroisoquinolin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



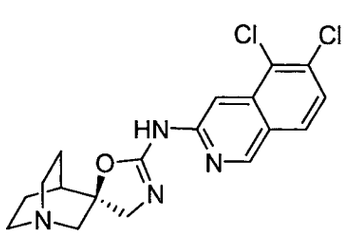
A 6,8-dicloro-3-isotiocianatoisoquinolina (0,17 g, 0,67 mmol) en DMF (10 ml) se añadió carbonato de cesio (0,543 g, 1,67 mmol) y diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (0,15 g, 0,67 mmol) a temperatura ambiente. La reacción se agitó a 70°C durante 2 horas. La reacción se enfrió hasta temperatura ambiente y se concentró a vacío. El producto se trató con N,N'-diisopropilcarbodiimida (0,31 ml, 2,0 mmol). La reacción se calentó hasta 90°C durante 4 horas. La reacción se enfrió hasta temperatura ambiente y se

concentró proporcionando el producto bruto. El producto bruto se purificó por cromatografía (Biotage: 85% de $CHCl_3$, 14% de MeOH, 1% de NH_4OH). El producto se suspendió en una pequeña cantidad de acetato de etilo, que dio lugar a la formación de un precipitado. Este se separó por filtración, se lavó con una pequeña cantidad de acetato de etilo, y se secó en un horno de vacío proporcionando (R)-N-(6,8-dicloroisoquinolin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,094 g, 0,24 mmol, 36,6 % de rendimiento) como un polvo blanco. RMN de ^1H (400 MHz, *DMSO-D6*) δ ppm 9,23 (s, 1 H), 8,71 - 8,83 (m, 1 H), 7,90 - 8,00 (m, 1 H), 7,57 - 7,67 (m, 1 H), 7,13 - 7,24 (m, 1 H), 3,79 - 3,90 (m, 1 H), 3,53 - 3,64 (m, 1 H), 2,93 - 3,04 (m, 2 H), 2,72 - 2,82 (m, 2 H), 2,61 - 2,70 (m, 2 H), 1,99 (s, 1 H), 1,90 (s, 1 H), 1,59 (d, *J*=4,78 Hz, 2 H), 1,40 - 1,50 (m, 1 H). MS (LC/MS) T. R. = 1,68; $[M+H]^+$ = 377,1.

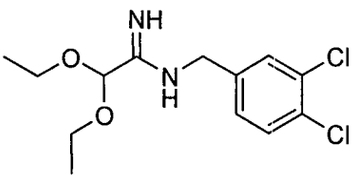
EJEMPLO 280



(R)-N-(6,7-Dicloroisoquinolin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



Etapa A: N-(3,4-Diclorobencil)-2,2-dietoxiacetimidamida



Se añadió (3,4-diclorofenil)metanamina (2 g, 11,4 mmol) a una solución de 2,2-dietoxiacetimidato de metilo (2,04 g, 12,6 mmol) en metanol (10 ml). La mezcla se calentó a 70°C durante 1 h. La mezcla se purificó por cromatografía (Biotage: acetato de etilo al 100%). Las fracciones deseadas se concentraron proporcionando N-(3,4-diclorobencil)-2,2-dietoxiacetimidamida (2,8 g, 9,2 mmol, 72,7 % de rendimiento) como un aceite viscoso incoloro. RMN de ^{1}H (500 MHz, *CDCl$_3$*) δ ppm 7,45 (m, 1 H), 7,40 (m, 1 H), 7,19 (dd, *J*=8,09, 1,98 Hz, 1 H), 4,94 (s, 1 H), 4,43 (s, 2 H), 3,47 - 3,77 (m, 4 H), 1,41 - 1,79 (m, 6 H). LC/MS RT=2,15; $[M+H]^+$ = 305,1.

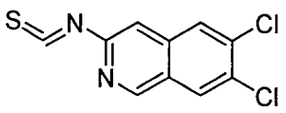
Etapa B: 6,7-Dicloroisoquinolin-3-amina y 5,6-dicloroisoquinolin-3-amina

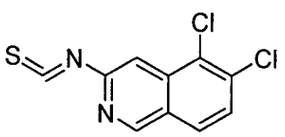


A ácido sulfúrico (4 ml, 75 mmol) se añadió N-(3,4-diclorobencil)-2,2-dietoxiacetimidamida (2 g, 6,6 mmol) a temperatura ambiente. La reacción se calentó hasta 40°C durante 49 horas. TLC y LC/MS indicaron la presencia de producto. La reacción se enfrió hasta temperatura ambiente y se inactivó con NaOH acuoso (~15 M) hasta que la mezcla de reacción tenía ~pH 7. El

producto bruto se extrajo con acetato de etilo (2 x 50 ml) y los orgánicos se secaron con $MgSO_4$, se filtraron y se concentraron a vacío proporcionando el producto. El producto bruto se purificó por cromatografía (Biotage: acetato de etilo al 100% hasta [acetato de etilo/MeOH 90/10%]) proporcionando aproximadamente una mezcla 1:1 de regioisómeros 6,7-dicloroisoquinolin-1-amina y 5,6-dicloroisoquinolin-3-amina (1,2 g, 5,64 mmol, 86,0 % de rendimiento) como un polvo amarillo oscuro. Se continuó con los regioisómeros sin separación. RMN de ^1H : RMN de ^1H (500 MHz, *DMSO-D_6*) δ ppm 8,90 (s, 1 H), 8,83 (s, 1 H), 8,12 (s, 1 H), 7,89 (s, 1 H), 7,84 (d, *J*=8,54 Hz, 1 H), 7,28 (d, *J*=8,85 Hz, 1 H), 6,83 (s, 1 H), 6,58 (s, 1 H), 6,48 (s, 2 H), 6,25 (s, 2 H). MS (LC/MS) T. R. = 1,59; $[M+H]^+$ = 213,0.

Etapa C: 6,7-Dicloro-3-isotiocianatoisoquinolina y 5,6-dicloro-3-isotiocianatoisoquinolina

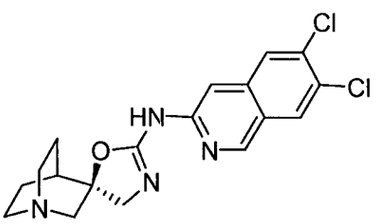




A 6,7-dicloroisoquinolin-3-amina y 5,6-dicloroisoquinolin-3-amina (0,410 g, 1,924 mmol) en diclorometano (20 ml) se añadió 1,1'-tiocarbonildipiridin-2(1H)-ona (0,469 g, 2,021 mmol) y la mezcla de reacción se agitó a 40°C durante 4 horas. La reacción se enfrió hasta temperatura ambiente y se sometió a cromatografía (Biotage: acetato de etilo al 10-100%/hexanos) proporcionando los regioisómeros separados, 6,7-dicloro-3-isotiocianatoisoquinolina (0,2 g, 0,784 mmol, 40,7 % de rendimiento) y 5,6-dicloro-3-isotiocianatoisoquinolina (0,23 g, 0,902 mmol, 46,8 % de rendimiento)

como sólidos amarillos. 5,6-dicloro-3-isotiocianatoisoquinolina: RMN de ^{1}H (500 MHz, *CDCl$_3$*) δ ppm 9,10 (s, 1 H), 7,87 (d, *J*=8,85 Hz, 1 H), 7,82 (s, 1 H), 7,66 (d, *J*=8,55 Hz, 1 H). MS (LC/MS) T. R. = 3,63; $[M+H]^+$ = 255,0. 6,7-dicloro-3-isotiocianatoisoquinolina: RMN de ^{1}H (500 MHz, *CDCl$_3$*) δ ppm 9,04 (s, 1 H), 8,11 (s, 1 H), 7,94 (s, 1 H), 7,37 (s, 1 H). MS (LC/MS) T. R. = 3,42; $[M+H]^+$ = 255,0.

Etapa C: (R)-N-(6,7-Dicloroisoquinolin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

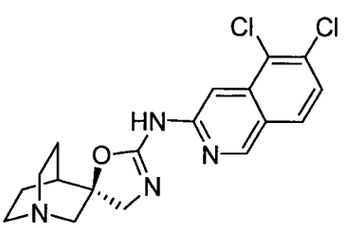


A 6,7-dicloro-3-isotiocianatoisoquinolina (0,13 g, 0,510 mmol) en DMF (10 ml) se añadió carbonato de cesio (0,42 g, 1,27 mmol) y diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (0,118 g, 0,515 mmol) a temperatura ambiente. La reacción se agitó a 70°C durante 2 horas. La reacción se enfrió hasta temperatura ambiente y se concentró a vacío. La urea bruta se purificó por cromatografía (Biotage: 85% de $CHCl_3$, 14% de MeOH, 1% de NH_4OH). El producto se trató entonces con DMF (10 ml) y N,N'-diisopropilcarbodiimida (0,238 ml, 1,529 mmol). La reacción se calentó hasta 90°C durante 18 horas. La reacción se enfrió hasta temperatura ambiente y se concentró proporcionando el producto bruto, que se purificó por cromatografía (Biotage: 85% de $CHCl_3$, 14% de MeOH, 1% de NH_4OH) proporcionando (R)-N-(6,7-dicloroisoquinolin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

(0,12 g, 0,312 mmol, 61,2 % de rendimiento). RMN de ^{1}H (500 MHz, *CDCl$_3$*) δ ppm 9,03 (s, 1 H), 8,87 (s, 1 H), 7,96 (s, 1 H), 7,83 (s, 1 H), 7,24 (s, 1 H), 3,88 - 4,06 (m, 1 H), 3,60 - 3,74 (m, 1 H), 3,42 (d, *J*=14,65 Hz, 1 H), 2,82 - 3,15 (m, 5 H), 2,23 - 2,34 (m, 1 H), 2,18 (s, 1 H), 1,72 - 1,87 (m, 1 H), 1,48 - 1,70 (m, 2 H). MS (LC/MS) T. R. = 1,63; $[M+H]^+$ = 377,1.

EJEMPLO 281

(R)-N-(5,6-Dicloroisoquinolin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

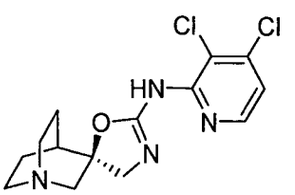


A 5,6-dicloro-3-isotiocianatoisoquinolina (0,11 g, 0,431 mmol) en DMF (10 ml) se añadió carbonato de cesio (0,351 g, 1,078 mmol) y diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (0,100 g, 0,435 mmol) a temperatura ambiente. La reacción se agitó a 70°C durante 2 horas. La reacción se enfrió hasta temperatura ambiente y se concentró a vacío. La urea bruta se purificó por cromatografía (Biotage: 85% de $CHCl_3$, 14% de MeOH, 1% de NH_4OH). El producto se trató entonces con DMF (10 ml) y N,N'-diisopropilcarbodiimida (0,202 ml, 1,293 mmol). La reacción se calentó hasta 90°C durante 18 horas. La reacción se enfrió hasta temperatura ambiente y se concentró proporcionando el producto bruto. El producto bruto se purificó por

cromatografía (Biotage: 85% de $CHCl_3$, 14% de MeOH, 1% de NH_4OH) proporcionando (R)-N-(5,6-dicloroisoquinolin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,084 g, 0,218 mmol, 50,6 % de rendimiento) como un polvo amarillo. RMN de ^1H (500 MHz, *$CDCl_3$*) δ ppm 9,09 (s, 1 H), 8,93 (s, 1 H), 7,63 - 7,82 (m, 2 H), 7,40 (d, *J*=8,55 Hz, 1 H), 3,99 (d, *J*=9,16 Hz, 1 H), 3,78 (d, *J*=8,85 Hz, 1 H), 3,51 (d, *J*=14,65 Hz, 1 H), 3,30 (d, *J*=14,65 Hz, 1 H), 2,90 - 3,23 (m, 4 H), 2,33 - 2,48 (m, 1 H), 2,29 (s, 1 H), 1,83 - 1,94 (m, 1 H), 1,62 - 1,83 (m, *J*=42,12 Hz, 2 H). MS (LC/MS) T. R. = 1,57; $[M+H]^+$ = 377,1.

EJEMPLO 282

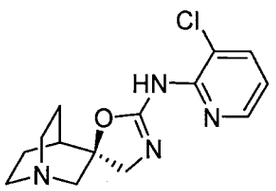
(R)-N-(3,4-Dicloropiridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



Se preparó (R)-N-(3,4-dicloropiridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina por el procedimiento del Ejemplo 267, partiendo de 2-amino-3,4-dicloropiridina. RMN de ^1H (500 MHz, *$DMSO\text{-}D_6$*) δ ppm 9,10 (s, 1 H), 8,08 (d, *J*=5,49 Hz, 1 H), 7,13 (d, *J*=5,49 Hz, 1 H), 3,86 (d, *J*=9,77 Hz, 1 H), 3,60 (d, *J*=9,77 Hz, 1 H), 2,96 - 3,05 (m, 2 H), 2,77 (t, *J*=7,63 Hz, 2 H), 2,66 (t, *J*=7,78 Hz, 2 H), 1,97 - 2,05 (m, 1 H), 1,86 - 1,94 (m, 1 H), 1,54 - 1,63 (m, 2 H), 1,43 - 1,51 (m, 1 H). MS (LC/MS) T. R. = 0,78; $[M+H]^+$ = 327,0.

EJEMPLO 283

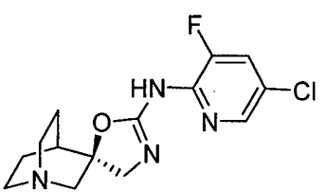
(R)-N-(3-Cloropiridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



Se preparó (R)-N-(3-Cloropiridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina por el procedimiento del Ejemplo 267, partiendo de 2-amino-3-cloropiridina. RMN de ^{1}H (500 MHz, *DMSO-D$_6$*) δ ppm 9,06 (s, 1 H), 8,14 - 8,19 (m, 1 H), 7,74 - 7,79 (m, *J*=7,78, 1,83, 1,83, 1,68 Hz, 1 H), 6,86 - 6,91 (m, 1 H), 3,81 - 3,89 (m, 1 H), 3,55 - 3,63 (m, 1 H), 2,96 - 3,04 (m, 2 H), 2,78 (t, *J*=7,63 Hz, 2 H), 2,67 (t, *J*=7,63 Hz, 2 H), 1,96 - 2,02 (m, 1 H), 1,86 - 1,92 (m, *J*=5,65, 3,20 Hz, 1 H), 1,54 - 1,63 (m, *J*=6,87, 3,66, 3,51 Hz, 2 H), 1,42 - 1,49 (m, 1 H). MS (LC/MS) T. R. = 0,26; $[M+H]^+$ = 293,0.

EJEMPLO 284

(R)-N-(5-Cloro-3-fluoropiridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

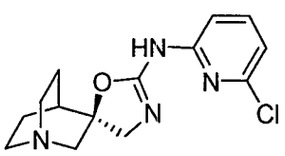


Se preparó (R)-N-(5-Cloro-3-fluoropiridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina por el procedimiento del Ejemplo 267, partiendo de

2-amino-3-fluoro-5-cloropiridina. RMN de ^{1}H (500 MHz, *DMSO-D$_6$*) δ ppm 8,81 (s, 1 H), 8,05 (s, 1 H), 7,79 (d, *J*=10,07 Hz, 1 H), 3,83 (d, *J*=9,46 Hz, 1 H), 3,58 (d, *J*=9,46 Hz, 1 H), 2,99 (s, 2 H), 2,71 - 2,80 (m, 2 H), 2,61 - 2,70 (m, 2 H), 2,00 (s, 1 H), 1,83 - 1,92 (m, 1 H), 1,53 - 1,62 (m, 2 H), 1,41 - 1,50 (m, 1 H). MS (LC/MS) T. R. = 0,52; $[M+]^+$ = 311,0.

EJEMPLO 285

(R)-N-(6-Cloropiridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

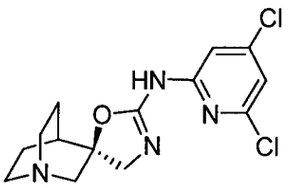


Se preparó (R)-N-(6-Cloropiridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina por el procedimiento del Ejemplo 267, partiendo de 2-amino-6-cloropiridina. RMN de ^{1}H (500 MHz, *DMSO-D$_6$*) δ ppm 8,33 - 8,42 (m, 1 H), 7,60 - 7,68 (m, 1 H), 6,94 (d, *J*=7,02 Hz, 1 H), 6,72 - 6,81 (m, 1 H), 3,86 (d, *J*=9,46 Hz, 1 H), 3,57 (d, *J*=10,07 Hz, 1 H), 2,97 (s, 2 H), 2,69 - 2,78 (m, 2 H), 2,63 - 2,68 (m, *J*=7,63, 7,63 Hz, 2 H), 1,95 - 2,03 (m, 1 H), 1,83 - 1,92 (m, 1 H), 1,53 - 1,62 (m, 2 H), 1,41 - 1,49 (m, 1 H). MS (LC/MS) T. R. = 0,43; $[M+H]^+$ = 293,0.

EJEMPLO 286

(R)-N-(4,6-Dicloropiridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-

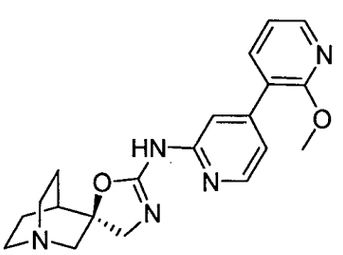
amina



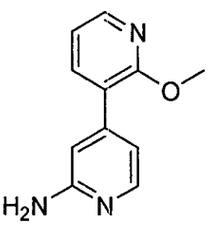
Se preparó (R)-N-(4,6-Dicloropiridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina por el procedimiento del Ejemplo 267, partiendo de 2-amino-4,6-dicloropiridina. RMN de ^{1}H (500 MHz, *DMSO-D6*) δ ppm 8,43 (s, 1 H), 7,13 (s, 1 H), 6,84 (s, 1 H), 3,86 (d, *J*=9,77 Hz, 1 H), 3,59 (d, *J*=10,07 Hz, 1 H), 2,98 (s, 2 H), 2,58 - 2,86 (m, 4 H), 1,94 - 2,13 (m, 1 H), 1,78 - 1,95 (m, 1 H), 1,36 - 1,65 (m, 3 H). MS (LC/MS) T. R. = 0,87; $[M+H]^+$ = 327,0.

EJEMPLO 287

(R)-N-(2-Metoxi-3-4'-bipiridin-2'-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

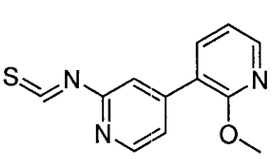


Etapa A: N-(2,4-Diclorobencil)-2,2-dietoxiacetimidamida



A 4-bromopiridin-2-amina (0,5 g, 2,8 mmol), ácido 2-metoxipiridin-3-ilborónico (0,52 g, 3,4 mmol) en DMF (25 ml) se añadió carbonato sódico 1N (10 ml, 2,3 mmol), seguido por complejo de dicloruro de 1,1'-bis(difenilfosfino)ferroceno-paladio(II) diclorometano (0,21 g, 0,26 mmol). La mezcla de reacción se agitó durante 3 horas a 85 °C y luego se enfrió hasta temperatura ambiente. El producto se extrajo con acetato de etilo (2 x 50 ml), se secó con $MgSO_4$, se filtró y se concentró a vacío. El producto bruto se purificó por cromatografía (Biotage: 100 a 90/10% acetato de etilo-acetato de etilo/metanol) proporcionando 2-metoxi-3,4'-bipiridin-2'-amina (0,53 g, 2,63 mmol, 93 % de rendimiento) como un polvo marrón. El producto se llevó directamente a la etapa siguiente.

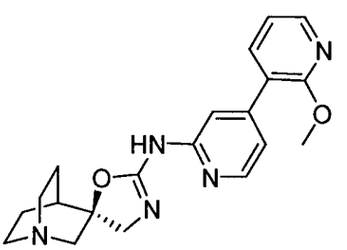
Etapa B: 2'-Isotiocianato-2-metoxi-3,4'-bipiridina



A 2-metoxi-3,4'-bipiridin-2'-amina (0,53 g, 2,63 mmol) en diclorometano (20 ml) se añadió 1,1'-tiocarbonildipiridin-2(1H)-ona (0,62 g, 2,7 mmol) y la mezcla de reacción se agitó a 40 °C durante 4 horas. La reacción se enfrió hasta temperatura ambiente y se sometió (Biotage: acetato de etilo al 10-

100%/hexanos) proporcionando 2'-isotiocianato-2-metoxi-3,4'-bipiridina (0,46 g, 1,9 mmol, 71,8 % de rendimiento). RMN de ^{1}H (500 MHz, *DMSO-D6*) δ ppm 8,67 (d, *J*=2,44 Hz, 1 H), 8,26 (dd, *J*=4,88, 1,53 Hz, 1 H), 8,15 (dd, *J*=8,24, 2,44 Hz, 1 H), 7,89 (dd, *J*=7,32, 1,53 Hz, 1 H), 7,48 (d, *J*=8,24 Hz, 1 H), 7,15 (dd, *J*=7,32, 4,88 Hz, 1 H), 3,91 (s, 3 H). MS (LC/MS) T. R. = 2,87; $[M+H]^+$ = 244,9.

Etapa D: (R)-N-(2-Metoxi-3-4'-bipiridin-2'-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

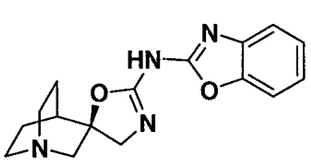


A 2'-isotiocianato-2-metoxi-3,4'-bipiridina (0,09 g, 0,37 mmol) en DMF (20 ml) se añadió Et_3N (0,11 ml, 0,81 mmol) y diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (0,09 g, 0,37 mmol) a temperatura ambiente. La reacción se agitó a 70 °C durante 2 horas. La reacción se enfrió hasta temperatura ambiente y se concentró a vacío. La urea bruta se purificó por cromatografía (Biotage: 85% de $CHCl_3$, 14% de MeOH, 1% de NH_4OH) proporcionando la urea intermedia pura. El producto se trató entonces con DMF (20 ml) y N,N'-diisopropilcarbodiimida (0,17 ml, 1,1 mmol). La reacción se calentó hasta 90 °C durante 18 horas. La reacción se enfrió hasta temperatura ambiente y se concentró proporcionando el producto bruto. El producto bruto se purificó por cromatografía (Biotage: 85% de $CHCl_3$, 14% de MeOH, 1% de NH_4OH) y se reunieron las fracciones que contenían producto. LC/MS y RMN

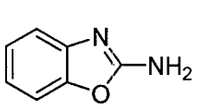
de ^{1}H indicaron que puede haber algunas impurezas presentes. El producto impuro se sometió a HPLC de fase inversa proporcionando (R)-N-(2-metoxi-3,4'-bipiridin-2'-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,02 g, 0,05 mmol, 14,05 % de rendimiento) como un polvo blanco. RMN de ^{1}H (500 MHz, *DMSO-D6*) δ ppm 9,07 (s, 1 H), 8,43 (s, 1 H), 8,17 (dd, *J*=4,73, 1,68 Hz, 1 H), 7,79 (d, *J*=7,32 Hz, 2 H), 7,10 (dd, *J*=7,32, 4,88 Hz, 1 H), 6,79 - 6,92 (m, 1 H), 3,76 - 3,97 (m, 4 H), 3,51 - 3,66 (m, 1 H), 2,92 - 3,09 (m, 2 H), 2,59 - 2,82 (m, 4 H), 1,85 - 2,03 (m, 2 H), 1,53 - 1,71 (m, 2 H), 1,35 - 1,49 (m, 1 H). MS (LC/MS) T. R. = 1,05; $[M+H]^+$ = 366,1.

EJEMPLO 288

(R)-N-(Benzo[d]oxazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



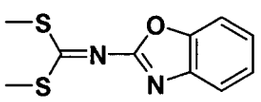
Etapa A: Benzo[d]oxazol-2-amina



Se cargó un matraz de fondo redondo secado en horno con di(1H-imidazol-1-il)metanimina (500 mg, 3,10 mmol), 2-aminofenol (188 mg, 1,724 mmol) y THF anhidro (20ml) a temperatura ambiente. La suspensión resultante

se llevó a reflujo en N_2 durante 2 hr dando conversión completa en base a LC/MS. El disolvente se eliminó a vacío y el residuo se purificó en un Biotage Flash Collector, eluyendo con EtOAc al 30-80%/Hexano (1200 ml) proporcionando el producto esperado, benzo[d]oxazol-2-amina (200 mg, 1,5 mmol, 87 % de rendimiento), como un sólido blanco. RMN de ^1H (400 MHz, *CDCl*$_3$) δ ppm 6,20 (s ancho, 2 H) 7,02 - 7,11 (m, 1 H) 7,17 - 7,22 (m, 1 H) 7,29 (d, *J*=7,53 Hz, 1 H) 7,36 (d, *J*=7,03 Hz, 1 H). MS (LC/MS) T. R. = 1,05; $[M+H]^+$ = 134,96.

Etapa B: Benzo[d]oxazol-2-ilcarbonimidoditioato de dimetilo



A una solución incolora de benzo[*d*]oxazol-2-amina (200 mg, 1,491 mmol) en DMF (10ml) se añadió hidróxido sódico (20N, 149 µl, 2,98 mmol), dando una suspensión verde. La mezcla se agitó durante 15 min a temperatura ambiente. Se añadió disulfuro de carbono (225 µl, 3,73 mmol) dando una solución marrón oscuro. La reacción se agitó durante 15 min a temperatura ambiente, seguido por la adición de hidróxido sódico (20N, 149 µl, 2,98 mmol) y se agitó durante otros 10 minutos. Se añadió entonces yodometano (224 µl, 3,58 mmol) gota a gota. Después de 12 minutos precipitó un sólido verde. La reacción se agitó durante otras 2 horas. El sólido se recogió por filtración, se lavó con DMF (2x1ml), H_2O (2x1ml), se secó a vacío de la instalación durante 30 min y se volvió a secar en un horno a vacío durante la noche

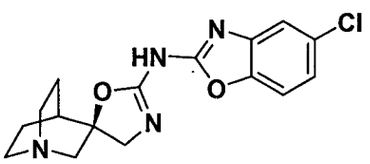
proporcionando el producto esperado, benzo[*d*]oxazol-2-ilcarbonimidoditioato de dimetilo (258,5 mg, 1,085 mmol, 72,7 % de rendimiento), como un sólido blanco. RMN de ^{1}H (400 MHz, *CDCl$_3$*) δ ppm 2,70 (s, 6 H) 7,24 - 7,34 (m, 2 H) 7,45 - 7,50 (m, 1 H) 7,66 - 7,74 (m, 1 H). MS (LC/MS) T. R. = 1,76, $[M+H]^+$ = 238,96.

Etapa C: (R)-N-(Benzo[d]oxazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

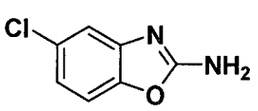
Se cargó un vial de 10 ml con sal (S)-3-(aminometil)quinuclidin-3-ol•2 HCl (69,5 mg, 0,361 mmol), DMF (2ml), DIEA (0,063 ml, 0,361 mmol) y Cs_2CO_3 (235 mg, 0,722 mmol) a temperatura ambiente, seguido por benzo[d]oxazol-2-ilcarbonimidoditioato de dimetilo (86 mg, 0,361 mmol). La suspensión resultante se agitó a temperatura ambiente durante 1 hr. LC/MS indicaron luego el consumo del material de partida. La mezcla se diluyó con MeOH y se purificó por HPLC preparativa proporcionando el producto esperado, (R)-N-(benzo[d]oxazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (101,5 mg, 0,323 mmol, 90 % de rendimiento), como una goma color castaño. RMN de ^{1}H (400 MHz, Acetona-d_6) δ ppm 2,07 - 2,14 (m, 2 H) 2,20 (ddd, *J*=8,78, 5,27, 3,26 Hz, 2 H) 2,33 - 2,45 (m, 1 H) 2,62 (d, *J*=2,26 Hz, 1 H) 3,34 - 3,47 (m, 3 H) 3,48 - 3,58 (m, 1 H) 3,75 - 3,88 (m, 2 H) 4,15 (d, *J*=10,54 Hz, 1 H) 4,32 (d, *J*=10,54 Hz, 1 H) 7,13 - 7,26 (m, 2 H) 7,41 (td, *J*=3,70, 1,63 Hz, 1 H) 9,24 (s ancho, 1H). MS (LC/MS) T. R. = 0,792, $[M+H]^+$ = 299,17.

EJEMPLO 289

(R)-N-(5-Clorobenzo[d]oxazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



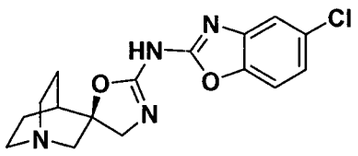
Etapa A: 5-Clorobenzo[d]oxazol-2-ilcarbonimidoditioato de dimetilo



A una solución marrón de 5-clorobenzo[d]oxazol-2-amina (700mg, 4,15 mmol) en DMF (5ml) se añadió hidróxido sódico (20N, 415 µl, 8,30 mmol) dando una suspensión gris. La mezcla se agitó durante 15 min a temperatura ambiente. Se añadió disulfuro de carbono (626 µl, 10,38 mmol) a temperatura ambiente dando una solución marrón. La mezcla se agitó durante 15 min a temperatura ambiente, luego se añadió metóxido sódico (20N, 208 µl, 4,16mmol). Después de 10 min, se añadió gota a gota yodometano (623 µl, 9,97 mmol). Se formó un sólido gris de la solución. La reacción se volvió a agitar a temperatura ambiente durante 2 hr. El sólido se recogió por filtración, se lavó con DMF/H_2O(50:50, 2x2ml), se secó al vacío de la instalación durante 30 min y se volvió a secar en un horno a 65 °C a vacío durante 1 1/2 hr proporcionando el producto esperado, 5-clorobenzo[d]oxazol-2-ilcarbonimidoditioato de dimetilo (780mg, 2,86 mmol, 68,9 % de rendimiento),

como un sólido blanquecino que era suficientemente puro para usar en la siguiente etapa. RMN de ^{1}H (400 MHz, DMSO-d_6) δ ppm 2,69 (s, 6 H) 7,37 (dd, *J*=8,53, 2,26 Hz, 1 H) 7,66 (d, *J*=9,03 Hz, 1 H) 7,75 (d, *J*=1,76 Hz, 1 H). MS (LC/MS) T. R. = 1,44; $[M+H]^+$ = 272,9.

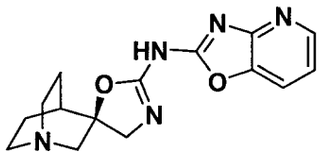
Etapa B: (R)-N-(5-Clorobenzo[d]oxazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



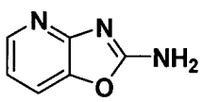
Se cargó un vial de 10 ml con sal (S)-3-(aminometil)quinuclidin-3-ol•2 HCl (106 mg, 0,550 mmol), DMF (2ml), DIEA (0,096 ml, 0,550 mmol), y Cs_2CO_3(358 mg, 1,100 mmol) a temperatura ambiente, seguido por 5-clorobenzo[d]oxazol-2-ilcarbonimidoditioato de dimetilo (150mg, 0,550 mmol). La suspensión resultante se agitó a temperatura ambiente durante 1 hora. LC/MS indicaron luego consumo de material de partida. La mezcla de reacción se diluyó MeOH y se purificó por HPLC preparativa proporcionando el producto esperado, (R)-N-(5-clorobenzo[d]oxazol-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (106,5 mg, 0,3 mmol, 53,0 % de rendimiento), como un sólido blanco. RMN de ^{1}H (400 MHz, Acetona-d_6) δ ppm 2,08 - 2,30 (m, 3 H) 2,35 - 2,48 (m, 1 H) 2,60 - 2,73 (m, 1 H) 3,48 (cd, *J*=7,53, 7,28 Hz, 3 H) 3,54 - 3,68 (m, 1 H) 3,79 - 4,00 (m, 2 H) 4,18 (d, *J*=10,54 Hz, 1 H) 4,35 (d, *J*=10,54 Hz, 1 H) 7,19 (dd, *J*=8,53, 2,01 Hz, 1 H) 7,30 - 7,47 (m, 2 H) 9,10 (s ancho, 1 H). MS(LC/MS) T. R. = 1,56; $[M+H]^+$ = 333,13.

EJEMPLO 290

(R)-N-(Oxazolo[4,5-b]piridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

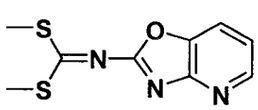


Etapa A: Oxazolo[4,5-b]piridin-2-amina



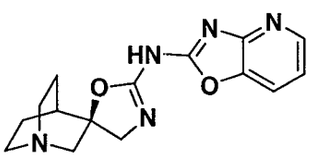
Se cargó un matraz de fondo redondo secado en horno con di(1H-imidazol-1-il)metanimina (500 mg, 3,10 mmol), 2-aminopiridin-3-ol (171 mg, 1,551 mmol) y THF anhidro (20ml) a temperatura ambiente. La suspensión resultante se llevó a reflujo en N_2 durante 1 hr. LC/MS indicó consumo completo del material de partida. El disolvente se eliminó a vacío y el residuo se usó en la etapa siguiente sin purificación posterior. MS(LC/MS) T. R. = 0,235; $[M+H]^+$ = 136,09.

Etapa B: Oxazolo[4,5-b]piridin-2-ilcarbonimidoditioato de dimetilo



A la oxazolo[4,5-b]piridin-2-amina bruta (811 mg, 6 mmol) de la etapa A, en DMF (12ml), se añadió NaOH (20 N, 600 µl, 12,00 mmol) dando una solución castaña que se agitó durante 15 min a temperatura ambiente. Se añadió entonces disulfuro de carbono (904 µl, 15,00 mmol) dando una solución naranja. La mezcla se agitó durante 15 min a temperatura ambiente, luego se añadió NaOH (20 N, 600 µl, 12,00 mmol) y continuó la agitación durante 10 min dando una solución rojo oscuro. Se añadió gota a gota yodometano (900 µl, 14,40 mmol) dando lugar a un sólido amarillo que precipitó después de 1 hr dando ~80% de conversión. La mezcla se diluyó con MeOH y se purificó por HPLC preparativa proporcionando el producto esperado, oxazolo[4,5-*b*]piridin-2-ilcarbonimidoditioato de dimetilo (35 mg, 0,146 mmol, 2,4 % de rendimiento), como un sólido blanco. RMN de ^{1}H (400 MHz, *CDCl$_3$*) δ ppm 2,71 (s, 6 H) 7,22 (dd, *J*=8,03, 5,02 Hz, 1 H) 7,72 (dd, *J*=8,03, 1,25 Hz, 1 H) 8,49 (dd, *J*=5,02, 1,51 Hz, 1 H). MS (LC/MS) T. R. = 1,358; [M+H] = 240,04.

Etapa C: (R)-N-(Oxazolo[4,5-b]piridin-2-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

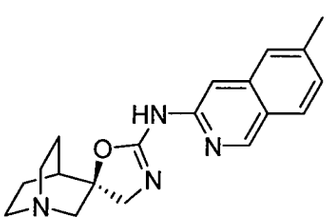


Se cargó un vial de 10 ml con sal (S)-3-(aminometil)quinuclidin-3-ol•2 HCl (8,53 mg, 0,044 mmol), DMF (2 ml), DIEA (7,74 µl, 0,04 mmol) y Cs_2CO_3(28,9 mg, 0,089 mmol) a temperatura ambiente, seguido por oxazolo[4,5-*b*]piridin-2-ilcarbonimidoditioato de dimetilo (10,6 mg, 0,044 mmol).

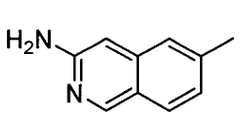
La suspensión resultante se agitó a temperatura ambiente durante 1 hr. LC/MS indicó consumo completo del material de partida. La mezcla de reacción se diluyó con MeOH y se purificó por HPLC preparativa proporcionando el producto esperado, (R)-N-(oxazolo [4, 5-*b*] piridin-2-il)-4H-1'-azaspiro[oxazol-5, 3'-biciclo [2.2.2] octan]-2-amina (13 mg, 0,038 mmol, 86 % de rendimiento), como un sólido blanco. RMN de ^{1}H (400 MHz, Acetona-d_6) δ ppm 1,54 - 1,60 (m, 1 H) 1,71 - 1,77 (m, 2 H) 2,16 - 2,24 (m, 1 H) 2,77 - 2,82 (m, 2 H) 2,89 (t, *J*=7,91 Hz, 4 H) 3,13 - 3,25 (m, 2 H) 3,90 (d, *J*=10,29 Hz, 1 H) 4,22 (d, *J*=10,29 Hz, 1 H) 7,13 (dd, *J*=8,03, 5,02 Hz, 1 H) 7,70 (dd, *J*=7,91, 1,13 Hz, 1 H) 8,27 (dd, *J*=5,14, 1,13 Hz, 1 H) 9,11 (s ancho, 1 H). MS (LC/MS) T. R. = 0,443; $[M+H]^+$ = 300,16.

EJEMPLO 291

(2R)-N-(6,8-Dimetil-3-isoquinolinil)-4'H-spiro[4-azabiciclo[2.2.2]octano-2,5'-[1,3]oxazol]-2'-amina

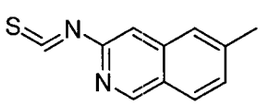


Etapa A: 6-Metilisoquinolin-3-amina



A una solución de 2,2-dietoxiacetimidato de metilo (1,1 g, 6,82 mmol) en metanol (8 ml) se añadió p-tolilmetanamina (0,788 g, 6,50 mmol) gota a gota a temperatura ambiente. El matraz de reacción se colocó entonces en un baño de aceite precalentado y se agitó a 70 °C durante 16 h, luego se retiró y se dejó enfriar. Los volátiles se eliminaron a presión reducida y el material bruto se añadió gota a gota a ácido sulfúrico (5 ml) a temperatura ambiente. La mezcla de reacción se agitó durante 72 h, luego se colocó el matraz en un baño de hielo-agua, se diluyó con agua (50 ml), y se neutralizó lentamente hasta pH = 10 con hidróxido sódico (10 N). Cuando la mezcla de reacción se hizo básica se formó un precipitado gris. Este precipitado se filtró, se lavó con agua, y se secó proporcionando 6-metilisoquinolin-3-amina (0,65g, 63%), como un polvo gris. RMN de ^{1}H (400 MHz, DMSO-d_6) δ ppm 8,73 (s, 1 H), 7,69 (d, *J*=8,28 Hz, 1 H),7,29 (s, 1 H), 7,00 (d, *J*=8,28 Hz, 1 H), 5,81 (s, 1 H), 2,40 (s, 3 H). MS (LC/MS) T. R. = 1,37; $[M+H]^+$ = 159,10.

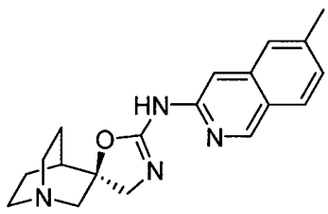
Etapa B: 3-Isotiocianato-6-metilisoquinolina



A una solución de 1,1'-tiocarbonildipiridin-2(1H)-ona (220 mg, 0,948 mmol) en diclorometano (10 ml) a temperatura ambiente se añadió 6-metilisoquinolin-3-amina (125 mg, 0,790 mmol). La mezcla de reacción se colocó en un baño de aceite precalentado y se agitó a 40 °C durante 18 h, luego se retiró del baño de aceite y se enfrió hasta temperatura ambiente. La

mezcla se concentró y el material bruto se purificó por cromatografía sobre gel de sílice (acetato de etilo del 5-30% en hexanos) proporcionando 3-isotiocianato-6-metilisoquinolina (75 mg, 0,375 mmol, 47,4 % de rendimiento), como un sólido blanquecino, RMN de ^{1}H (400 MHz, *CDCl$_3$*) δ ppm 9,03 (s, 1 H), 7,88 (d, *J*=8,24 Hz, 1 H), 7,56 (s, 1 H), 7,46 (dd, *J*=8,24, 1,53 Hz, 1 H) , 7,39 (s, 1 H) 2,57 (s, 3 H). MS (LC/MS) T. R. = 1,92; $[M+H]^+$ = 201,13.

Etapa C: (R)-N-(6-Metilisoquinolin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

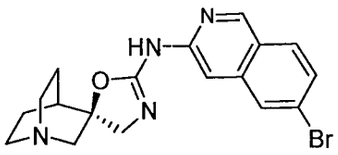


A diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (65,8 mg, 0,285 mmol) en N,N-dimetilformamida (6 ml) se añadió trietilamina (0,090 ml, 0,63 mmol) y 3-isotiocianato-6-metilisoquinolina (57 mg, 0,285 mmol). La suspensión se colocó en un baño de aceite precalentado y se agitó a 70 ºC durante 2 h y 30 min. Se añadió entonces N,N'-diisopropilcarbodiimida (0,177 ml, 1,14 mmol) y la mezcla se agitó a 85 ºC durante 16 h. La mezcla se concentró y se purificó por cromatografía sobre gel de sílice (0-40 % de [metanol:hidróxido amónico 9:1] en cloroformo) seguido por purificación por HPLC preparativa de fase inversa (0-40 % de TFA-metanol-agua). La solución de producto se filtró a través de un cartucho UCT Clean-up CHQAX15M25 con MeOH (3x10ml) y se concentró proporcionando el producto esperado, (S)-1-((3-hidroxiquinuclidin-3-

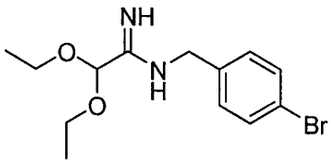
il)metil)-3-(6-metilisoquinolin-3-il)tiourea, como una goma color castaño. RMN de ^{1}H (400 MHz, MeOD) δ ppm 9,11 (s, 1 H), 8,02 (d, *J*=8,53 Hz, 1 H), 7,80 (s, 1 H), 7,74 (s, 1 H), 7,47 (d, *J*=8,53 Hz, 1 H), 4,47 (d, *J*=10,54 Hz, 1 H), 4,31 (d, *J*=10,54 Hz, 1 H), 4,10 (d, *J*=14,81 Hz, 1 H), 3,92 (d, *J*=14,81 Hz, 1 H), 3,53 - 3,71 (m, 2 H), 3,27 - 3,51 (m, 3 H), 2,84 (s ancho, 1 H), 2,55 (s, 3H), 2,48 (m, 1 H),) 2,10 – 2,30 (m, 3H). MS (LC/MS) T. R. = 1,24; $[M+H]^+$ = 323,2.

Ejemplo 292

(R)-N-(6-Bromoisoquinolin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



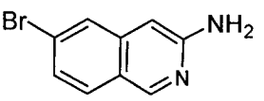
Etapa A: N-(4-Bromobencil)-2,2-dietoxiacetimidamida



Se añadieron clorhidrato de (4-bromofenil)metanamina (2,359 g, 10,39 mmol) y metóxido sódico (2,376 ml, 10,39 mmol) a una solución de 2,2-dietoxiacetimidato de metilo (3,35 g, 20,78 mmol) en metanol (10 ml). La mezcla turbia se calentó a 70ºC durante 1,5 horas y se concentró la mezcla amarilla resultante. El residuo se purificó por gel de sílice con acetato de etilo al 100% dando un aceite amarillo viscoso (2,04 g, 62%). RMN de ^{1}H (400 MHz, *CDCl$_3$*) δ ppm 7,47 (2 H, d, *J*=8,56 Hz), 7,23 (2 H, d, *J*=8,06 Hz), 6,76 (1 H, s

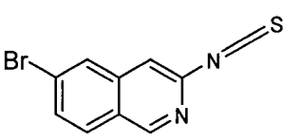
ancho), 5,31 (1 H, s ancho), 4,94 (1 H, s ancho), 4,45 (2 H, s ancho), 3,47 - 3,77 (4 H, m), 1,26 (6 H, t, *J*=7,05 Hz). LCMS: T.R. = 2,12; $[M+2]^+$ = 317,2.

Etapa B: 6-Bromoisoquinolin-3-amina



Se calentó N-(4-bromobencil)-2,2-dietoxiacetimidamida (1,53 g, 4,85 mmol) en ácido sulfúrico (4 ml, 95-98 %) a 40 °C durante 14 h. La mezcla se neutralizó con NaOH 1 M hasta pH 7 y se filtró la suspensión resultante. El residuo se purificó por cromatografía sobre gel de sílice con acetato de etilo al 20-55% en hexanos. Las fracciones deseadas se concentraron dando un sólido amarillo parduzco (0,434 g, 40%). LCMS: T. R. = 1,62; $[M+2]^+$ = 225,1.

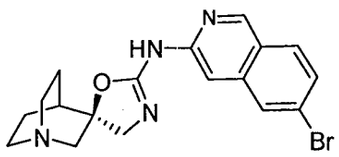
Etapa C: 6-Bromo-3-isotiocianatoisoquinolina



A una solución de 1,1'-tiocarbonildipiridin-2(1H)-ona (0,251 g, 1,080 mmol) en diclorometano a temperatura ambiente se añadió 6-bromoisoquinolin-3-amina (0,241 g, 1,080 mmol). La solución se agitó a temperatura ambiente durante 3 horas. LC/MS indicó la formación del producto deseado. La solución naranja intenso se purificó por cromatografía sobre gel de sílice (acetato de etilo del 0-10%-hexanos) proporcionando 6-bromo-3-isotiocianatoisoquinolina (0,1 g, 0,377 mmol, 35 % de rendimiento) como un aceite amarillo. T. R. = 2,54;

$[M+H]^+$ = 267,04.

Etapa D: (R)-N-(6-bromoisoquinolin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina

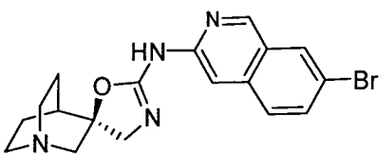


A diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (0,086 g, 0,377 mmol) en N,N-dimetilformamida (15 ml) se añadió Cs_2CO_3 (0,307 g, 0,943 mmol) y 6-bromo-3-isotiocianatoisoquinolina (0,1 g, 0,377 mmol). La suspensión se agitó a temperatura ambiente durante 30 minutos. Se añadió entonces N,N'-diisopropilcarbodiimida (0,176 ml, 1,132 mmol) y la mezcla se agitó durante otras 18 horas. La mezcla se concentró y se purificó por cromatografía sobre gel de sílice (5-25 % de [metanol:hidróxido amónico 9,5:0,5]-acetato de etilo) proporcionando (R)-N-(6-bromoisoquinolin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,054 g, 0,135 mmol, 36 % de rendimiento) como un sólido amarillo. RMN de ^1H (400 MHz, *MeOD*) δ ppm 9,04 (1 H, s), 7,80 - 8,05 (2 H, m), 7,55 (1 H, dd, *J*=8,81, 1,76 Hz), 7,37 (1 H, s ancho), 4,10 (1 H, d, *J*=10,58 Hz), 3,87 (1 H, d, *J*=10,83 Hz), 3,68 - 3,77 (1 H, m), 3,56 - 3,67 (1 H, m), 3,29 - 3,49 (4 H, m), 2,45 (1 H, s ancho), 2,28 - 2,41 (1 H, m), 1,86 - 2,15 (3 H, m). LCMS: T. R. = 1,76; $[M+]^+$ = 387,21.

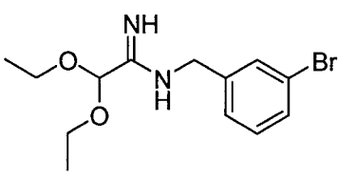
Ejemplo 293

(R)-N-(7-Bromoisoquinolin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-

2-amina

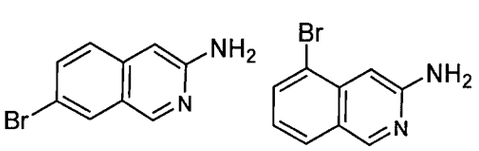


Etapa A: N-(3-Bromobencil)-2,2-dietoxiacetimidamida



Se añadieron clorhidrato de (3-bromofenil)metanamina (3,62 g, 15,64 mmol) y metóxido sódico (3,58 ml, 15,64 mmol) a una solución de 2,2-dietoxiacetimidato de metilo (5,042 g, 31,3 mmol) en metanol (15 ml). La mezcla turbia se calentó a 70ºC durante 1,5 h y la mezcla amarilla resultante se concentró. El residuo se purificó por cromatografía sobre gel de sílice con acetato de etilo al 100%. Las fracciones deseadas se concentraron dando un aceite amarillo viscoso (2,5 g, 51%). LCMS: T. R. = 2,11; $[M+2]^+$ = 317,06.

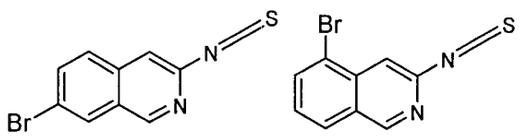
Etapa B: 7-Bromoisoquinolin-3-amina y 5-bromoisoquinolin-3-amina



Se calentó N-(3-bromobencil)-2,2-dietoxiacetimidamida (2,5 g, 7,93 mmol) en ácido sulfúrico (5 ml, 95-98 %) a 40 ºC durante 54 h. La mezcla se neutralizó con NaOH acuoso 10 M hasta pH 7 y se filtró la suspensión

resultante. El residuo se purificó por cromatografía sobre gel de sílice con acetato de etilo del 20-55% en hexanos, luego acetato de etilo al 100%. Las fracciones se concentraron dando un sólido marrón que contenía una mezcla de productos. (1,0 g, 57%). LCMS: T. R. = 1,56; $[M+2]^+$ = 225,1. La mezcla se usó como tal para la etapa siguiente.

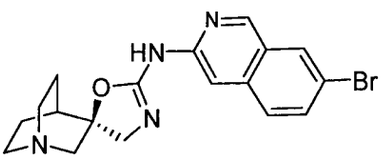
Etapa C: 7-Bromo-3-isotiocianatoisoquinolina y 5-bromo-3-Isotiocianatoisoquinolina



A una solución de 1,1'-tiocarbonildipiridin-2(1H)-ona 1,145 g, 4,93 mmol) en diclorometano a temperatura ambiente se añadió la mezcla de 7-bromoisoquinolin-3-amina y 5-bromoisoquinolin-3-amina de la etapa B (1,0 g, 4,5 mmol). La solución naranja se agitó a temperatura ambiente durante 18 horas. LCMS indicó la formación de producto. La solución naranja intenso se purificó por cromatografía sobre gel de sílice (0-5 % de acetato de etilo-hexanos). Las primeras fracciones de producto se reunieron y se concentraron a vacío proporcionando 7-bromo-3-isotiocianatoisoquinolina (0,27 g, 0,377 mmol, 22 % de rendimiento) como un sólido amarillo. RMN de ^{1}H (400 MHz, *Acetona*) δ ppm 9,19 (1 H, s), 8,41 (1 H, s), 7,86 - 8,02 (2 H, m), 7,76 (1 H, s). T. R. = 4,28; $[M+H]^+$ = 267,04. Las segundas fracciones de producto se reunieron y se concentraron a vacío proporcionando 5-bromo-3-isotiocianatoisoquinolina (0,25 g, 0,377 mmol, 21 % de rendimiento) como un sólido amarillo. RMN de ^{1}H (400 MHz, *Acetona*) δ ppm 9,24 (1 H, s), 8,23 (1 H,

d), 8,15 (1 H, d), 7,81 (1 H, s), 7,64 (1 H, t). LCMS: T. R. = 4,61; $[M+H]^+$ = 267,04.

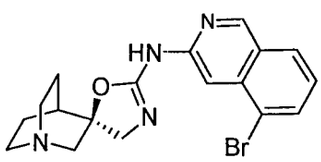
Etapa D: (R)-N-(7-Bromoisoquinolin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



A diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (0,207 g, 0,905 mmol) en N,N-dimetilformamida (20 ml) se añadió Cs_2CO_3 (0,737 g, 2,263 mmol) y 7-bromo-3-isotiocianatoisoquinolina (0,24 g, 0,905 mmol). La suspensión se agitó a temperatura ambiente durante 30 minutos. Se añadió entonces N,N'-diisopropilcarbodiimida (0,423 ml, 2,72 mmol) y la mezcla se agitó a temperatura ambiente durante 18 horas. La mezcla se concentró y se purificó por cromatografía sobre gel de sílice usando 5-15% de [metanol:hidróxido amónico 9:1] en acetato de etilo. Las fracciones deseadas se concentraron y se purificaron otra vez usando 5-15% de [metanol:hidróxido amónico 9,5:0,5] en acetato de etilo proporcionando ((R)-N-(7-bromoisoquinolin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,061 g, 0,156 mmol, 17 % de rendimiento) como un sólido amarillo. RMN de ^1H (400 MHz, *MeOD*) δ ppm 8,96 (1 H, s), 8,12 (1 H, s), 7,66 (2 H, s), 7,32 (1 H, s), 4,01 (1 H, d), 3,73 (1 H, d), 3,35 - 3,42 (1 H, m), 3,22 - 3,29 (1 H, m), 2,84 - 3,17 (4 H, m), 2,13 - 2,35 (2 H, m), 1,62 - 1,96 (3 H, m). LCMS: T. R. = 1,76; $[M+]^+$ = 387,21.

Ejemplo 294

((R)-N-(5-Bromoisoquinolin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina



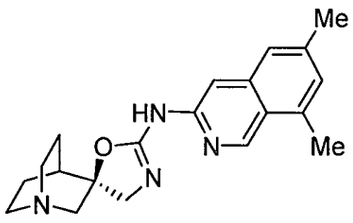
A diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (0,207 g, 0,905 mmol) en N,N-dimetilformamida (20 ml) se añadió Cs_2CO_3 (0,737 g, 2,263 mmol) y 5-bromo-3-isotiocianatoisoquinolina (0,24 g, 0,905 mmol). La suspensión se agitó a temperatura ambiente durante 30 minutos. Se añadió entonces N,N'-diisopropilcarbodiimida (0,423 ml, 2,72 mmol) y la mezcla se agitó a temperatura ambiente durante 18 horas. La mezcla se concentró y se purificó por cromatografía sobre gel de sílice (5-15 % de [metanol:hidróxido amónico 9,5:0,5]-acetato de etilo). Las fracciones deseadas se concentraron y se purificaron otra vez usando 5-15% de [metanol:hidróxido amónico 9,5:0,5] en acetato de etilo proporcionando (R)-N-(5-bromoisoquinolin-3-il)-4H-1'-azaspiro[oxazol-5,3'-biciclo[2.2.2]octan]-2-amina (0,248 g, 0,634 mmol, 70 % de rendimiento) como un sólido amarillo.

RMN de ^{1}H (400 MHz, *MeOD*) δ ppm 8,99 (1 H, s), 7,91 (2 H, dd), 7,55 (1 H, s ancho), 7,28 (1 H, t), 3,96 (1 H, d), 3,65 (1 H, d), 3,17 - 3,26 (1 H, m), 3,03 - 3,13 (1 H, m), 2,70 - 2,99 (4 H, m), 2,03 - 2,30 (2 H, m), 1,47 - 1,87 (3 H, m).

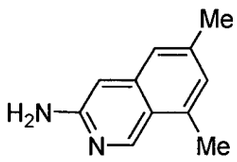
LCMS: T. R. = 1,69; $[M+2]^+$ = 389,21.

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(2R)-N-(6,8-Dimetil-3-isoquinolinil)-4'H-spiro[4-azabiciclo[2.2.2]octano-2,5'-[1,3]oxazol]-2'-amina

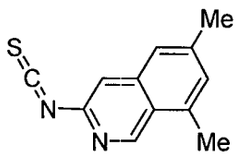


Etapa A: 6,8-Dimetilisoquinolin-3-amina



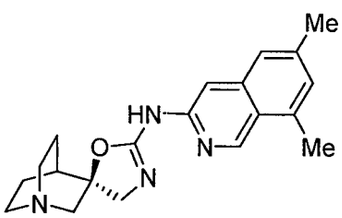
A una solución de 2,2-dietoxiacetimidato de metilo (1,5 g, 9,3 mmol) en metanol (4,9 ml) se añadió (2,4-dimetilfenil)metanamina (1,2 g, 8,9 mmol) gota a gota a temperatura ambiente. El matraz de reacción se colocó entonces en un baño de aceite precalentado y se agitó a 70 ºC durante 16 h, luego se enfrió y se eliminaron los volátiles a presión reducida. El material bruto se añadió gota a gota a ácido sulfúrico (19,7 ml) a temperatura ambiente y se agitó durante 72 h. Se colocó entonces el matraz en un baño de hielo agua, se diluyó con agua (50 ml) y se neutralizó lentamente hasta pH = 10 con hidróxido sódico (10 N). Cuando la mezcla de reacción se hizo básica, se formó un precipitado naranja. Este precipitado se filtró, se lavó con agua y se secó proporcionando 6,8-dimetilisoquinolin-3-amina (1,37 g, 7,95 mmol, 90 %). RMN de ^{1}H (400 MHz, MeOD) δ ppm 8,82 (s, 1 H), 7,17 (s, 1 H), 6,90 (s, 1 H), 6,72 (s, 1 H), 2,61 (s, 3 H), 2,37 (s, 3 H). MS (LC/MS) T. R. = 0,77; $[M+H]^+$ = 173,15.

Etapa B: 3-Isotiocianato-6,8-dimetilisoquinolina



A una solución de 1,1'-tiocarbonildipiridin-2(1H)-ona (1,35 g, 5,8 mmol) en diclorometano (19 ml) a temperatura ambiente se añadió 6,8-dimetilisoquinolin-3-amina (1 g, 5,8 mmol). La mezcla de reacción se colocó en un baño de aceite precalentado y se agitó a 40 °C durante 18 h, luego se enfrió, se concentró y el material bruto se purificó por cromatografía sobre gel de sílice (acetato de etilo del 10-35% en hexanos) proporcionando 3-isotiocianato-6,8-dimetilisoquinolina (93,7 mg, 0,437 mmol, 8 %) como un sólido amarillo. RMN de ^{1}H (400 MHz, *CDCl$_3$*) δ ppm 9,20 (s, 1 H), 7,36 - 7,44 (m, 2 H), 7,23 (s, 1 H), 2,75 (s, 3 H), 2,51 (s, 3 H). MS (LC/MS) T. R. = 2,03; $[M+H]^+$ = 215,1.

Etapa C: (2R)-N-(6,8-Dimetil-3-isoquinolinil)-4'H-spiro[4-azabiciclo[2.2.2]octano-2,5'-[1,3]oxazol]-2'-amina



A diclorhidrato de (S)-3-(aminometil)quinuclidin-3-ol (99 mg, 0,43 mmol) en N,N-dimetilformamida (1,4 ml) se añadió trietilamina (0,18 ml, 1,3 mmol) y 3-

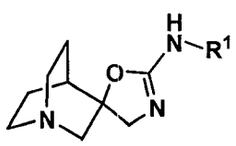
isotiocianato-6,8-dimetilisoquinolina (93 mg, 0,43 mmol). La suspensión se colocó en un baño de aceite precalentado y se agitó a 70 °C durante 2 h y 30 min. Se añadió entonces N,N'-diisopropilcarbodiimida (0,27 ml, 1,7 mmol) y la mezcla se agitó a 85 °C durante 16 h. La mezcla se concentró y se purificó por cromatografía sobre gel de sílice (0-40 % de [metanol:hidróxido amónico 9:1] en cloroformo) seguido por purificación por HPLC preparativa de fase inversa (0-40 % de [TFA al 0,1%]-metanol-agua) proporcionando (2R)-N-(6,8-dimetil-3-isoquinolinil)-4'H-spiro[4-azabiciclo[2.2.2]octano-2,5'-[1,3]oxazol]-2'-amina como la sal del ácido trifluoroacético (24 mg, 0,053 mmol, 12 % de rendimiento) como un sólido blanco. RMN de ^{1}H (400 MHz, MeOD) δ ppm 9,29 (s, 1 H), 7,54 (s, 1 H), 7,43 (s, 1 H), 7,34 (s, 1 H), 4,38 (d, J=11,04 Hz, 1 H), 4,17 (d, J=11,04 Hz, 1 H), 3,94- 4,10 (m, 1 H), 3,86 (dd, J=15,06, 2,26 Hz, 1 H), 3,51 - 3,67 (m, 1 H), 3,37 - 3,51 (m, 3 H), 2,77 (s, 3 H), 2,73 (d, J=3,51 Hz, 1 H), 2,48 - 2,57 (m, 3 H), 2,30 - 2,46 (m, 1 H), 1,94 - 2,28 (m, 3 H). MS (LC/MS) T. R. = 0,90; $[M+H]^+$ = 337,38.

Será evidente para un experto en la técnica que la presente revelación no queda limitada a los ejemplos ilustrativos anteriores, y que ésta se puede realizar en otras formas específicas sin apartarse de sus atributos esenciales. Por tanto se desea que los ejemplos se consideren en todos los aspectos como meramente ilustrativos y no limitantes, haciéndose referencia a las reivindicaciones adjuntas, en lugar de a los ejemplos anteriores, y por tanto se pretende que estén abarcados todos los cambios que estén dentro del significado y rango de equivalencia de las reivindicaciones.

Habiendo descrito la invención como antecede, se declara como propiedad lo contenido en las siguientes

REIVINDICACIONES

1. Un compuesto de fórmula I, o uno de sus estereoisómeros,



I

en la que

R^1 se selecciona del grupo constituido por isoxazolilo, pirazolilo, oxazolilo, tiazolilo, imidazolilo, oxadiazolilo, tiadiazolilo, triazolilo, piridinilo, pirazinilo, piridazinilo, pirimidinilo, triazinilo, quinolinilo, isoquinolinilo, quinoxalinilo, quinazolinilo, naftiridinilo, indazolilo, indolilo, 2-indolonilo, bencisoxazolilo, benzoisotiazolilo, benzoxazolilo, benzotiazolilo, bencimidazolilo, furopiridinilo, tienopiridinilo, tienopirimidinilo, isotiazolopiridinilo, tiazolopiridinilo, tiazolopiridinonilo, tiazolopirazinilo, tiazolopirimidinilo, triazolopiridinilo, triazolopirazinilo, pirrolotriazinilo, 5,6-dihidrobenzo[h]quinazolinilo, 5H-cromeno[4,3-d]pirimidinilo, 6,7-dihidro-5H-ciclopenta[d]pirimidinilo, 5,6,7,8-tetrahidroquinazolinilo, 7,8-dihidroquinazolin-5(6H)-onilo y tetrahidrobenzotiazolilo, y está sustituido con 0-3 sustituyentes seleccionados independientemente del grupo constituido por alquilo C_{1-4}, cicloalquilo C_{3-7}, haloalquilo C_{1-4}, alcoxi C_{1-4}, haloalcoxi C_{1-4}, cicloalcoxi C_{3-7}, (alquil C_{1-4})tio,

fenoxi, benciloxi, halo, hidroxi, ciano, (alquil C_{1-4})sulfonilo, NR^2R^3, pirrolidinonilo, metilendioxi, furilo, tienilo, triazolilo, pirimidinilo, naftilo, (alquil C_{1-4})amido, $CONR^2R^3$, piridilo, fenilo y bencilo, y donde piridilo, fenilo y bencilo están sustituidos con 0-2 sustituyentes seleccionados independientemente del grupo constituido por halo, alquilo C_{1-4}, alcoxi C_{1-4}, haloalquilo C_{1-4}, haloalcoxi C_{1-4} y NR^2R^3;

R^2 es hidrógeno, alquilo C_{1-4}, hidroxialquilo C_{1-4} o aminoalquilo C_{1-4};

R^3 es hidrógeno, alquilo C_{1-4}, hidroxialquilo C_{1-4} o aminoalquilo C_{1-4};

o R_2 y R_3 tomados junto con el átomo de nitrógeno al que están unidos es azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, N-(alquil C_{1-4})piperazinilo, morfolinilo u homopiperidinilo;

o una de sus sales farmacéuticamente aceptables.

2. Un compuesto de la reivindicación 1 en el que R^1 se selecciona del grupo constituido por dimetilisoxazolilo, (metil)(fenil)isoxazolilo, metilpirazolilo, dimetilpirazolilo, tienilpirazolilo, metoxifenilpirazolilo, tiazolilo, bromotiazolilo, cianotiazolilo, metiltiazolilo, dimetiltiazolilo, (metil)(fenil)tiazolilo, isopropiltiazolilo, butiltiazolilo, benciltiazolilo, metoxifenilmetiltiazolilo, feniltiazolilo, clorofeniltiazolilo, metoxifeniltiazolilo, (metoxifenil)(metil)tiazolilo, piridiniltiazolilo, (fenil)(metil)imidazolilo, metiloxadiazolilo, etiloxadiazolilo, metiltiadiazolilo, fluorofeniltiadiazolilo, furiltiadiazolilo,

(dimetilcarboxamido)(metil)tiazolilo, (pirrolidinilCO)tiazolilo, feniltriazolilo, piridinilo, bromopiridinilo, cloropiridinilo, (cloro)(fluoro)piridinilo, (cloro)(metil)piridinilo, dicloropiridinilo, fluoropiridinilo, cianopiridinilo, (ciano)(metil)piridinilo, (ciano)(dimetil)piridinilo, metoxipiridinilo, (metilpirrolidinil)piridinilo, fenilpiridinilo, metoxipiridinilpiridinilo, piridazinilo, bromopiridazinilo, cloropiridazinilo, metilpiridazinilo, metoxipiridazinilo, metiltiopiridazinilo, pirrolidinilpiridazinilo, pirrolidinonilpiridazinilo, fenilpiridazinilo, piridinilpiridazinilo, metoxipiridinilpiridazinilo, pirimidinilo, (bromo)(isopropil)pirimidinilo, (bromo)(dimetil)pirimidinilo, (bromo)(ciclopropil)pirimidinilo, (bromo)(metoxi)pirimidinilo, (bromo)(fenil)pirimidinilo, (bromo)(piridinil)pirimidinilo, cloropirimidinilo, (cloro)(dimetil)pirimidinilo, (metil)(metoxi)pirimidinilo, metilpirimidinilo, etilpirimidinilo, (metil)(fenil)pirimidinilo, dimetilpirimidinilo, butilpirimidinilo, isopropilpirimidinilo, ciclopropilpirimidinilo, metoxipirimidinilo, dimetoxipirimidinilo, isopropoxipirimidinilo, ciclopentoxipirimidinilo, difluorometoxipirimidinilo, trifluoroetoxipirimidinilo, fenoxipirimidinilo, metiltiopirimidinilo, fenilpirimidinilo, clorofenilpirimidinilo, metilfenilpirimidinilo, metoxifenilpirimidinilo, (fenil)(triazolil)pirimidinilo, piridinilpirimidinilo, metoxipiridinilpirimidinilo, metoxipirimidinilpirimidinilo, naftilpirimidinilo, pirazinilo, bromopirazinilo, (bromo)(metoxi)pirazinilo, cloropirazinilo, metilpirazinilo, dimetilpirazinilo, butilpirazinilo, cianopirazinilo, metoxipirazinilo, isopropoxipirazinilo, trifluorometilpirazinilo y fenilpirazinilo y dimetiltriazinilo;

o una de sus sales farmacéuticamente aceptables.

3. Un compuesto de la reivindicación 1 en el que R^1 se selecciona del grupo constituido por dimetilpiridinoisoxazolilo, benzoxazolilo, clorobenzoxazolilo, fluorofenilbenzoxazolilo, etilfenilbenzoxazolilo, dimetilaminofenilbenzoxazolilo, piridinilbenzoxazolilo, benzotiazolilo, acetamidobenzotiazolilo, bromobenzotiazolilo, clorobenzotiazolilo, (cloro)(metil)benzotiazolilo, (cloro)(metoxi)benzotiazolilo, fluorobenzotiazolilo, difluorobenzotiazolilo, cianobenzotiazolilo, metilbenzotiazolilo, dimetilbenzotiazolilo, (metil)(metoxi)benzotiazolilo, etilbenzotiazolilo, trifluorometilbenzotiazolilo, hidroxibenzotiazolilo, metoxibenzotiazolilo, etoxibenzotiazolilo, isopropoxibenzotiazolilo, trifluorometoxibenzotiazolilo, difluorometoxibenzotiazolilo, dimetoxibenzotiazolilo, morfolinilbenzotiazolilo, (pirrolidinilCO)benzotiazolilo, metilsulfonilbenzotiazolilo, clorotiazolopiridinilo, dimetiltiazolopiridinilo, benciloxitiazolopiridinilo, difluorometoxitiazolopiridinilo, benzotriazolilo, indolonilo, indazolilo, bromoindazolilo, cloroindazolilo, fluoroindazolilo, (metil)(metoxi)indazolilo, metoxiindazolilo, trifluorometilindazolilo, trifluorometoxiindazolilo, difluorometoxiindazolilo, bencimidazolilo, fluorobencimidazolilo, metilbencimidazolilo, (metil)(metoxi)bencimidazolilo, metoxibencimidazolilo, tetrahidrobenzotiazolilo, furopiridinilo, dimetilfuropirimidinilo, tienopirimidinilo, isopropiltienopirimidinilo, dimetiltienopirimidinilo, clorotriazolopiridinilo, metiltriazolopiridinilo, trifluorometiltriazolopiridinilo, metoxitriazolopiridinilo, triazolopirazinilo, bromopirrolotriazinilo, dimetilaminotiazolopirimidinilo, tiazolopiazinilo, bromotiazolopiazinilo, metoxitiazolopiazinilo, metiltiotiazolopiazinilo, metoxitiazolopirimidinilo, (metil)(metoxi)tiazolopirimidinilo, quinolinilo, bromoquinolinilo, fluoroquinolinilo, metilquinolinilo, (metil)(metoxi)quinolinilo,

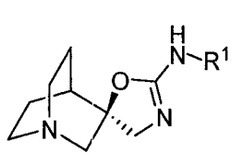
isoquinolinilo, bromoisoquinolinilo, dicloroisoquinolinilo, metilisoquinolinilo, dimetilisoquinolinilo, quinoxalinilo, cloroquinoxalinilo, metilquinoxalinilo, metoxiquinoxalinilo, quinazolinilo, bromoquinazolinilo, naftiridinilo, 5,6-dihidrobenzo[h]quinazolinilo, 5H-cromeno[4,3-d]pirimidinilo, 6,7-dihidro-5H-ciclopenta[d]pirimidinilo, 5,6,7,8-tetrahidroquinazolinilo y 7,8-dihidroquinazolin-5(6H)-onilo;

o una de sus sales farmacéuticamente aceptables.

4. Un compuesto de la reivindicación 1 en el que R^1 se selecciona del grupo constituido por feniltiazolilo, (cloro)(metil)piridinilo, (bromo)(fenil)pirimidinilo, metoxipirimidinilo, difluorometoxipirimidinilo, difluoroetoxipirimidinilo, ciclopentoxipirimidinilo, (metilfenil)pirimidinilo, (metoxifenil)pirimidinilo, bromopirazinilo, cloropirazinilo, metiltiopirazinilo, metoxibenzotiazolilo, etoxibenzotiazolilo, difluorometoxibenzotiazolilo, tiazolopiridinonilo, trifluorometilindazolilo, bencimidazolilo, isoquinoinilo y quinazolinilo;

o una de sus sales farmacéuticamente aceptables.

5. El estereoisómero de la reivindicación 1 de acuerdo con la Fórmula Ia;



Ia

o una de sus sales farmacéuticamente aceptables.

6. Un compuesto de la reivindicación 5 en el que R^1 se selecciona del grupo constituido por dimetilisoxazolilo, (metil)(fenil)isoxazolilo, metilpirazolilo, dimetilpirazolilo, tienilpirazolilo, metoxifenilpirazolilo, tiazolilo, bromotiazolilo, cianotiazolilo, metiltiazolilo, dimetiltiazolilo, (metil)(fenil)tiazolilo, isopropiltiazolilo, butiltiazolilo, benciltiazolilo, metoxifenilmetiltiazolilo, feniltiazolilo, clorofeniltiazolilo, metoxifeniltiazolilo, (metoxifenil)(metil)tiazolilo, piridiniltiazolilo, (fenil)(metil)imidazolilo, metiloxadiazolilo, etiloxadiazolilo, metiltiadiazolilo, fluorofeniltiadiazolilo, furiltiadiazolilo, (dimetilcarboxamido)(metil)tiazolilo, (pirrolidinilCO)tiazolilo, feniltriazolilo, piridinilo, bromopiridinilo, cloropiridinilo, (cloro)(fluoro)piridinilo, (cloro)(metil)piridinilo, dicloropiridinilo, fluoropiridinilo, cianopiridinilo, (ciano)(metil)piridinilo, (ciano)(dimetil)piridinilo, metoxipiridinilo, (metilpirrolidinil)piridinilo, fenilpiridinilo, metoxipiridinilpiridinilo, piridazinilo, bromopiridazinilo, cloropiridazinilo, metilpiridazinilo, metoxipiridazinilo, metiltiopiridazinilo, pirrolidinilpiridazinilo, pirrolidinonilpiridazinilo, fenilpiridazinilo, piridinilpiridazinilo, metoxipiridinilpiridazinilo, pirimidinilo, (bromo)(isopropil)pirimidinilo, (bromo)(dimetil)pirimidinilo, (bromo)(ciclopropil)pirimidinilo, (bromo)(metoxi)pirimidinilo, (bromo)(fenil)pirimidinilo, (bromo)(piridinil)pirimidinilo, cloropirimidinilo, (cloro)(dimetil)pirimidinilo, (metil)(metoxi)pirimidinilo, metilpirimidinilo, etilpirimidinilo, (metil)(fenil)pirimidinilo, dimetilpirimidinilo, butilpirimidinilo, isopropilpirimidinilo, ciclopropilpirimidinilo, metoxipirimidinilo,

dimetoxipirimidinilo, isopropoxipirimidinilo, ciclopentoxipirimidinilo, difluorometoxipirimidinilo, trifluoroetoxipirimidinilo, fenoxipirimidinilo, metiltiopirimidinilo, fenilpirimidinilo, clorofenilpirimidinilo, metilfenilpirimidinilo, metoxifenilpirimidinilo, (fenil)(triazolil)pirimidinilo, piridinilpirimidinilo, metoxipiridinilpirimidinilo, metoxipirimidinilpirimidinilo, naftilpirimidinilo, pirazinilo, bromopirazinilo, (bromo)(metoxi)pirazinilo, cloropirazinilo, metilpirazinilo, dimetilpirazinilo, butilpirazinilo, cianopirazinilo, metoxipirazinilo, isopropoxipirazinilo, trifluorometilpirazinilo y fenilpirazinilo y dimetiltriazinilo;

o una de sus sales farmacéuticamente aceptables.

7. Un compuesto de la reivindicación 5 en el que R^1 se selecciona del grupo constituido por dimetilpiridinoisoxazolilo, benzoxazolilo, clorobenzoxazolilo, fluorofenilbenzoxazolilo, etilfenilbenzoxazolilo, dimetilaminofenilbenzoxazolilo, piridinilbenzoxazolilo, benzotiazolilo, acetamidobenzotiazolilo, bromobenzotiazolilo, clorobenzotiazolilo, (cloro)(metil)benzotiazolilo, (cloro)(metoxi)benzotiazolilo, fluorobenzotiazolilo, difluorobenzotiazolilo, cianobenzotiazolilo, metilbenzotiazolilo, dimetilbenzotiazolilo, (metil)(metoxi)benzotiazolilo, etilbenzotiazolilo, trifluorometilbenzotiazolilo, hidroxibenzotiazolilo, metoxibenzotiazolilo, etoxibenzotiazolilo, isopropoxibenzotiazolilo, trifluorometoxibenzotiazolilo, difluorometoxibenzotiazolilo, dimetoxibenzotiazolilo, morfolinilbenzotiazolilo, (pirrolidinilCO)benzotiazolilo, metilsulfonilbenzotiazolilo, clorotiazolopiridinilo, dimetiltiazolopiridinilo, benciloxitiazolopiridinilo, difluorometoxitiazolopiridinilo, benzotriazolilo, indolonilo, indazolilo, bromoindazolilo, cloroindazolilo,

fluoroindazolilo, (metil)(metoxi)indazolilo, metoxiindazolilo, trifluorometilindazolilo, trifluorometoxiindazolilo, difluorometoxiindazolilo, bencimidazolilo, fluorobencimidazolilo, metilbencimidazolilo, (metil)(metoxi)bencimidazolilo, metoxibencimidazolilo, tetrahidrobenzotiazolilo, furopiridinilo, dimetilfuropirimidinilo, tienopirimidinilo, isopropiltienopirimidinilo, dimetiltienopirimidinilo, clorotriazolopiridinilo, metiltriazolopiridinilo, trifluorometiltriazolopiridinilo, metoxitriazolopiridinilo, triazolopirazinilo, bromopirrolotriazinilo, dimetilaminotiazolopirimidinilo, tiazolopiazinilo, bromotiazolopiazinilo, metoxitiazolopiazinilo, metiltiotiazolopiazinilo, metoxitiazolopirimidinilo, (metil)(metoxi)tiazolopirimidinilo, quinolinilo, bromoquinolinilo, fluoroquinolinilo, metilquinolinilo, (metil)(metoxi)quinolinilo, isoquinolinilo, bromoisoquinolinilo, dicloroisoquinolinilo, metilisoquinolinilo, dimetilisoquinolinilo, quinoxalinilo, cloroquinoxalinilo, metilquinoxalinilo, metoxiquinoxalinilo, quinazolinilo, bromoquinazolinilo, naftiridinilo, 5,6-dihidrobenzo[h]quinazolinilo, 5H-cromeno[4,3-d]pirimidinilo, 6,7-dihidro-5H-ciclopenta[d]pirimidinilo, 5,6,7,8-tetrahidroquinazolinilo y 7,8-dihidroquinazolin-5(6H)-onilo;

o una de sus sales farmacéuticamente aceptables.

8. Un compuesto de la reivindicación 5 en el que R^1 se selecciona del grupo constituido por feniltiazolilo, (cloro)(metil)piridinilo, (bromo)(fenil)pirimidinilo, metoxipirimidinilo, difluorometoxipirimidinilo, difluoroetoxipirimidinilo, ciclopentoxipirimidinilo, (metilfenil)pirimidinilo, (metoxifenil)pirimidinilo, bromopirazinilo, cloropirazinilo, metiltiopirazinilo,

metoxibenzotiazolilo, etoxibenzotiazolilo, difluorometoxibenzotiazolilo, tiazolopiridinonilo, trifluorometilindazolilo, bencimidazolilo, isoquinoinilo y quinazolinilo;

o una de sus sales farmacéuticamente aceptables.

9. Un compuesto de la reivindicación 5 en el que R^1 se selecciona del grupo constituido por tiazolilo, piridinilo, piridazinilo, pirimidinilo, pirazinilo, benzotiazolilo, tiazolopiridinilo, indazolilo, bencimidazolilo, isoquinoinilo, y quinazolinilo, y está sustituido con 0-3 sustituyentes seleccionados independientemente del grupo constituido por alquilo C_{1-4}, cicloalquilo C_{3-7}, haloalquilo C_{1-4}, alcoxi C_{1-4}, haloalcoxi C_{1-4}, cicloalcoxi C_{3-7}, (alquil C_{1-4})tio, fenoxi, benciloxi, halo, hidroxi, ciano, (alquil C_{1-4})sulfonilo, NR^2R^3, pirrolidinonilo, metilendioxi, furilo, tienilo, triazolilo, pirimidinilo, naftilo, (alquil C_{1-4})amido, $CONR^2R^3$, piridilo, fenilo y bencilo, y donde piridilo, fenilo y bencilo están sustituidos con 0-2 sustituyentes seleccionados independientemente del grupo constituido por halo, alquilo C_{1-4}, alcoxi C_{1-4}, haloalquilo C_{1-4}, haloalcoxi C_{1-4} y NR^2R^3;

o una de sus sales farmacéuticamente aceptables.

10. Un compuesto de la reivindicación 9 en el que R^1 se selecciona del grupo constituido por piridinilo, pirimidinilo, pirazinilo, tiazolopiridinilo, e isoquinoinilo, y está sustituido con 0-3 sustituyentes seleccionados independientemente del grupo constituido por alquilo C_{1-4}, cicloalquilo C_{3-7},

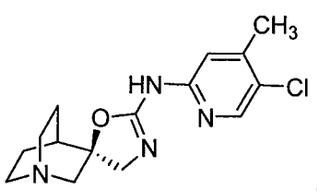
haloalquilo C_{1-4}, alcoxi C_{1-4}, haloalcoxi C_{1-4}, cicloalcoxi C_{3-7}, (alquil C_{1-4})tio, fenoxi, benciloxi, halo, hidroxi, ciano, (alquil C_{1-4})sulfonilo, NR^2R^3, pirrolidinonilo, metilendioxi, furilo, tienilo, triazolilo, pirimidinilo, naftilo, (alquil C_{1-4})amido, $CONR^2R^3$, piridilo fenilo, y bencilo, y donde piridilo, fenilo y bencilo están sustituidos con 0-2 sustituyentes seleccionados independientemente del grupo constituido por halo, alquilo C_{1-4}, alcoxi C_{1-4}, haloalquilo C_{1-4}, haloalcoxi C_{1-4} y NR^2R^3;

o una de sus sales farmacéuticamente aceptables.

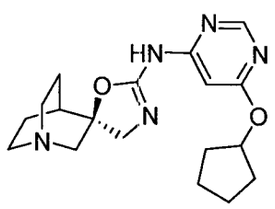
11. Un compuesto de la reivindicación 10 en el que R^1 se selecciona del grupo constituido por piridinilo e isoquinoinilo, y está sustituido con 0-3 sustituyentes seleccionados independientemente del grupo constituido por alquilo C_{1-4}, cicloalquilo C_{3-7}, haloalquilo C_{1-4}, alcoxi C_{1-4}, haloalcoxi C_{1-4}, cicloalcoxi C_{3-7}, (alquil C_{1-4})tio, fenoxi, benciloxi, halo, hidroxi, ciano, (alquil C_{1-4})sulfonilo, NR^2R^3, pirrolidinonilo, metilendioxi, furilo, tienilo, triazolilo, pirimidinilo, naftilo, (alquil C_{1-4})amido, $CONR^2R^3$, piridilo, fenilo y bencilo, y donde piridilo, fenilo y bencilo están sustituidos con 0-2 sustituyentes seleccionados independientemente del grupo constituido por halo, alquilo C_{1-4}, alcoxi C_{1-4}, haloalquilo C_{1-4}, haloalcoxi C_{1-4} y NR^2R^3;

o una de sus sales farmacéuticamente aceptables.

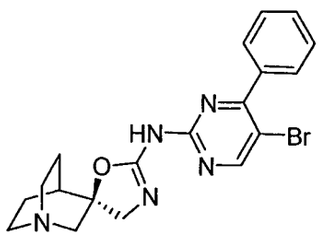
12. Un compuesto seleccionado del grupo constituido por



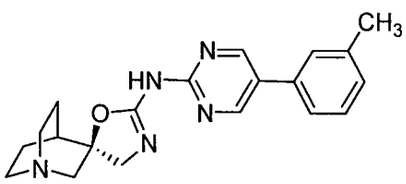
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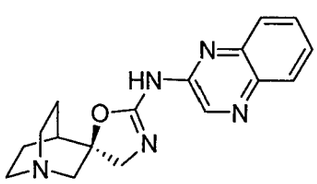
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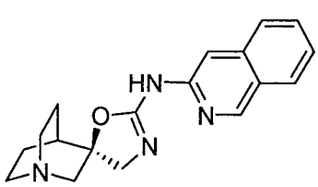
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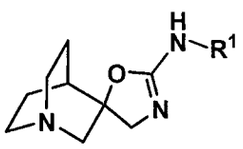
o una de sus sales farmacéuticamente aceptables.

13. Una composición farmacéutica que comprende una cantidad terapéuticamente eficaz de un compuesto de la reivindicación 1, o una de sus sales farmacéuticamente aceptables, y un vehículo farmacéuticamente aceptable.

14. Un procedimiento para el tratamiento de esquizofrenia o enfermedad de Alzheimer que comprende administrar a un paciente una cantidad terapéuticamente eficaz de un compuesto de la reivindicación 1.

RESUMEN

La revelación proporciona compuestos de fórmula I, incluyendo sus sales, así como composiciones y procedimientos de uso de los compuestos. Los compuestos son ligandos para el receptor nicotínico α7 y pueden ser útiles para el tratamiento de diversos trastornos del sistema nervioso central, en especial trastornos afectivos y neurodegenerativos.



I

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SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO PROPIETARIOS

PATENTE DE INVENCION ____ PCT X MODELO DE UTILIDAD ____ DISEÑO INDUSTRIAL ___

(21) N° de solicitud:
(22) Fecha de solicitud:
(51) Clasificación Internacional :

(71)Solicitante(s): BRISTOL-MYERS SQUIBB COMPANY

(72) Inventor(es): COOK II, James, H.; MCDONALD, Ivar, M.; KING, Dalton; OLSON, Richard, E.; WANG, Nenghui; IWUAGWU, Christiana, I.; ZUSI, F., Christopher; MACOR, John, E.

(74) Apoderado: ALVARO CORREA ORDOÑEZ

(30) Prioridad	(31) *No. Prioridad*	32) *Fecha*	(33) *País*
	61/047,211	Abril 23, 2008	US
	12/423,299	Abril 14, 2009	US

(85) Fecha inicio fase nacional: Noviembre 23, 2010
(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: Abril 20, 2009
No. de solicitud: PCT/US2009/041076

(87) Publicación internacional
Fecha: Octubre 29, 2009
N° publicación: WO 2009/131926

(54) Titúlo: COMPUESTOS DE QUINUCLIDINA COMO LIGANDOS DEL RECEPTOR NICOTÍNICO DE ACETILCOLINA ALFA-7

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO TEMATICO

PATENTE DE INVENCION ___ PCT _X_ MODELO DE UTILIDAD ___ DISEÑO INDUSTRIAL ___

(21) N° de solicitud: (22) Fecha de solicitud:
(51) Clasificación Internacional :

(71)Solicitante(s): BRISTOL-MYERS SQUIBB COMPANY

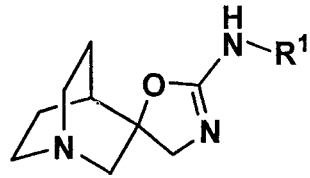
(72) Inventor(es) : COOK II, James, H.; MCDONALD, Ivar, M.; KING, Dalton; OLSON, Richard, E.; WANG, Nenghui; IWUAGWU, Christiana, I.; ZUSI, F., Christopher; MACOR, John, E.

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	61/047,211	Abril 23, 2008	US
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(85) Fecha límite inicio fase nacional: Noviembre 23, 2010
(86) Datos relativos a la presentación de la solic. PCT
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No. de solicitud: PCT/US2009/041076

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Fecha: 29 October 2009
No. Publicación: WO2009/131926



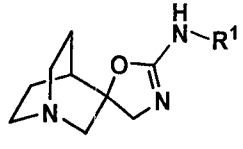
(54) Titulo:

COMPUESTOS DE QUINUCLIDINA COMO LIGANDOS DEL RECEPTOR NICOTÍNICO DE ACETILCOLINA ALFA-7

(57) Resumen:
La revelación proporciona compuestos de fórmula I, incluyendo sus sales, así como composiciones y procedimientos de uso de los compuestos. Los compuestos son ligandos para el receptor nicotínico $\alpha 7$ y pueden ser útiles para el tratamiento de diversos trastornos del sistema nervioso central, en

CONTINUA AL RESPALDO ...

especial trastornos afectivos y neurodegenerativos.



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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

(21) N° de solicitud:

22) Fecha de solicitud:

(30) Prioridad (31) *No.* 32) *Fecha* (33) *País*
61/047,211 Abril 23, 2008 US
12/423,299 Abril 14, 2009 US

(51) Int Cl:

(71)Solicitante(s) BRISTOL-MYERS SQUIBB COMPANY

(72) Inventor(es) COOK II, James, H.; MCDONALD, Ivar, M.; KING, Dalton; OLSON, Richard, E.; WANG, Nenghui; IWUAGWU, Christiana, I.; ZUSI, F., Christopher; MACOR, John, E.

(74) Apoderado: **ALVARO CORREA ORDOÑEZ**

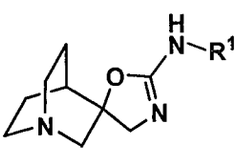
(85) Fecha limite inicio fase nacional: Noviembre 23, 2010
(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: Abril 20, 2009
No. de solicitud: PCT/US2009/041076

(87) Publicación internacional
Fecha: Octubre 29, 2009
N° publicación: WO 2009/131926

(54) Titulo: COMPUESTOS DE QUINUCLIDINA COMO LIGANDOS DEL RECEPTOR NICOTÍNICO DE ACETILCOLINA ALFA-7

Reivindicación(es):

1. Un compuesto de fórmula I, o uno de sus estereoisómeros,



I

en la que

R^1 se selecciona del grupo constituido por isoxazolilo, pirazolilo, oxazolilo, tiazolilo, imidazolilo, oxadiazolilo, tiadiazolilo, triazolilo, piridinilo, pirazinilo, piridazinilo, pirimidinilo, triazinilo, quinolinilo, isoquinolinilo, quinoxalinilo, quinazolinilo, naftiridinilo, indazolilo, indolilo, 2-indolonilo, bencisoxazolilo, benzoisotiazolilo, benzoxazolilo, benzotiazolilo, bencimidazolilo, furopiridinilo, tienopiridinilo, tienopirimidinilo, isotiazolopiridinilo, tiazolopiridinilo, tiazolopiridinonilo, tiazolopirazinilo, tiazolopirimidinilo, triazolopiridinilo, triazolopirazinilo, pirrolotriazinilo, 5,6-dihidrobenzo[h]quinazolinilo, 5H-cromeno[4,3-d]pirimidinilo, 6,7-dihidro-5H-ciclopenta[d]pirimidinilo, 5,6,7,8-tetrahidroquinazolinilo, 7,8-dihidroquinazolin-5(6H)-onilo y tetrahidrobenzotiazolilo, y está sustituido con 0-3 sustituyentes seleccionados independientemente del grupo constituido por alquilo C_{1-4}, cicloalquilo C_{3-7}, haloalquilo C_{1-4}, alcoxi C_{1-4}, haloalcoxi C_{1-4}, cicloalcoxi C_{3-7}, (alquil C_{1-4})tio, fenoxi, benciloxi, halo, hidroxi, ciano, (alquil C_{1-4})sulfonilo, NR^2R^3, pirrolidinonilo, metilendioxi, furilo, tienilo, triazolilo, pirimidinilo, naftilo, (alquil C_{1-4})amido, $CONR^2R^3$, piridilo, fenilo y bencilo, y donde piridilo, fenilo y bencilo están sustituidos con 0-2 sustituyentes seleccionados independientemente del grupo constituido por halo, alquilo C_{1-4}, alcoxi C_{1-4}, haloalquilo C_{1-4}, haloalcoxi C_{1-4} y NR^2R^3;

R^2 es hidrógeno, alquilo C_{1-4}, hidroxialquilo C_{1-4} o aminoalquilo C_{1-4};

R^3 es hidrógeno, alquilo C_{1-4}, hidroxialquilo C_{1-4} o aminoalquilo C_{1-4};

o R_2 y R_3 tomados junto con el átomo de nitrógeno al que están unidos es azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, N-(alquil C_{1-4})piperazinilo, morfolinilo u homopiperidinilo;

o una de sus sales farmacéuticamente aceptables.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-131169- -00000-0000

Fecha: 2010-10-22 13:47:05 Dep. 2020 DIR.NUEVASCR
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Act. 411 PRESENTACION Folios: 382

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SUPERINTENDENCIA

LISTA DE CHEQUEO
ADMISIÓN A TRÁMITE – NUEVAS CREACIONES

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 ☐