

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 11-181048-00000-0000

Fecha: 2011-12-29 16:43:55 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Evs: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 81



Industria y Comercio

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL
DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE
INVENCION

TITULO: AGONISTAS DE GPR119

SOLICITANTE: ELI LILLY AND COMPANY

DIRECCIÓN: Lilly Corporate Center, Indianapolis, Indiana 46285 E.U.A.

APODERADO: CARLOS R. OLARTE

BOGOTÁ 29 de Diciembre de 2011

P2011/000215

OLARTEMORE

OLARTE MOURE & ASOC

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 11-181048-00000-0000

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PETITORIO - FORMULARIO ÚNICO DE SOLICITUD

PATENTE PCT

ENTRADA EN FASE NACIONAL

P2011/000215

SOLICITUD DE:

1



Patente de Invención.



Patente de Modelo de Utilidad.



Capítulo I.



Capítulo II.

2

**SOLICITANTE
(71)**

Nombre: ELI LILLY AND COMPANY

Dirección: Lilly Corporate Center,
Indianápolis, Indiana 46285

Nacionalidad o Domicilio: Estadounidense

Lugar de Constitución: Estados Unidos de
América

Teléfono: _____

Fax: _____

E-mail: _____

IDENTIFICACIÓN

C.C. ☐ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número _____

**REPRESENTANTE
O APODERADO**

Nombre: CARLOS R. OLARTE

Dirección: Carrera 5 No. 34-03 Bogotá

Teléfono: 601-7700 Fax: 601-7799

E-mail: office@olartemoure.com

IDENTIFICACIÓN

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número 79.782.747Bta
TP 74.295

**INVENTOR (ES)
(72)**

Nombre: VER PAGINA ADJUNTA.

Dirección: VER PAGINA ADJUNTA.

Nacionalidad o Domicilio: VER PAGINA ADJUNTA.

5

PCT (86)

Solicitud Internacional No. PCT/US2010/041645 Fecha Julio 12, 2010

Publicación Internacional No. WO 2011/008663 Fecha Enero 20, 2011

6

Título (54) AGONISTAS DE GPR119

Clasificación Internacional (51) C07D 401/12; C07D 401/14; A61K 31/4427; A61P
3/10.

Prioridad

(33) País de Origen

(32) Fecha

(31) Número de Solicitud

EP

Julio 15, 2009

09382114.8

US

Septiembre 24, 2009

61/245,445

SI ☒

NO ☐

9

Comprobante de pago No. 11-

Fecha Diciembre de 2011



ANEXOS



Comprobante de pago de la tasa de presentación de la solicitud.



Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.



Poderes, si fuere el caso. Adjunto copia simple ver expediente No. 08-110.817



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



Declaraciones. Declaración bajo la regla 4.17 (ii) del PCT.



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



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



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



Traducción del examen preliminar internacional efectuado por la IPEA.



De ser el caso, copia del contrato de acceso.



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



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



Arte final 12 x 12.



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



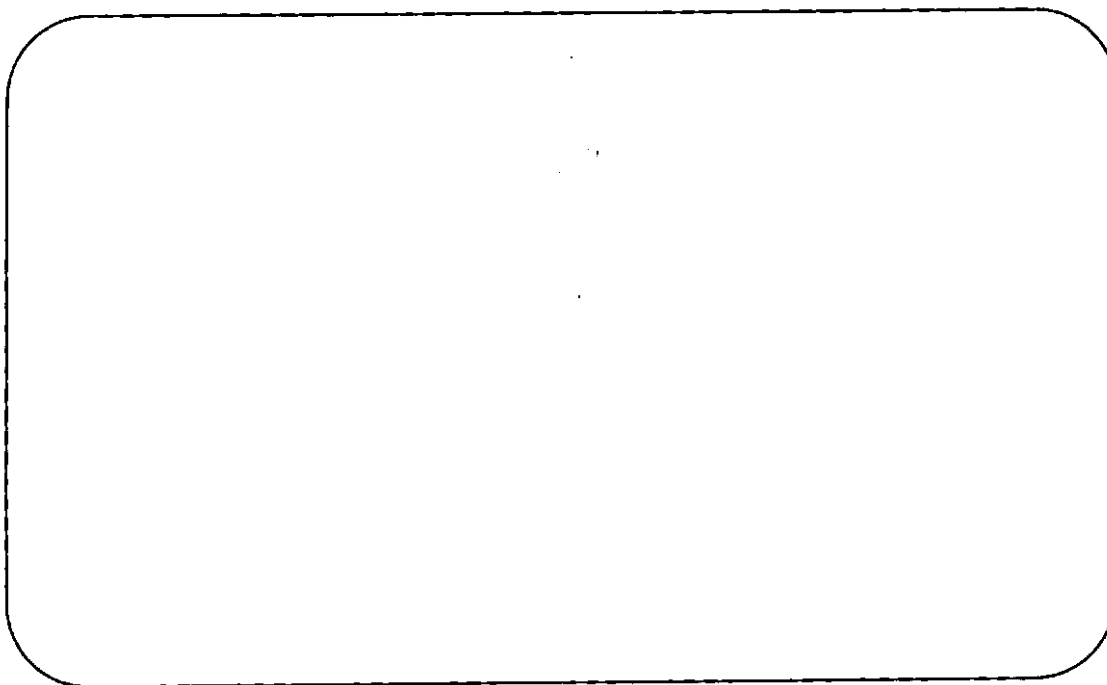
De ser el caso, modificaciones efectuadas a la solicitud internacional.



Otros. Búsqueda Internacional



FIGURA CARACTERÍSTICA:



Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

2

LISTA DE INVENTORES

PCT/US2010/041645

David Gene BARRETT

Eli Lilly and Company,
Lilly Corporate Center,
Indianápolis, Indiana 46285
Estado Unidos
Nacionalidad: Estadounidense

Ana Belen BUENO MELENDO

LILLY S.A.
Avenida de la Industria 30
28108 Alcobendas, Madrid,
España
Nacionalidad: Española

Jeffrey Bernard FRANCISKOVICH

Eli Lilly and Company,
Lilly Corporate Center,
Indianápolis, Indiana 46285
Estado Unidos
Nacionalidad: Estadounidense

Bin LIU

Eli Lilly and Company,
Lilly Corporate Center,
Indianápolis, Indiana 46285
Estado Unidos
Nacionalidad: Estadounidense

Kumiko TAKEUCHI

Eli Lilly and Company,

Lilly Corporate Center,

Indianápolis, Indiana 46285

Estado Unidos

Nacionalidad: Estadounidense

4

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

 Industria y Comercio SUPERINTENDENCIA	RECIBO DE CAJA	No. 11 - 126953
		Bogotá D.C., Diciembre 29 de 2011 - 10:45:33

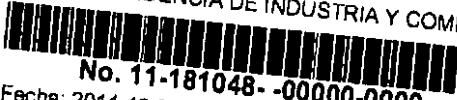
RECIBIDO DE : OLARTE MOURE & ASOCIADOS	NI 830.122.870
--	----------------

*** Soporte del Pago ***					
TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	409132802	28/12/2011	6.677.000.00

*** Conceptos Pagados ***				
CANT.	RENTISTICO	CONCEPTO	Vr. UNIDITARIO	Vr. CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCIÓN	571.000.00	571.000.00
				<u>\$571.000.00</u>

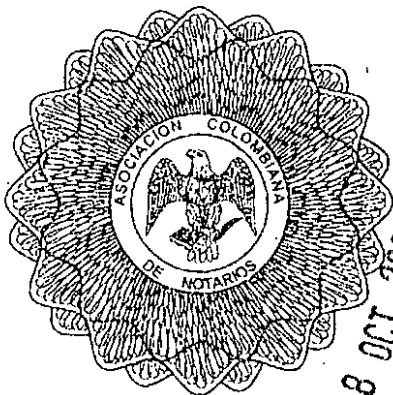
SON: **QUINIENTOS SETENTA Y UN MIL PESOS MONEDA CORRIENTE**

Responsable: _____
Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-181048- -00000-0000
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Tra. 11 PATENTEIYII Eve: 379 FASENACIONALI
Act. 411 PRESENTACION Folios: 81

5

WK 9397304



ESCRITURA PUBLICA NUMERO : (1 2 2 7)

MIL DOSCIENTOS VEINTISIETE

En la ciudad de Bogotá, Distrito
Capital, República de Colombia, a los
Veintiocho -- (28) días del mes de
Octubre -- -- del año dos mil ocho
(2008), ante mi MARIA EUGENIA

ROJAS DE URUETA NOTARIA(O) VEINTISIETE (27) DEL
CIRCULO DE BOGOTA, se otorgó la escritura pública que se
consigna en los siguientes términos:-----

CLASE DE ACTO: PROTOCOLIZACION DE PODER.-----

JAMES IAN RAISBECK LLÍNAS Y CARLOS REINALDO
OLARTE GARCIA.-----

C.C. No. 79.376.996 Y 79.782.747.-----

Comparecieron JAMES IAN RAISBECK LLÍNAS, mayor de edad
vecino de ésta ciudad, identificado con la cédula de ciudadanía
número 79.376.996 de estado civil casado con sociedad conyugal
vigente y CARLOS REINALDO OLARTE GARCIA, mayor de
edad, vecino de Bogotá, identificado con la cédula de
ciudadanía número 79.782.747, de estado civil casado con
sociedad conyugal vigente, obrando en sus propios nombres y
dijeron: -----

PRIMERO.- Que presentan para su protocolización y custodia en
los archivos de ésta notaría, bajo el número y lugar que a ésta
escritura corresponda, en cinco (5) folios autenticados, un poder y
sus traducciones los cuales son del siguiente tenor: -----

PODER -----

El suscrito ELI LILLY AND COMPANY, domiciliado en Lilly
Corporate Center, Indianápolis, Indiana 46285 US por medio del

ESTE PAPEL NO TIENE COSTO PARA EL USUARIO

6

presente otorga a Carlos R. Olarte, J. Ian Raisbeck y Ana María Frieri, poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de patentes, modelos de Utilidad y Diseños Industriales de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, apelaciones, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial o extrajudicialmente, responder en juicio a todas las reclamaciones y demandas que por motivo de encomendado se presentaren, dándoles asimismo facultades para sustituir el presente y revocar dichas sustituciones.-----

Firma (ilegible) -----

Fecha 17 July 2003-----

City, Country/ Ciudad, País: Indianápolis, Indiana, United Status of America.- -----

Traducción oficial del Inglés por Marlén Neira Castro resolución 2117 del Ministerio de Justicia de Colombia.- -----

APOSTILLA EN PODER DE DE REPRESENTACION DE ELY LILLY AND COMPANY.

Bilingüe inglés- español otorgado en Indianapoles, Indiana, Estados Unidos el 17 de julio de 2003 y firmado por Meter G. Stringer, Director Ejecutivo y patentes Internacionales de Ely Lilly & Company.- -----

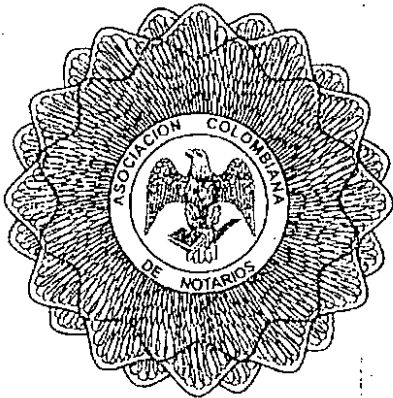
Todd Rokita Secretario de Estado-----

Secretario de Estado de Indiana Estado de Indiana-----

APOSTILLA

(Convencion de la Haya del 5 octubre 1961)

WK 9397305



1. País: Estados Unidos de América-
este documento público -----
2. Ha sido firmado por: Catherine Michel
3. Quien ejerce funciones de Secretario
de la Corte del Circuito en y para el
condado Jonson -----
- 4 Lleva el sello del Secretario de la Corte

del Circuito en y para el estado de Indiana -----

Certificado

5. En: Indianapoles, Indiana -----
6. El: 22 de julio de 2003.-----
7. Por el Secretario de Estado de Indiana 8 No. A2003-1279-----
9. Gran Sello del Estado de Indiana -----
10. Firma ilegible de Todd Rokita- Secretario de Estado de Indiana
- * Vigente desde el 1 de mayo de 2003, todas las apostillas de
Secretario y de Estado de Indiana tienen el sello impreso
electrónicamente. -----
- The Statehouse, Indianapoles, Indiana 46204, (307) 232-6531, fax
(317) 233-3283- -----

CERTIFICACION NOTARIAL

Bilingüe inglés- español, el 17 de julio de 2003 el suscrito notario
Catherine Michel certifica que Meter G. Stringer, domiciliado en
7620 Castleton Faros, West Drive Indianápolis, Indiana- 46256
Estados Unidos ejercía funciones de Director Ejecutivo y Patentes
Internacionales de Ely Lilly & Company, con sede en Indianápolis,
Indiana, Estados Unidos.-----

MARLEN NEIRA CASTRO Traductor e Intérprete Oficial inglés-
Español- Inglés-----

Resolución No. 2117 del 7 Oct 1987.- -----

El otorgante fundamenta sus certificaciones en este documento:
Delegación de Autoridad concerniente a Ciertas Materias de
Patentes, suscrito el 20 de enero de 2003: conforme al poder

ESTE PAPEL NO TIENE COSTO PARA EL USUARIO

2

otorgado al Asesor General de la Compañía por el Comité Ejecutivo de la Junta Directiva de Eli Lilly and Company.-----

Firma del notario público Catherine Michel certifica sus funciones vencen el 21 de octubre de 2008- residente en el condado Johnson

Sello de notario público de Indiana.-----

Es traducción fiel de inglés, con copia archivo para confrontación, Bogotá 28 de julio-2003.-----

MARLEN NEIRA CASTRO Traductor e Intérprete Oficial Inglés-Español- inglés -----

Resolución No. 2117 del 7 Oct 1987.-----

SEGUNDO.- Que solicita a la señora Notaria la incorporación de dichos documentos al protocolo de ésta notaría para que de su tenor se expidan las copias que más adelante se soliciten -----

Se advierte que la protocolización de documentos no da mayor fuerza o autenticidad de la que tienen dichos documentos.-----

Esta escritura pública fue firmada fuera del Despacho Notarial, de conformidad con el artículo 12 del Decreto 2148 de 1.983. -----

Se advirtió a los otorgantes de esta escritura de la obligación que tienen de leer la totalidad de su texto, a fin de verificar la exactitud de todos los datos en ella consignados, con el fin de aclarar, modificar o corregir lo pertinente antes de firmarla, la firma de la misma demuestra su aprobación total del texto, en consecuencia, la notaria no asume ninguna responsabilidad por errores o inexactitudes establecidas con posterioridad a la firma de (el, los) otorgante(s) y de la notaría, en tal caso, este (os) debe(n) ser corregidos mediante el otorgamiento de una nueva escritura, suscrita por todos los que intervinieron en la inicial y sufragada por los mismos (artículo 35, decreto ley 960 de 1970).-----

Traducción oficial del Inglés por Marlén Neira Castro, resolución 2117 del Ministerio de Justicia de Colombia

APOSTILLA EN PODER DE REPRESENTACIÓN DE
ELI LILLY AND COMPANY

Bilingüe inglés- español otorgado en Indianapolis, Indiana, Estados Unidos el 17 de julio de 2003 y firmado por Peter G. Stringer, Director Ejecutivo y Patentes Internacionales de Ely Lilly & Company.

Todd Rokita Secretario de Estado
Secretario de Estado de Indiana Estado de Indiana

APOSTILLA

(Convención de la Haya del 5 de octubre de

1. País: Estados Unidos de América- Este documento Público
2. ha sido firmado por Catherine Michel
3. Quien ejerce funciones de Secretario de la Corte del Condado en y por el condado Johnson
4. Lleva el sello del Secretario de la Corte del Circuito en y para el estado de Indiana

CERTIFICADO

5. En Indianapolis, Indiana
6. El 22 de julio de 2003
7. Por el Secretario de Estado de Indiana
8. No. A2003- 1127
9. Gran Sello del Estado de Indiana
10. Firma legible de Todd Rokita- Secretario de Estado de Indiana

* Vigente desde el 1 mayo de 2003, todas las apostillas del Secretario de Estado de Indiana tienen el sello impreso electrónicamente.

The Statehouse, Indianapolis, Indiana 46204, (317) 232-6531, fax (317) 233-3283

CERTIFICACION NOTARIAL

Bilingüe inglés- español, el 17 de julio de 2003 el suscrito notario Catherine Michel certifica que Peter G. Stringer, domiciliado en 7620 Castleton Farms, West Drive, Indianapolis, Indiana - 46256 Estados Unidos ejercía funciones de Director Ejecutivo y Patentes Internacionales de Ely Lilly & Company, con sede en Indianapolis, Indiana, Estados Unidos.

Marlén Neira
MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
inglés - Español - Inglés
Resolución No. 2117 del 7 Oct 1987

El otorgante fundamenta sus certificaciones en este documento: Delegación de Autoridad concerniente a Ciertas Materias de Patentes, suscrito el 20 de enero de 2003: conforme al poder otorgado al Asesor General de la Compañía por el Comité ejecutivo de la Junta Directiva de Eli Lilly and Company.

Firma del notario público Catherine Michel certifica

Sus funciones vencen el 21 de octubre de 2008 - residente en el condado Johnson
Sello de notario público de Indiana

Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 28 de julio-2003.

Marlen Neira C



MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Inglés
Resolución No. 2117 del 7 Oct 1987

OLARTE RAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER - TORRE C
CALLE 100 No. 8A-55 PISO 10
BOGOTÁ, COLOMBIA
TELEPHONE: +57-1 638-6200
Fax: +57-1 638-6201

www.olarteraisbeck.com

Power of Attorney

The undersigned,

domiciled in

Lilly Corporate Center, Indianapolis, Indiana 46285 US

by means of these presents hereby grants to **Carlos R. Olarte, J. Ian Raisbeck and Ana María Frieri** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's Patents, Utility Models and Industrial Designs in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, appeals, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

Signature/Firma

Date/Fecha: / 7 July 2003

City/Country/Ciudad,País: Indianapolis, Indiana, United States of America

Poder

El suscrito,

domiciliado en

por medio del presente otorga a **Carlos R. Olarte, J. Ian Raisbeck y Ana María Frieri** poder especial, amplio y suficiente para

presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de Patentes, Modelos de Utilidad y Diseños Industriales de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, apelaciones, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

NOTARIA FRIERI
17/07/2003 - 10:00 AM



Todd Rokita
Secretary of State

SECRETARY OF STATE
STATE OF INDIANA

APOSTILLE

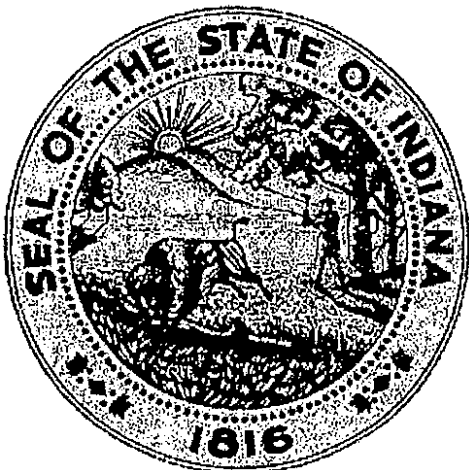
(Convention de la Haye du 5 Octobre 1961)

1. Country: United States of America
2. This public document has been signed by *Catherine Michel*
3. acting in the capacity of circuit court clerk in & for *Johnson County*
4. and bears the seal/stamp of circuit court clerk in & for the State of Indiana

Certified

5. at Indianapolis, Indiana
6. this *Twenty-second* day of *July*, 2003
7. by Secretary of State of Indiana
8. No. A2003- 11279
9. Seal/Stamp:

10. Signature:



Todd Rokita

Indiana Secretary of State

*Effective May 1, 2003 all apostilles from the Indiana Secretary of State will have an electronically printed seal.

The Statehouse, Indianapolis, Indiana 46204, (317) 232-6531, Fax (317) 233-3283

OLARTE RAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER - TORRE C
CALLE 100 No. 8A-55 PISO 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-6200
Fax: +57-1 638-6201

www.olarteraisbeck.com

Notarial Certification

On this date,

17 July 2003

The undersigned Notary Public certifies:

1. That

of legal age and domiciled in

7620 Castleton Farms, West Drive,
signed the foregoing document.

2. That the grantor has executed the foregoing
document as Executive Director, International
Patents
of ELI LILLY AND COMPANY

3. That ELI LILLY AND COMPANY
having its principal place of business located in
Indianapolis, Indiana, United States of
America

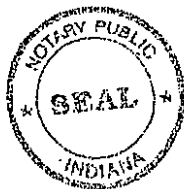
is duly incorporated, is currently in existence, and
that the purposes for which the Power of Attorney is
granted are within the scope of its corporate
purposes.

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

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

Delegation of Authority Concerning Certain
Patent Matters, executed January 20, 2003;
pursuant to the authority granted to the
General Counsel of the Company by the
executive Committee of the Board of
Directors of Eli Lilly and Company

NOTARY PUBLIC (Signature):



Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que

Peter G. Stringer

mayor de edad y domiciliado
Indianapolis, Indiana 46256 US
suscribió el documento que antecede.

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

de

4. Que

con sede principal ubicada en

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

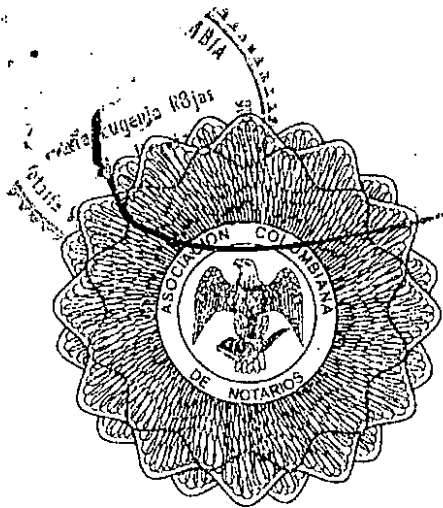
4. Que el otorgante tiene la representación para
suscibir el poder, y que ésta es legítima.

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

Catherine Michel
My Commission Expires October 21, 2008
Resident of Johnson County

NOTARIO PÚBLICO
Catherine Michel
Eugenio Rojas de Arango

WK 9397306



ADVERTENCIA, OTORGAMIENTO Y
AUTORIZACION.- Leído el presente
instrumento por el (los) compareciente
(s) y advertido (s) sobre las
formalidades legales, lo aprueban y
firman conmigo y ante mí la(el)
Notaria(o) quién lo autoriza. ---Se

utilizaron las hojas de papel Notarial Nos. WK 9397304, WK 9397305 Y
WK 9397306 .

DERECHOS LEGALES: \$ 39.630,00

RESOLUCION 8850 DE 2007

IVA \$ 10.781,00

James Ian Raisbeck Llínas



JAMES IAN RAISBECK LLÍNAS

C.C.No. 79.376.996 BOGOTÁ

TEL: 601-7700

Carlos Reinaldo Olarte García



CARLOS REINALDO OLARTE GARCIA

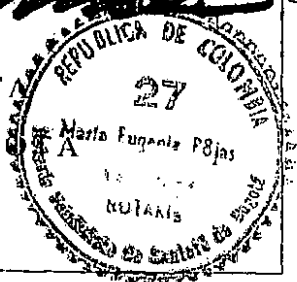
C.C.No. 79.782.744 BOGOTÁ.

TEL: 601-7700

Marta Eugenia Rojas de Urue

MARTA EUGENIA ROJAS DE URUE
NOTARIA(O) VENTISIETE (27) DE BOG

redb.



ESTE PAPEL NO TIENE COSTO PARA EL USUARIO

11

Es fiel y Segunda 2ª
fotocopia de la Escritura Pública No. 1227
de fecha 28 de Octubre de 2008
tomada de su original que expido en
Sers (6) hojas útiles de papel
común autorizado (Decreto 1343 de 1970) en destino a

Interesado

Dado en Santafé de Bogotá D.C. a 28 OCT 2008
El Notario Veintisiete de Santafé de Bogotá



ESPACIO EN BLANCO

PCT REQUEST

Original (for SUBMISSION)

VIII-2-1	Declaration: Entitlement to apply for and be granted a patent Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	In relation to this international application ELI LILLY AND COMPANY is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(i)		ELI LILLY AND COMPANY is entitled as employer of the inventor, BARRETT, David, Gene
VIII-2-1(i)		ELI LILLY AND COMPANY is entitled as employer of the inventor, FRANCISKOVICH, Jeffry, Bernard
VIII-2-1(i)		ELI LILLY AND COMPANY is entitled as employer of the inventor, LIU, Bin
VIII-2-1(i)		ELI LILLY AND COMPANY is entitled as employer of the inventor, TAKEUCHI, Kumiko
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VIII-3-1	Declaration: Entitlement to claim priority Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)) Name	In relation to this international application ELI LILLY AND COMPANY is entitled to claim priority of earlier application No. 09382114.8 by virtue of the following:
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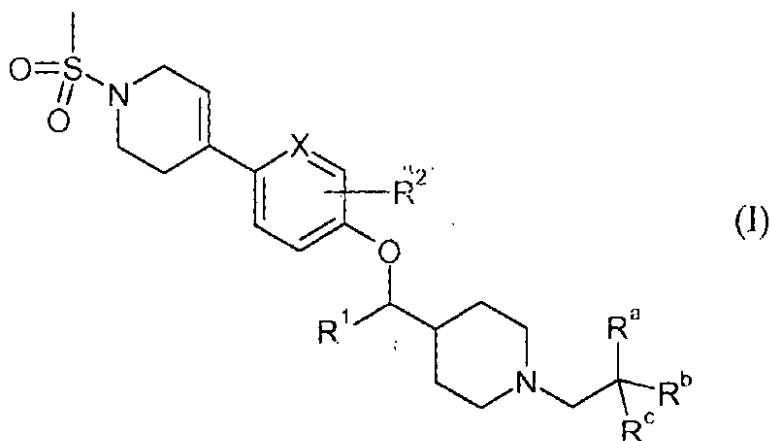
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(54) Title: GPR119 AGONISTS



(57) Abstract: Abstract GPR119 agonist compounds of the formula: (I) and pharmaceutical compositions for the treatment of diabetes and obesity.

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GPR119 AGONISTS

GPR119 is a G-protein-coupled receptor largely confined in humans to pancreatic (β -cells) and intestinal tissues (enteroendocrine cells) and has been studied and described
5 using various synonyms including SNORF25, RUP3, GPCR2, 19AJ, OSGPR116 and glucose-dependent insulinotropic receptor.

The pharmacology and therapeutic potential for GPR119 has been reviewed recently (Br. J. Pharmacol. 2008, 153, S76-S81), disclosing GPR119 as an interesting target for the treatment of diabetes and obesity.

10 A number of synthetic agonists of GPR119 have been disclosed for the treatment of diabetes and obesity, for example those disclosed in WO 09/038974. There remains a need for alternative GPR119 agonists as antidiabetic and antiobesity therapies.

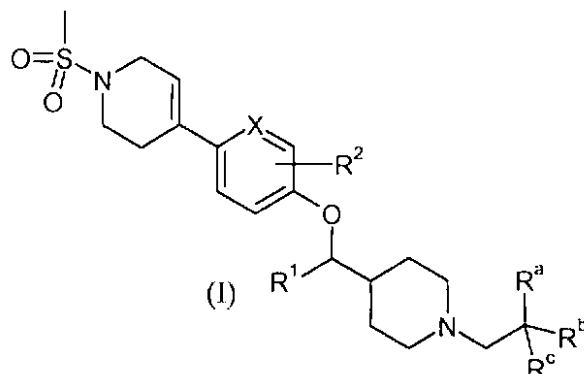
Oral administration is typically the preferred route of administration for antidiabetic and antiobesity therapies. For compounds to display good oral bioavailability,
15 they typically must have sufficient aqueous solubility to allow absorption, and sufficient metabolic stability to minimize first pass degradation in the liver.

The compounds of Formula I have been found to be agonists of GPR119 *in vitro*. Certain compounds of the present invention have been shown to stimulate GIP secretion *in vivo*. Certain compounds of the present invention exhibit greater potency than existing
20 agonists. Certain compounds of the present invention have good oral bioavailability.

The present invention is directed to compounds of Formula I which are agonists of the G-protein-coupled receptor GPR119, pharmaceutical compositions containing them as active ingredient, and to their use in the treatment or prevention of diabetes or obesity, in particular Type II diabetes.

25 The present invention provides a compound of the formula:

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wherein;

X is selected from N and CH;

R^a is selected from F and CF₃;

5 R^b and R^c are independently selected from F and methyl or combine to form a C₃₋₅ cycloalkyl ring;

R¹ is selected from H and methyl;

R² is selected from H and F;

or a pharmaceutically acceptable salt thereof.

10 The present invention provides a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier.

The present invention provides a compound of Formula I, or a pharmaceutically acceptable salt thereof, for use in therapy. The present invention also provides a
15 compound of Formula I, or a pharmaceutically acceptable salt thereof for use in the treatment of diabetes and obesity. The present invention further provides a compound of Formula I, or a pharmaceutically acceptable salt thereof for use in the treatment of diabetes or obesity. In another aspect of the present invention, there is provided the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the
20 manufacture of a medicament for the treatment of diabetes and obesity. The present invention further provides the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of diabetes or obesity

The present invention also provides a method for the treatment of diabetes and
25 obesity, which comprises administering an effective amount of a compound of Formula I,

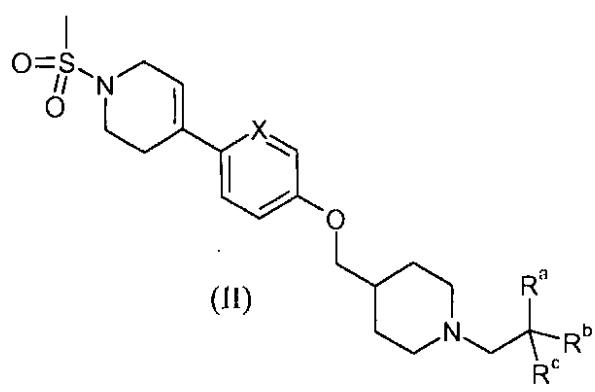
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-3-

or a pharmaceutically acceptable salt thereof, to a human being or animal in need thereof. The present invention further provides a method for the treatment of diabetes or obesity, which comprises administering an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, to a human being or animal in need thereof.

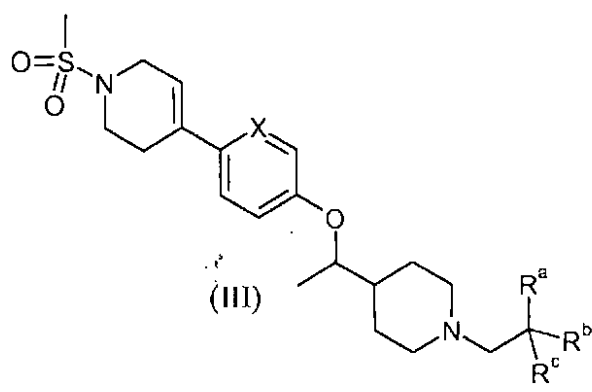
- 5 It is preferred that the compounds of the present invention be used in the treatment of diabetes or obesity, in particular type II diabetes.

A preferred species of the compounds of Formula I are compounds of the formula:



- or a pharmaceutically acceptable salt thereof, wherein X, R^a, R^b, and R^c are as defined herein.

A preferred species of the compounds of Formula I are compounds of the formula:



- or a pharmaceutically acceptable salt thereof, wherein X, R^a, R^b, and R^c are as defined herein.
- 15 Certain classes of compounds of Formula I, II or III are preferred. The following enumerated selections describe such preferred classes:

- 1) X is N;
- 2) X is CH;

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- 3) R^2 is H;
4) R^a is F;
5) R^a is CF_3 ;
6) R^b and R^c are independently selected from F and methyl or combine to
5 form C_3 cycloalkyl;
7) R^b and R^c are methyl or combine to form C_3 cycloalkyl;
8) X is N and R^b and R^c are methyl or combine to form C_3 cycloalkyl;
9) X is CH and R^b and R^c are methyl or combine to form C_3 cycloalkyl;
10) R^b and R^c are methyl and R^a is F;
10 11) R^b and R^c combine to form C_3 cycloalkyl and R^a is CF_3 .

Pharmaceutically acceptable salts of each of the compounds of the present invention are contemplated within the scope of the present application.

Preferred compounds of the present invention include 5-[1-(2-Fluoro-2-methyl-propyl)-piperidin-4-ylmethoxy]-1'-methanesulfonyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl;
15 and 1-Methanesulfonyl-4-{4-[1-(1-trifluoromethyl-cyclopropylmethyl)-piperidin-4-ylmethoxy]-phenyl}-1,2,3,6-tetrahydro-pyridine.

As used throughout this specification, it is to be understood that where a group is qualified by "defined herein" or "herein defined" that said group encompasses the first occurring and broadest definition as well as each and all of the particular definitions of
20 that group.

As used above and throughout the description of the invention, the following terms, unless otherwise indicated, will have the following meaning:

As used herein the term " C_3 - C_5 cycloalkyl" is taken to mean cyclopropyl, cyclobutyl and cyclopentyl. Preferred C_3 - C_5 cycloalkyl groups include cyclopropyl and
25 cyclobutyl; another preferred group is cyclopropyl.

As used herein the terms "isomer 1" and "isomer 2" relate to the specific enantiomers of final compounds or intermediates, "isomer 1" relating to the first compound to elute from the described chromatographic process and "isomer 2" the second. Where the term "isomer 1" or "isomer 2" is first attributed to an intermediate, the
30 term is retained through to the final compound.

A

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As used herein the term "pharmaceutically acceptable salts" refers to salts of the compounds of the present invention which are substantially non-toxic to living organisms. Such salts and common methodology for preparing them are well known in the art. See, *e.g.*, P. Stahl, *et al.*, Handbook of Pharmaceutical Salts: Properties Selection and Use, (VCHA/Wiley-VCH, 2002); and J. Pharm. Sci. **66**, 2-19 (1977). Preferred
5 pharmaceutically acceptable salts include hydrochloride, mesylate and fumarate; more preferred salts are hydrochloride and mesylate.

The compounds of the present invention are preferably formulated as pharmaceutical compositions administered by a variety of routes. Most preferably, such
10 compositions are for oral administration. Such pharmaceutical compositions and processes for preparing same are well known in the art. See, *e.g.*, Remington: The Science and Practice of Pharmacy (A. Gennaro, *et al.*, eds., 19th ed., Mack Publishing Co., 1995). Preferred pharmaceutical compositions include a compound of the present invention admixed with vehicle selected from the group consisting of 0.5 M phosphoric
15 acid (100 mg/ml maximum concentration); hydroxyethylcellulose (1% w/v), polysorbate 80 (0.25% v/v), antifoam (0.05% v/v) and deionised water (110 mg/ml maximum concentration); and vitamin E TPGS (d-alpha-tocopheryl polyethylene glycol 1000 succinate) (10% v/v), antifoam (0.05% v/v) and deionised water (250 mg/ml maximum concentration).

20 In a further aspect of the invention the present compounds are administered in combination with one or more therapeutic ingredients. Such therapeutic ingredients include for example metformin or a DPPIV inhibitor *e.g.* sitagliptin.

Administration in combination includes simultaneous, separate or sequential administration.

25 For administration in combination for the treatment of diabetes it is preferred that the compounds of the present invention are simultaneously, separately or sequentially administered with metformin. For administration in combination for the treatment of obesity it is preferred that the compounds of the present invention are simultaneously, separately or sequentially administered with sitagliptin.

30 The following Schemes, Preparations and Examples are provided to better elucidate the practice of the present invention. Suitable reaction conditions for the steps of these Schemes, Preparations and Examples are well known in the art and appropriate

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modification of reaction conditions, including substitution of solvents and co-reagents are within the ability of the skilled artisan. Temperatures indicated in the following Preparations and Examples correspond to external bath temperature, unless otherwise indicated.

5 Furthermore, the skilled artisan will appreciate that in some circumstances, the order in which moieties are introduced is not critical. The particular order of steps required to produce the compounds of Formula I is dependent upon the particular compound being synthesized, the starting compound, and the relative lability of the substituted moieties, as is well appreciated by the skilled chemist. The skilled artisan will
10 appreciate that not all substituents are compatible with all reaction conditions. These compounds may be protected or modified at a convenient point in the synthesis by methods well known in the art.

Suitable protecting groups include those described in T.W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, N.Y., 1991, hereafter
15 referred to as "Greene". Greene indicates appropriate conditions for "protection" and "deprotection" of suitable protecting groups to be used by the skilled artisan.

The intermediates and final products of the present invention may be further purified, if desired by common techniques such as recrystallization or chromatography over solid supports such as silica gel or alumina.

20 The compound names for the Examples of the present invention are generated using AutoNom 2000.

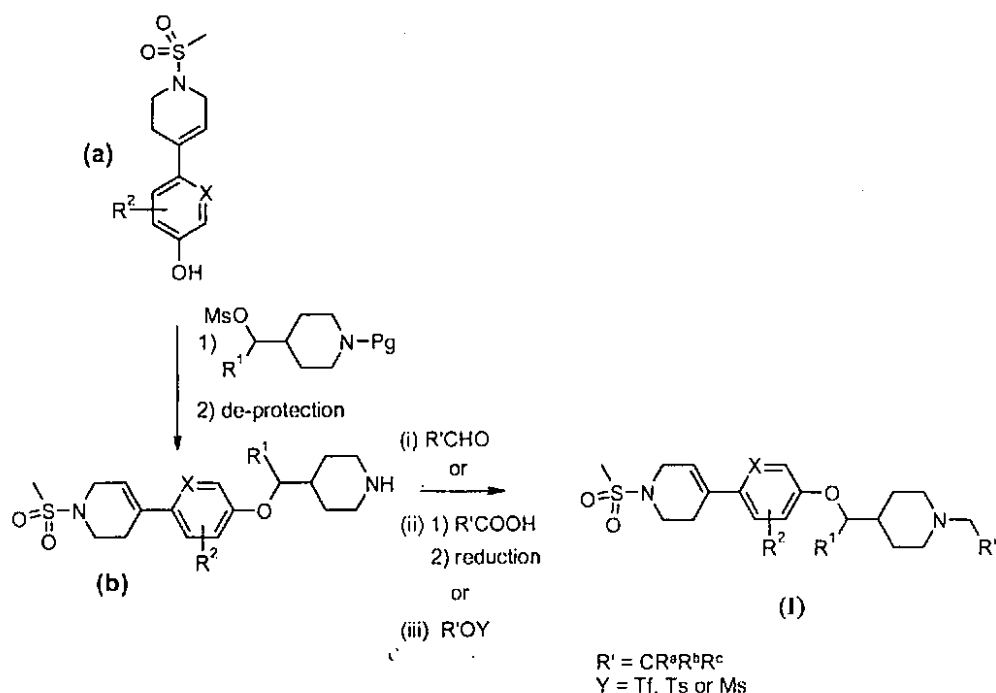
Abbreviations used herein are defined as follows:

"h" means hours; "min" means minutes; "cAMP" means Cyclic Adenosine Monophosphate; "DMEM" means Dulbecco's Modified Eagle's Medium; "HTRF" means
25 Homogenous Time-Resolved Fluorescence; "PBS" means Phosphate Buffered Saline; "IBMX" means Isobutylmethylxanthine; "BSA" means Bovine Serum Albumin; "FBS" means Fetal Bovine Serum; "EBSS" means Earle's Balanced Salt Solution; "EDTA" means Ethylene Diamine Tetraacetic Acid; "NADPH" means Nicotinamide Adenosine Dinucleotide Phosphate; "HEC" means Hydroxyethyl Cellulose; LC-ESI/MS" means
30 Liquid Chromatography - Electrospray Ionization Mass Spectrometry; "Pg" means Protecting Group; "Tf" means trifluoromethyl sulfonyl; "Ts" means para-toluene sulfonyl; and "Ms" means methyl sulfonyl.

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Scheme A

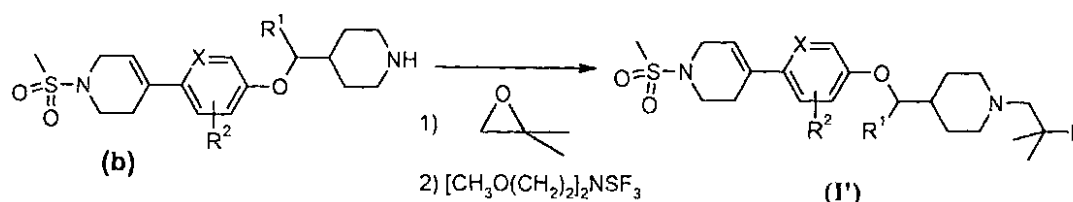


The starting hydroxyl (a) is reacted with a mesylate bearing a piperidine with an appropriate protecting group such as carboxylic acid *tert*-butyl ester and a suitable base such as potassium carbonate in a suitable solvent such as acetonitrile at elevated temperature. The isolated product is de-protected under conditions well known to the skilled artisan to provide compound (b). Compound (b) is reacted with an aldehyde under standard reductive amination conditions, with a suitable reducing agent such as sodium triacetoxyborohydride in a suitable solvent such as dichloromethane to provide the final compound (I). Alternatively compound (b) is reacted with an appropriately substituted acid using a coupling reagent such as *o*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate and a suitable base such as diisopropylethylamine in a suitable solvent such as dimethylformamide at elevated temperature. The isolated product is reacted with a suitable reducing agent such as lithium aluminum hydride in a suitable solvent such as tetrahydrofuran at elevated temperature to provide the final compound (I). Alternatively compound (b) is reacted with R^1 OY and a suitable base such as potassium carbonate in a suitable solvent such as acetonitrile at elevated temperature to provide the final compound (I).

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Alternatively, where R^a is F and both R^b and R^c are methyl the compounds 1' may be prepared as described below in Scheme B.

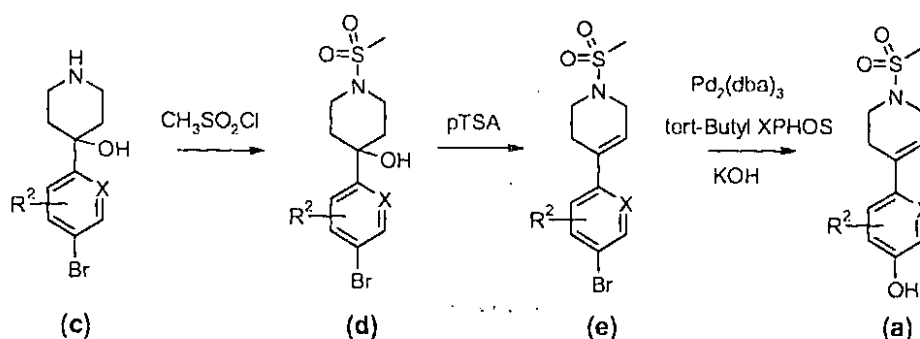
Scheme B



5 The starting piperidine (b) is reacted with 2,2-dimethyloxirane under an inert atmosphere such as nitrogen in a suitable solvent such as methanol. The isolated product is reacted with a suitable fluorinating agent such as bis(2-methoxyethyl)aminosulfur trifluoride in a suitable solvent such as dichloromethane to provide the final compound (I').

10 The requisite hydroxyl (a) may be prepared as described below in Scheme C.

Scheme C

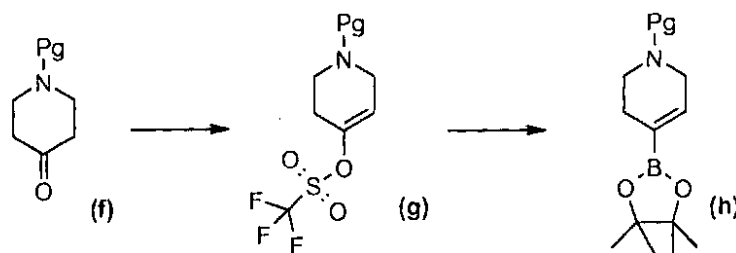


The starting piperidin-4-ol (c) is reacted with methanesulfonyl chloride and a suitable base such as triethylamine or pyridine in a suitable solvent such as dichloromethane or tetrahydrofuran to provide compound (d). Compound (d) is reacted with p-toluenesulfonic acid in a suitable solvent such as toluene at elevated temperature to provide the tetrahydro-pyridine (e). Compound (e) is reacted by the method described in J. Am. Chem. Soc 2006, 128, 10694-10695 using potassium hydroxide, 2-di-tert-butylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl and tris(dibenzylideneacetone)dipalladium in a suitable solvent such as dioxane/water at elevated temperature to provide the tetrahydro-pyridine compound (a).

Alternatively, the requisite bromo (c) and hydroxyl (a) may be prepared as described in Schemes D and E.

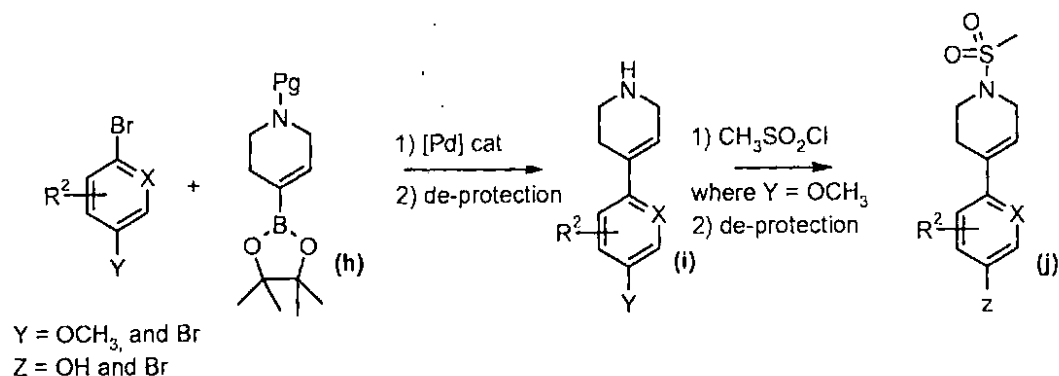
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Scheme D



The starting piperidone (f) is mixed with a suitable base such as lithium diisopropylamide in a suitable solvent such as tetrahydrofuran at reduced temperature and reacted with *N*-phenylbis(trifluoromethanesulfonimide) to provide the compound (g). The tetrahydro-pyridine compound (g) is reacted with bis(pinacolato)diboron, (1,1'-bis(diphenylphosphino)ferrocene)palladium(II) chloride, 1,1'-bis(diphenylphosphino)ferrocene, and potassium acetate in a suitable solvent such as 1,4-dioxane at elevated temperature to provide the compound (h).

10 Scheme E



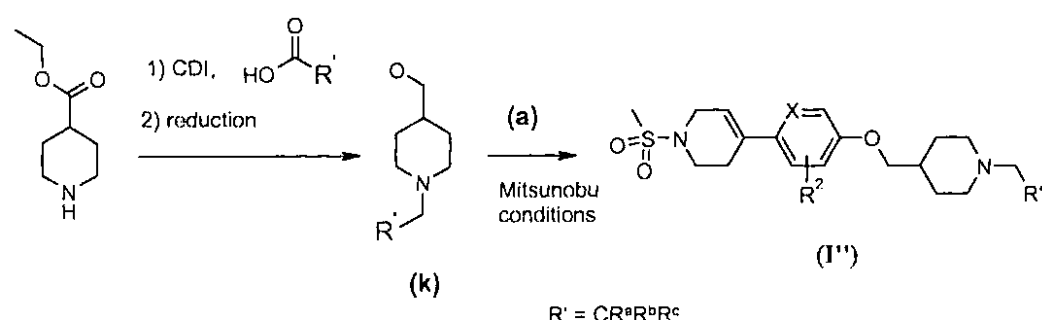
The starting bromide is reacted with a boronate compound (h) bearing an appropriate protecting group such as carboxylic acid *tert*-butyl ester, a suitable palladium catalyst such as tetrakis(triphenylphosphine)palladium and a suitable base such as cesium carbonate in a suitable solvent such as dioxane/water at elevated temperature. The isolated product is de-protected under conditions well known to the skilled artisan to provide compound (i). Compound (i) is reacted with methanesulfonyl chloride and a suitable base such as triethylamine in a suitable solvent such as dichloromethane to provide the compound (j). Where the substituent Y is OCH₃ an additional deprotection

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step, using conditions well known to the skilled artisan, is required to provide compound (j).

Alternatively, compounds where R¹ is H may be prepared as described below in Scheme F.

5 **Scheme F**



An appropriately substituted acid is reacted with 1,1'-Carbonyldiimidazole in a suitable solvent such as tetrahydrofuran, to which is added piperidine-4-carboxylic acid ethyl ester. The isolated product is reacted with a suitable reducing agent such as lithium aluminium hydride in a suitable solvent such as tetrahydrofuran to provide the compound (k). The compound (k) is reacted with compound (a) using standard Mitsunobu conditions such as diisopropyl azodicarboxylate and triphenylphosphine, at reduced temperature, in a suitable solvent such as tetrahydrofuran to provide the final compound (I'').

15

Preparation 1

4-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-phenol

1: 4-(4-Bromo-phenyl)-1-methanesulfonyl-piperidin-4-ol.

Methanesulfonyl chloride (21.91 g, 14.81 mL, 191.30 mmol) is added slowly (10 min) to a solution of 4-(4-bromophenyl)-4-piperidinol (50.00 g, 191.30 mmol) and triethylamine (29.04 g, 40.00 mL, 286.95 mmol) in tetrahydrofuran (575 mL) at 23 °C (internal temperature) under nitrogen atmosphere. The mixture is stirred at 23 °C for 30 min. 500 mL of 1 M aq hydrochloric acid are added and the mixture is stirred for 10 min. The mixture is extracted with ethyl acetate (2 x 500 mL) the organic layers are combined, dried over anhydrous sodium sulfate, filtered and the solvent is removed to obtain 60.0 g of the title compound as a white solid. MS *m/e* (⁷⁹Br/⁸¹Br) 333, 335 (M+1).

2: 4-(4-Bromo-phenyl)-1-methanesulfonyl-1,2,3,6-tetrahydro-pyridine.

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A mixture of 4-(4-bromo-phenyl)-1-methanesulfonyl-piperidin-4-ol (60.00 g, 179.51 mmol) and p-toluenesulfonic acid (9.37 g, 53.85 mmol) in toluene (1.08 L) is stirred at 100 °C for 16 h. The reaction is cooled to 23 °C and successively washed with 2 M aq. sodium hydroxide to pH 10, and water. The phases are separated and the organic layer is dried over anhydrous sodium sulfate, filtered and the solvent is removed. Methyl *tert*-butyl ether (200 mL) is added and the solid is filtered and washed with methyl *tert*-butyl ether to obtain 35.0 g of the title compound as a pale brown solid. MS *m/e* (⁷⁹Br/⁸¹Br) 315, 317 (M+1).

3: 4-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-phenol.

A mixture of 4-(4-bromo-phenyl)-1-methanesulfonyl-1,2,3,6-tetrahydro-pyridine (23.50 g, 74.32 mmol), potassium hydroxide (14.72 g, 222.95 mmol), 2-di-*tert*-butylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl (2.52 g, 5.95 mmol) and tris(dibenzylideneacetone)dipalladium (0) (1.36 g, 1.49 mmol) is purged with nitrogen, and then deoxygenated 1,4-dioxane (150 mL) and deoxygenated water (150 mL) are added. The mixture is stirred at 100 °C for 1 h. The mixture is cooled to 23 °C and 1 M aq hydrochloric acid is added until pH 2-3. The aqueous layer is extracted with ethyl acetate. The organic layers are combined, dried over anhydrous sodium sulfate, filtered, and the solvent is removed to obtain a red solid. Diethyl ether is added and the solid is filtered to obtain 16 g of the title compound as an off-white solid. MS (*m/z*) 254 (M+1).

Preparation 2

1-Methanesulfonyl-4-[4-(piperidin-4-ylmethoxy)-phenyl]-1,2,3,6-tetrahydro-pyridine

1: 4-Methanesulfonyloxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester.

Methanesulfonyl chloride (29.26 g, 19.77 mL, 255.47 mmol) is added slowly (10 min) under nitrogen atmosphere to a solution of *tert*-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (50.00 g, 232.24 mmol) and triethylamine (35.25 g, 48.56 mL, 348.36 mmol) in anhydrous dichloromethane (700 mL) at 9 °C (internal temperature). The mixture is stirred at 23 °C for 16 h. The reaction mixture is successively washed with 1 M aq hydrochloric acid, water, and brine. The organic layer is dried over anhydrous sodium sulfate, filtered, and the solvent is removed to obtain 60 g of the title compound as a white solid. MS (*m/z*) 316 (M+23).

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2: 4-[4-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-phenoxy-methyl]-piperidine-1-carboxylic acid *tert*-butyl ester.

A mixture of 4-methanesulfonyloxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester (17.95 g, 61.19 mmol), Preparation 1 (15.50 g, 61.19 mmol) and potassium carbonate (16.91 g, 122.37 mmol) in acetonitrile (120 mL) is heated under reflux for 18 h. The reaction is cooled to 23 °C and the solvent is removed. The residue is dissolved with a mixture of 1 L of dichloromethane and 500 mL of water and phases are separated. The organic layer is washed with brine, dried over sodium sulfate, filtered and evaporated. The solid obtained is treated with 250 mL of methyl *tert*-butyl ether to afford 22.0 g of the title product. MS (m/z) 473 (M+23).

3: 1-Methanesulfonyl-4-[4-(piperidin-4-ylmethoxy)-phenyl]-1,2,3,6-tetrahydro-pyridine.

Trifluoroacetic acid (2.98 g, 1.97 mL, 26.10 mmol) is added to a solution of 4-[4-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-phenoxy-methyl]-piperidine-1-carboxylic acid *tert*-butyl ester (1.20 g, 2.61 mmol) in dichloromethane (13 mL). The mixture is stirred at 23 °C for 30 min. 2 M aq. sodium hydroxide is added. The resulting white precipitate is filtered and washed with water. The mother liquor is extracted with dichloromethane. The combined organic layers are dried over anhydrous sodium sulfate, filtered, and the solvent is removed to obtain a white solid which is combined with the initial precipitate and dried under high vacuum for 16 h. Diethyl ether is added and the solid is filtered and washed with ethyl acetate to obtain 0.810 g of an off-white solid. MS (m/z) 351 (M+1).

Preparation 3

4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester

1: 4-Trifluoromethanesulfonyloxy-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester.

In a 3 necked flask with addition funnel, temperature probe and magnetic stirrer, a solution of diisopropylamine (32.30 g, 44.93 mL, 319.20 mmol) in tetrahydrofuran (160 mL) is cooled to -10 °C (internal temperature). *n*-Butyl lithium (133.0 mL, 332.50 mmol, 2.5 M in hexanes,) is added dropwise (10 min, temperature change from -10 °C to 1 °C). The mixture is stirred at -10 °C for 10 min, and then cooled to -60 °C (internal temperature, -75 °C bath). A solution of *N*-*tert*-butoxycarbonyl-4-piperidone (53.00 g,

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266.00 mmol) in tetrahydrofuran (160 mL) is added dropwise (10 min). The mixture is stirred at -60 °C for 1.5 h, a solution of *N*-phenylbis(trifluoromethanesulphonimide) (99.78 g, 279.30 mmol) in tetrahydrofuran (160 mL) is added dropwise at -60 °C (5 min). More tetrahydrofuran (40 mL) is added and the mixture is allowed to warm to 23 °C for 16 h. Saturated aq sodium bicarbonate (400 mL) is added to the mixture, which is then extracted with ethyl acetate (3 x 400 mL). Combined organic layers are washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The resulting mixture is passed through a silica gel plug, eluting with hexane:ethyl acetate 4:1 to give 78.00 g of the title compound as a yellow oil. The material is used in the next step without further purification. ¹H NMR (CDCl₃) δ (ppm): 1.47 (s, 9H), 2.43-2.47 (m, 2H), 3.63 (t, 2H), 4.03-4.11 (m, 2H), 5.76 (s, 1H).

2: 4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester.

4-Trifluoromethanesulfonyloxy-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (235.43 mmol; 78.00 g) is dissolved in 1,4-dioxane (1170 mL) and the solution is degassed for 5 min. Bis(pinacolato)diboron (65.76 g, 258.97 mmol), 1,1'-bis(diphenylphosphino)ferrocene (6.53 g, 11.77 mmol), (1,1'-bis(diphenylphosphino)ferrocene)palladium(II) chloride (9.61 g, 11.77 mmol) and potassium acetate (69.32 g, 706.28 mmol) are added, and the mixture is stirred under nitrogen at 85 °C for 3 h. The mixture is cooled to 23 °C and stirred for 16 h. The mixture is filtered through diatomaceous earth, washed with ethyl acetate, and concentrated in vacuo. The crude product is purified by flash chromatography on silica gel, eluent hexane:ethyl acetate (12:1 to 4:1) to give 72.00 g of the title compound, which is used in the next step without further purification. MS (m/z) 254 (M-55).

Preparation 4

4-(1-Methanesulfonyloxy-ethyl)-piperidine-1-carboxylic acid *tert*-butyl ester

1: 4-(1-Hydroxy-ethyl)-piperidine-1-carboxylic acid *tert*-butyl ester.

To a solution of *N*-*tert*-butoxycarbonyl-4-piperidinecarboxaldehyde (32.20 g, 151.45 mmol) in tetrahydrofuran at -78 °C is added methyl magnesium bromide (2 M in diethyl ether, 100.96 mL, 302.89 mmol). The reaction is stirred at -78 °C for 4.5 h, and then warmed to -50 °C for 30 min. The reaction is quenched with water at -50 °C and

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allowed to warm to room temperature for 16 h. The solvents are removed and the material is partitioned between diethyl ether and 0.1 M hydrochloric acid. The mixture is extracted with diethyl ether. The combined organic layers are washed with 0.1 M hydrochloric acid, saturated aqueous sodium bicarbonate and brine, dried over
5 magnesium sulfate, filtered, and concentrated to dryness. The crude is purified by flash chromatography over silica gel to afford 16.90 g of the title compound as a colourless oil. MS (m/z) 229 (M+1).

2: 4-(1-Methanesulfonyloxy-ethyl)-piperidine-1-carboxylic acid *tert*-butyl ester.

To a solution of 4-(1-hydroxy-ethyl)-piperidine-1-carboxylic acid *tert*-butyl ester
10 (18.24 g, 79.54 mmol) in dichloromethane (400 mL) and triethylamine (12.20 mL, 87.49 mmol) at 0 °C is added methanesulfonyl chloride (9.23 mL, 119.30 mmol). The reaction is allowed to warm to room temperature over 16 h. The mixture is washed with 0.1 M hydrochloric acid, saturated aqueous sodium bicarbonate, water, and brine. The material is dried over magnesium sulfate, filtered, and concentrated to dryness. The crude material
15 is purified by flash chromatography over silica gel to afford 22.65 g of the title compound as a colourless oil. ¹H NMR (CDCl₃) δ (ppm): 1.19-1.30 (m, 2H), 1.39 (d, 3H), 1.44 (s, 9H), 1.6-1.8 (m, 3H), 2.66 (m, 2H), 2.99 (s, 3H), 4.16 (m, 2H), 4.62 (t, 1H).

Preparation 5

4-{1-[4-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-phenoxy]-ethyl}-piperidine
20

1: 4-{1-[4-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-phenoxy]-ethyl}-piperidine-1-carboxylic acid *tert*-butyl ester.

To a solution of Preparation 1 (2.35 g, 9.27 mmol) and Preparation 4 (2.85 g, 9.27 mmol) in acetonitrile (93.00 mL) is added cesium carbonate (3.02 g, 9.27 mmol) and 18-crown-6 (0.49 g, 1.85 mmol). The mixture is heated to 80 °C for 72 h. The mixture is concentrated in vacuo and the remaining material is partitioned between ethyl acetate and water. The organic layer is washed with 1 M sodium hydroxide and brine. The material is dried over magnesium sulfate, filtered, and concentrated to dryness. The resulting material is diluted with 10 mL of diethyl ether, sonicated for 3 min, and the remaining
25 solid filtered, and dried under vacuum to afford 2.02 g of the title product as a white solid. MS (m/z) 487 (M+32), 365 (M-55).
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2: 4-{1-[4-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-phenoxy]-ethyl}-piperidine.

To a solution of 4-{1-[4-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-phenoxy]-ethyl}-piperidine-1-carboxylic acid *tert*-butyl ester (1.16 g, 2.50 mmol) in dichloromethane (25 mL) is added trifluoroacetic acid (1.32 mL, 17.48 mmol). The reaction is stirred at room temperature for 18 h. The mixture is concentrated in vacuo and diluted with 3 mL of ethyl acetate. 2 M aqueous sodium hydroxide is added to produce a white solid. The solid is filtered and dried to afford 0.86 g of the title compound. MS (m/z) 365 (M+1). The title compound (0.320 g, 0.88 mmol) is separated into its enantiomers using an eluent of 0.2% dimethylethylamine in 2:3 acetonitrile:methanol on a 4.6 x 150 mm Chiralcel AD-H column at 1 mL/min to afford 0.115 g of isomer 1 (100% ee, RT = 5.27 min). MS (m/z) 365 (M+1) and 0.112 g of isomer 2 (100% ee, RT = 8.59 min). MS (m/z) 365 (M+1).

Preparation 6

4-(1'-Methanesulfonyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-5-yloxymethyl)-piperidinium dihydrochloride salt

1: 5-Bromo-3',6'-dihydro-2'H-[2,4']bipyridinyl-1'-carboxylic acid *tert*-butyl ester.

A mixture of 2,5-dibromopyridine (50.00 g, 211.07 mmol), Preparation 3 (71.79 g, 232.17 mmol), 2 M aqueous sodium carbonate (158.30 mL, 316.60 mmol) and tetrakis(triphenylphosphine)palladium (0) (7.32 g, 6.33 mmol) in 1,4-dioxane (633 mL) is heated at 100 °C under a nitrogen atmosphere overnight. The reaction is allowed to cool to room temperature, filtered through diatomaceous earth and washed with ethyl acetate. The organic layer is washed with 500 mL of water, dried over magnesium sulfate, filtered and evaporated. The crude material is purified by silica gel chromatography eluting with hexane:ethyl acetate 6:1 to afford 55 g of a white solid. MS *m/e* (⁷⁹Br/⁸¹Br) 339, 341 (M+1 of both isotopes).

2: 5-Bromo-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-1'-ium; dihydrochloride salt.

4 M Hydrogen chloride (170.24 g, 162.13 mL, 648.52 mmol) in 1,4-dioxane is added to a solution of 5-bromo-3',6'-dihydro-2'H-[2,4']bipyridinyl-1'-carboxylic acid *tert*-butyl ester (55.00 g, 162.13 mmol) in dichloromethane (810 mL). The mixture is stirred at room temperature for 12 h and heated at 40 °C for 6 h. The mixture is evaporated and

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the solid is filtered and washed with methyl *t*-butyl ether. The solid is dried in an oven at 40 °C for 12 h to provide 50 g of the title compound. MS *m/e* (⁷⁹Br/⁸¹Br) 238/240 (M+1).

3: 5-Bromo-1'-methanesulfonyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl.

The title compound is prepared essentially by the method of Preparation 1 (step 1) using 5-bromo-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-1'-ium; dihydrochloride salt as starting material. MS *m/e* (⁷⁹Br/⁸¹Br) 316/318 (M+1).

4: 1'-Methanesulfonyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-5-ol.

The title compound is prepared essentially by the method of Preparation 1 (step 3) using 5-bromo-1'-methanesulfonyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl as starting material. MS (*m/z*) 255 (M+1).

5: 4-(1'-Methanesulfonyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-5-yloxymethyl)-piperidine-1-carboxylic acid *tert*-butyl ester.

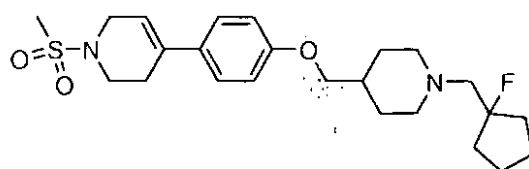
The title compound is prepared essentially by the method of Preparation 2 (step 2) using 1'-methanesulfonyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-5-ol as starting material. MS (*m/z*) 452 (M+1).

6: 4-(1'-Methanesulfonyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-5-yloxymethyl)-piperidinium; dihydrochloride salt.

The title compound is prepared essentially as in step 2 of this preparation. MS (*m/z*) 352 (M+1)

Example 1

4-{4-[1-(1-Fluoro-cyclopentylmethyl)-piperidin-4-ylmethoxy]-phenyl}-1-methanesulfonyl-1,2,3,6-tetrahydro-pyridine



1: 1-Oxa-spiro[2.4]heptane-2-carbonitrile.

A 1 M solution of potassium *ter*-butoxide in *tert*-butyl alcohol (184.4 mL, 184.4 mmol) is added slowly to a solution of chloroacetonitrile (10.8 mL, 167.6 mmol) and cyclopentanone (15.0 mL, 167.6 mmol) in anhydrous *t*-butyl alcohol (33 mL). The reaction is stirred at room temperature for 16 h. The mixture is filtered through diatomaceous earth, the solvent is removed, and the residue is diluted with water. The

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mixture is neutralized with 30% aq. sodium dihydrogen phosphate solution and extracted with diethyl ether. The organic layers are combined, dried over anhydrous sodium sulfate, filtered, and the solvent is removed. The residue is purified by flash chromatography over silica gel to obtain 14.1 g of the title compound as a colourless oil.

5 ¹H NMR (CDCl₃) δ (ppm): 3.46 (s, 1H), 1.65–2.20 (m, 8H).

2: (1-Fluoro-cyclopentyl)-hydroxy-acetonitrile.

Anhydrous dichloromethane (3 mL) and a 70% w/w solution of hydrogen fluoride (2.68 mL, 20.44 mmol) in pyridine are mixed in a polyethylene bottle at 0 °C under a nitrogen atmosphere. A solution of 1-oxa-spiro[2.4]heptane-2-carbonitrile (3.30 g, 26.76 mmol) in anhydrous dichloromethane (3.2 mL) is added slowly. The reaction is stirred at 10 0 °C for 1 h and at room temperature for 1 h. The mixture is cooled at 0 °C and a saturated solution of sodium carbonate is added carefully. The aqueous layer is extracted with diethyl ether. The organic layers are combined, washed with water and brine, dried over anhydrous sodium sulfate, filtered, and the solvent is removed. The residue is purified by 15 chromatography in a 20 g silica gel cartridge eluting with hexane:diethyl ether (100:0 to 80:20) to obtain 1.7 g of desired compound as a colourless oil. ¹H NMR (CDCl₃) δ (ppm): 4.47 (d, 1H), 3.50 (bs, 1H), 2.12–1.67 (m, 8H).

3: 1-Fluoro-cyclopentanecarbaldehyde.

A solution 25% of sodium hydroxide (7.00 mL, 72.8 mmol) in water is added to a 20 solution of (1-fluoro-cyclopentyl)-hydroxy-acetonitrile (0.50 g, 3.5 mmol) in ethanol (10 mL) and the reaction is stirred at room temperature for 15 min. The mixture is diluted with water and diethyl ether and the aqueous layer is extracted with diethyl ether. The organic layers are combined, washed with water and brine, dried over anhydrous sodium sulfate, filtered, and the solvent is removed under vacuum to obtain 430 mg of a yellow 25 oil that is used without further purification.

4: 4-{4-[1-(1-Fluoro-cyclopentyl)methyl]-piperidin-4-ylmethoxy}-phenyl-1-methanesulfonyl-1,2,3,6-tetrahydro-pyridine.

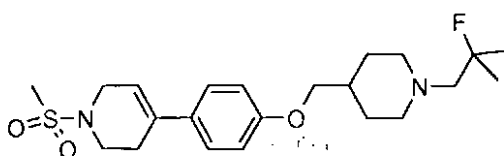
Acetic acid (0.024 mL, 0.42 mmol) and 1-fluoro-cyclopentanecarbaldehyde (0.367 mL, 3.70 mmol) are added to a suspension of Preparation 2 (150 mg, 0.427 mmol) 30 in dichloromethane (4 mL) and the mixture is stirred at 40 °C for 45 min. Sodium triacetoxyborohydride (236.22 mg, 1.07 mmol) is added and the mixture is stirred at 40 °C for 1.5 h. Saturated aqueous solution of sodium bicarbonate is added and the mixture

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is extracted with ethyl acetate. The organic layers are combined, washed with water and brine, dried over anhydrous sodium sulfate, filtered, and the solvent is removed. The residue is chromatographed on a 10 g silica gel cartridge eluting with dichloromethane:ethyl acetate 20%, 50%, and 100% to obtain a pale yellow solid. The compound is triturated with diethyl ether and filtered to obtain 25 mg of the title compound as a white solid. MS (m/z) 451 (M+1).

Example 2

4-{4-[1-(2-Fluoro-2-methyl-propyl)-piperidin-4-ylmethoxy]-phenyl}-1-methanesulfonyl-1,2,3,6-tetrahydro-pyridine



1: 2-Fluoro-1-{4-[4-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-phenoxy-methyl]-piperidin-1-yl}-2-methyl-propan-1-one.

Diisopropylethylamine (1.60 g, 2.16 mL, 12.40 mmol) is added to a suspension of Preparation 2 (1.60 g, 4.13 mmol), o-benzotriazol-1-yl-*N,N,N'*-tetramethyluronium tetrafluoroborate (1.99 g, 6.20 mmol) and 2-fluoro-2-methyl-propionic acid (0.48 g, 0.54 mL, 4.55 mmol) in anhydrous dimethylformamide (20 mL) and the mixture is stirred at 40 °C for 1 h. The reaction mixture is diluted with ethyl acetate and washed successively with 1 M aqueous hydrochloric acid, water, and 2 M aqueous sodium hydroxide. The organic layer is dried over anhydrous sodium sulfate, filtered, and the solvent is removed. The residue is purified by silica gel chromatography on a silica gel cartridge eluting with dichloromethane:ethyl acetate 0%, 5% then 10% to obtain 1.0 g of the title compound as a pale brown solid. MS (m/z) 439 (M+1).

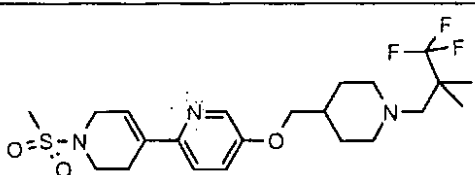
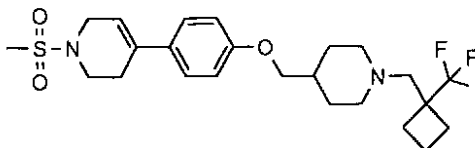
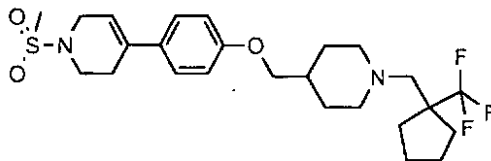
2: 4-{4-[1-(2-Fluoro-2-methyl-propyl)-piperidin-4-ylmethoxy]-phenyl}-1-methanesulfonyl-1,2,3,6-tetrahydro-pyridine.

To a solution of 2-fluoro-1-{4-[4-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-phenoxy-methyl]-piperidin-1-yl}-2-methyl-propan-1-one (1.00 g, 2.28 mmol) in tetrahydrofuran (23 mL) at rt is added via cannula a 1 M solution of lithium aluminum hydride in tetrahydrofuran (7.18 g, 7.98 mL, 7.98 mmol). After 1 h, sodium sulfate decahydrate is added carefully. The mixture is stirred for 15 min and the solid is filtered

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off and washed with dichloromethane. The solvent is removed and the residue is purified via silica gel chromatography, eluting with dichloromethane:ethyl acetate 5.6:1 to 2:1 to obtain a solid. Diethyl ether is added and the solid is filtered and washed with diethyl ether and ethyl acetate to obtain 0.245 g of the title compound as a white solid. MS (m/z) 425 (M+1).

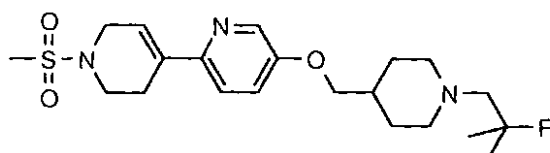
The following compounds are prepared essentially by the same method as outlined in Example 2.

Example	Chemical name / structure	MS (m/z)
3	 1'-Methanesulfonyl-5-[1-(3,3,3-trifluoro-2,2-dimethylpropyl)-piperidin-4-ylmethoxy]-1',2',3',6'-tetrahydro-[2,4']bipyridinyl	476 (M+1)
4	 1-Methanesulfonyl-4-{4-[1-(1-trifluoromethylcyclobutylmethyl)-piperidin-4-ylmethoxy]-phenyl}-1,2,3,6-tetrahydro-pyridine	487 (M+1)
5	 1-Methanesulfonyl-4-{4-[1-(1-trifluoromethylcyclopentylmethyl)-piperidin-4-ylmethoxy]-phenyl}-1,2,3,6-tetrahydro-pyridine	501 (M+1)

Example 6

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5-[1-(2-Fluoro-2-methyl-propyl)-piperidin-4-ylmethoxy]-1'-methanesulfonyl-
1',2',3',6'-tetrahydro-[2,4']bipyridinyl



1: 4-(1'-Methanesulfonyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-5-yloxymethyl)-
5 piperide.

Preparation 6 (47 g, 114.5 mmol) is dissolved in 2 M aqueous solution of sodium hydroxide (500 mL) and extracted with dichloromethane (2 x 500 mL). The organic layer is dried over magnesium sulphate, filtered and evaporated to obtain 40 g of the title compound as a light yellow solid. MS (m/z) 352 (M+1).

10 2: 1-[4-(1'-Methanesulfonyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-5-yloxymethyl)-piperidin-1-yl]-2-methyl-propan-2-ol

To a solution of 4-(1'-methanesulfonyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-5-yloxymethyl)-piperide (40 g, 113.81 mmol) in methanol (230 mL) at 25°C under nitrogen atmosphere is added 2,2-dimethyloxirane (15.18 mL; 170.71 mmol) in one portion and
15 the reaction is stirred at 25°C for 16 h. Water (500 mL) is added and the precipitate is filtered, washed with methyl *t*-butyl ether (250 mL) and dried to obtain 33 g of the title compound as a light yellow solid. MS (m/z) 424 (M+1).

3: 5-[1-(2-Fluoro-2-methyl-propyl)-piperidin-4-ylmethoxy]-1'-methanesulfonyl-
1',2',3',6'-tetrahydro-[2,4']bipyridinyl

20 To a solution of 2-methyl-1-[4-[[6-(1-methylsulfonyl-3,6-dihydro-2H-pyridin-4-yl)-3-pyridyl]oxymethyl]-1-piperidyl]propan-2-ol (33 g; 77.91 mmoles) in dichloromethane (155 mL) is added bis(2-methoxyethyl)aminosulfur trifluoride (16.63 mL; 85.70 mmoles) at an internal temperature of 22-23°C. The reaction is stirred at 25°C for 2 h. Aqueous saturated solution of sodium bicarbonate is added to pH 7. Layers are
25 separated, the aqueous layer is extracted with dichloromethane (2 x 500 mL), the combined organic layers are dried over magnesium sulphate, filtered and concentrated. The crude material is purified by silica gel chromatography eluting with 98:2 dichloromethane:methanol. The solid is triturated with 500 mL of methyl *t*-butyl ether

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and filtered. The solid is dried in an oven at 40°C for 3 days to obtain 24 g of the title compound as a white solid. MS (m/z) 426 (M+1).

An alternative method for the preparation of Example 6 is as follows:

1: 4-[4-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-phenoxy-methyl]-
5 piperidine-1-carboxylic acid *tert*-butyl ester

To a 3-necked flask with a mechanical stirrer are added 4-(1-hydroxy-methyl)-
piperidine-1-carboxylic acid *tert*-butyl ester (350 g, 1.63 mol), triethylamine (247 g, 2.44
mol) and dichloromethane (1750 mL). The solution is stirred at 0°C for 30 min.
Methanesulfonyl chloride (223.5 g, 1.95 mol) is added slowly at 0~5 °C. The mixture is
10 stirred at ~5 °C for 1.5h. 1050 mL of 0.5 N solution of aq. hydrochloride are added to the
mixture dropwise at 0~15 °C and the resulting solution is stirred for 30 min. Layers are
separated and the organic layer is washed with 1050 mL of water and concentrated to
dryness. 700 mL of methyl *tert*-butyl ether are added and the mixture is refluxed for 0.5
h. After the mixture is slowly cooled to ~5 °C, the suspension is filtered. The solid is
15 stirred with 500 mL of methyl *tert*-butyl ether and filtered to dryness to provide 434 g of
an off-white solid with 98.6% HPLC purity.

2: 4-(1'-Methanesulfonyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-5-yloxymethyl)-
piperidine-1-carboxylic acid *tert*-butyl ester

To a 3-necked flask is added 1'-methanesulfonyl-1',2',3',6'-tetrahydro-
20 [2,4']bipyridinyl-5-ol (254.3 g, 1.0 mol) followed by 4-(1-methanesulfonyloxy-ethyl)-
piperidine-1-carboxylic acid *tert*-butyl ester (396.1 g, 1.34 mol) and potassium carbonate
(248.8 g, 1.8 mol). Dimethylformamide (3800 mL) is added and the mixture is heated at
80~90 °C for 6 h. 3810 mL of water are added dropwise at 70~80 °C. The mixture is
cooled slowly to 20~30 °C and filtered. The cake is slurried with 1000 mL of water,
25 concentrated and dried under vacuum to provide 407 g of a solid with 97.13% HPLC
purity.

3: 4-(1'-Methanesulfonyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-5-yloxymethyl)-
piperidine

To a 3-necked flask with a mechanical stirrer is added 4-(1'-methanesulfonyl-
30 1',2',3',6'-tetrahydro-[2,4']bipyridinyl-5-yloxymethyl)- piperidine-1-carboxylic acid *tert*-butyl
ester (407 g, 0.90 mol) and 6N aq hydrogen chloride (2000 mL, 12.0 mol) is added
dropwise at 25°C. The mixture is stirred mechanically at 25°C for 0.5 h. 1000 mL of

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dichloromethane are added at 25°C and the mixture is stirred for 20~30 min. Layers are separated and aqueous NaOH (1500 mL, 11.6 mol) is added dropwise to the aqueous solution to pH=9~10 at 25 °C. 3200 mL of dichloromethane are added and the mixture is stirred at 25~30 °C for 40 min. Aqueous solution of NaOH (300 mL, 2.3 mol) is added dropwise to pH >14, until complete dissolution of the solid, the solution is stirred for 20 to 30 min and layers are separated. The aqueous layer is extracted with 1700 mL of dichloromethane. The combined organic layers are washed with 900 mL of water and concentrated. The residue is used for the next step without further purification.

4: 1-[4-(1'-Methanesulfonyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-5-yloxymethyl)-piperidin-1-yl]-2-methyl-propan-2-ol

4-(1'-Methanesulfonyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-5-yloxymethyl)-piperidine is suspended in 800 mL of methanol and added to an autoclave with a mechanical stirrer. 1500 mL of methanol are added and then dimethyloxirane (117 g, 1.62 mol) is added. The mixture is stirred at 60~70°C for 88 h, cooled to 25~30 °C and concentrated to ~1000 mL. The mixture is heated at 60~70 °C and 4200 mL of water are added. The resulting mixture is stirred at 60~70 °C during 30 min and cooled slowly to 0~5 °C in 1.5~2h. It is stirred at this temperature for 30 minutes and filtered. The cake is slurried with H₂O: MeOH=3:1 (600 mL) pre-cooled to 0~5 °C and concentrated (2x). The product is dried under vacuum at 40~50°C to provide 320 g of off-white solid with 98.3% HPLC purity.

5: 5-[1-(2-Fluoro-2-methyl-propyl)-piperidin-4-ylmethoxy]-1'-methanesulfonyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl

1-[4-(1'-Methanesulfonyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-5-yloxymethyl)-piperidin-1-yl]-2-methyl-propan-2-ol (300 g, 0.58 mol) is dissolved in 3000 mL of dichloromethane and the solution is concentrated to 1 L volume at <35 °C. This process is repeated with a volume of 500 mL of dichloromethane and then with a volume of 1000 mL of dichloromethane. After the concentration to 1 L volume at <35 °C, the solution is diluted with 1000 mL of dichloromethane. In another flask deoxofluor (173 g, 0.74 mol) is dissolved in 1250 mL of dichloromethane and cooled to -30~-40 °C. The solution of 1-[4-(1'-methanesulfonyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-5-yloxymethyl)-piperidin-1-yl]-2-methyl-propan-2-ol in dichloromethane is added to this solution while maintaining the

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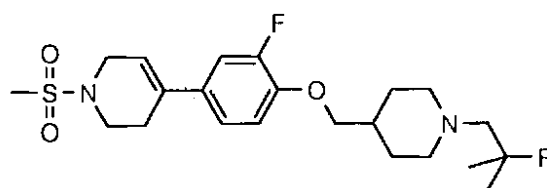
-23-

mixture at -30~-40 °C. The reaction is warmed slowly to 20~30 °C and stirred at this temperature for 16 h. The mixture is cooled to 0~10 °C and saturated solution of sodium bicarbonate is added dropwise to pH=6.0~6.5. The mixture is stirred for 30 min and the layers are separated. The aqueous layer is extracted with 1000 mL of dichloromethane.

- 5 The combined organic layers are washed with 1000 mL of water and concentrated to ~1L of mixture at <50 °C. 1750 mL of acetonitrile are added and the mixture is concentrated to ~1 L of mixture at <50 °C. 500 mL of acetonitrile are added and the mixture is heated at 80~82 °C for 30 min to obtain a clear solution. 1250 mL of water are added dropwise at 80~82 °C and the mixture is cooled slowly to 20~30 °C. The resulting suspension is
- 10 filtered. The cake is slurried with 500 mL of a 1:1 mixture of acetonitrile and water and concentrated. The residue is dried under vacuum to give 210 g of crude solid. The crude is purified by chromatography on silica gel eluting with dichloromethane/methanol: 98/2 to provide 165 g of the title compound in 98% purity. (DMSO-d₆, 400MHz), δ = 8.23 (dd, 1H, J=2.8 Hz), 7.49 (d, 1H, J=8.8Hz), 7.36 (dd, 1H, J=8.8, 2.8Hz), 6.56 (bs, 1H),
- 15 3.89-3.86 (m, 4H), 3.37-3.33 (m, 4H), 2.91 (s, 3H), 2.90-2.88 (m, 2H), 2.65-2.63 (m, 2H), 2.42-2.39 (m, 1H), 2.38-2.36 (m, 1H), 2.08-2.03 (m, 2H), 1.71-1.67 (m, 3H), 1.31 (s, 3H), 1.25 (s, 3H) ppm.

Example 7

- 20 4-{3-Fluoro-4-[1-(2-fluoro-2-methyl-propyl)-piperidin-4-ylmethoxy]-phenyl}-1-methanesulfonyl-1,2,3,6-tetrahydro-pyridine



1: 4-(3-Fluoro-4-methoxy-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester.

- 25 4-Bromo-2-fluoroanisole (2.68 g, 12.94 mmol), Preparation 3 (4.40 g, 14.23 mmol) and (1,1'-bis(diphenylphosphino)ferrocene)palladium(II) chloride (528.40 mg, 0.647 mmol) are placed in a resealable tube and purged with nitrogen. Dimethylformamide (40 mL) and a 2 M aqueous solution of sodium carbonate (23.71 mL, 38.82 mmol) are added and the tube is sealed and stirred at 90 °C for 1 h. The reaction is partitioned

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between ethyl acetate and water. The aqueous layer is extracted with ethyl acetate. The combined organic layers are washed with water and brine, dried over magnesium sulfate, filtered, and concentrated to dryness. The residue is purified by chromatography using a 20 g silica gel cartridge eluting with hexane:ethyl acetate (8:1) to provide 2.6 g of the title compound as a white oil. MS (m/z) 252 (M-55).

2: 4-(3-Fluoro-4-methoxy-phenyl)-1,2,3,6-tetrahydro-pyridine hydrochloride salt.

Prepared essentially as preparation 6 (step 2) using 4-(3-fluoro-4-methoxy-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester as starting material. MS (m/z) 208 (M+1).

10 3: 4-(3-Fluoro-4-methoxy-phenyl)-1-methanesulfonyl-1,2,3,6-tetrahydro-pyridine.

4-(3-Fluoro-4-methoxy-phenyl)-1,2,3,6-tetrahydro-pyridine hydrochloride salt (462.00 mg, 1.90 mmol) is suspended in dichloromethane (10 mL). Triethylamine (479.58 mg, 660.57 μ L, 4.74 mmol) and methanesulfonyl chloride (260.59 mg, 176.07 μ L, 2.27 mmol) are added and the reaction is capped and stirred at room temperature for 15 16 h. The reaction is partitioned between dichloromethane and water. The aqueous layer is extracted with dichloromethane. The combined organic layers are washed with brine, dried over magnesium sulfate, filtered, and concentrated to dryness. The crude material is purified by chromatography using a 5 g silica gel cartridge eluting with dichloromethane to provide 349 mg of the title compound as a white solid. MS (m/z) 286 (M+1).

20 4: 4-(3-Fluoro-4-hydroxy-phenyl)-1-methanesulfonyl-piperidin-4-ol.

4-(3-Fluoro-4-methoxy-phenyl)-1-methanesulfonyl-1,2,3,6-tetrahydro-pyridine (1.12 g, 3.93 mmol) is dissolved in dry dichloromethane (20 mL) under nitrogen. The solution is cooled to -78 °C and boron tribromide (11.52 g, 7.85 mL, 7.85 mmol) is added by syringe. The reaction is warmed to room temperature and stirred for 1 h followed by 25 the addition of 5% aqueous sodium bicarbonate and dichloromethane. An insoluble solid is formed and filtered to provide 729 mg of the title compound as a pink solid. ¹H NMR (CDCl₃) δ (ppm): 7.21 (dd, 1H), 7.09 (m, 1H), 6.89 (t, 1H), 3.30 (m, 2H), 3.18 (td, 2H), 2.88 (m, 3H), 2.06 (m, 2H), 1.80 (m, 2H).

5: 2-Fluoro-4-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-phenol.

30 4-(3-Fluoro-4-hydroxy-phenyl)-1-methanesulfonyl-piperidin-4-ol (726.00 mg, 2.51 mmol) is dissolved in 1,4-dioxane (10.36 g; 10.04 mL, 117.57 mmol). p-Toluenesulfonic acid (43.65 mg, 250.93 μ mol) is added and the mixture is heated at 60

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"C. Solid sodium carbonate is added and the reaction is concentrated. The residue is partitioned between water and ethyl acetate, the pH adjusted to 7 with 1 M hydrogen chloride and extracted with ethyl acetate. The organic layer is washed with brine, dried over magnesium sulfate, filtered, and concentrated to dryness to provide 714 mg of the
5 title compound as a white solid. MS (m/z) 272 (M+1).

6: 4-[2-Fluoro-4-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-phenoxy-methyl]-piperidine-1-carboxylic acid *tert*-butyl ester.

Prepared essentially as Preparation 2 (step 2) using 4-methanesulfonyloxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester and 2-fluoro-4-(1-methanesulfonyl-1,2,3,6-
10 tetrahydro-pyridin-4-yl)-phenol as starting materials. MS (m/z) 414 (M-55).

7: 4-[3-Fluoro-4-(piperidin-4-ylmethoxy)-phenyl]-1-methanesulfonyl-1,2,3,6-tetrahydro-pyridine hydrochloride salt.

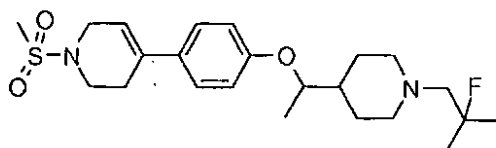
Prepared essentially as Preparation 6 (step 2) using 4-[2-fluoro-4-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-phenoxy-methyl]-piperidine-1-
15 carboxylic acid *tert*-butyl ester as starting material. MS (m/z) 369 (M+1).

8: 4-{3-Fluoro-4-[1-(2-fluoro-2-methyl-propyl)-piperidin-4-ylmethoxy]-phenyl}-1-methanesulfonyl-1,2,3,6-tetrahydro-pyridine.

Prepared essentially as Example 2 starting from 4-[3-fluoro-4-(piperidin-4-ylmethoxy)-phenyl]-1-methanesulfonyl-1,2,3,6-tetrahydro-pyridine hydrochloride salt
20 and 2-fluoro-2-methyl-propionic acid. MS (m/z) 443 (M+1).

Example 8

4-(4-{1-[1-(2-Fluoro-2-methyl-propyl)-piperidin-4-yl]-ethoxy}-phenyl)-1-methanesulfonyl-1,2,3,6-tetrahydro-pyridine

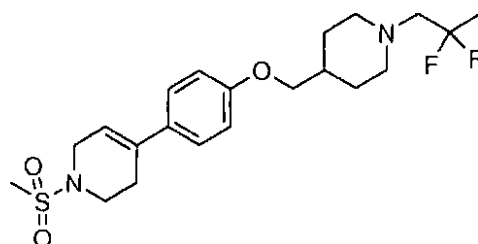


25 Prepared essentially as Example 2 using Preparation 5 (racemic) as starting material to provide the title compound. The title compound (0.194 g) is separated into its enantiomers using an eluent of 0.2% dimethylethylamine in 100 % methanol on a 420 x 250 mm Chiralpak OJ at 8 mL/min affording 77 mg of isomer 1 (96% ee, RT = 10.7min).

Example 9

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4-{4-[1-(2,2-Difluoro-propyl)-piperidin-4-ylmethoxy]-phenyl}-1-methanesulfonyl-
1,2,3,6-tetrahydro-pyridine



1: Toluene-4-sulfonic acid 2,2-difluoro-propyl ester.

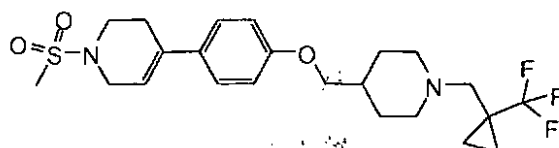
5 To a solution of 2,2-difluoropropanol (0.50 g, 5.20 mmol) in dichloromethane (52.0 mL) and triethylamine (0.50 g, 0.73 mL, 5.20 mmol) at 0 °C is added p-toluenesulfonyl chloride (0.99 g, 5.20 mmol). The mixture is allowed to slowly warm to room temperature over 24 h. The mixture is concentrated and is partitioned between diethyl ether and water. The organic layer is washed with water and brine, dried over
10 magnesium sulfate, filtered, and concentrated to dryness. The material is purified over silica gel to obtain 1.0 g of the title compound as clear crystals. MS (m/z) 250 (M+1).

2: 4-{4-[1-(2,2-Difluoro-propyl)-piperidin-4-ylmethoxy]-phenyl}-1-methanesulfonyl-1,2,3,6-tetrahydro-pyridine

To a mixture of Preparation 2 (0.25 g, 0.71 mmol) and toluene-4-sulfonic acid
15 2,2-difluoro-propyl ester (0.25 g, 0.91 mmol) is added 1,3-dimethyl-2-imidazolidinone (7 mL). The mixture is placed in a Biotage microwave reactor and heated to 175 °C for 1 hour and then 180 °C for 1 hour. The mixture is partitioned between ethyl acetate and water. The organic layer is washed with water and brine, dried over magnesium sulfate, filtered, and concentrated to dryness. The crude material is purified over silica gel to
20 afford 0.03 g of the title compound as a white solid. MS (m/z) 429 (M+1).

Example 10

1-Methanesulfonyl-4-{4-[1-(1-trifluoromethyl-cyclopropylmethyl)-piperidin-4-ylmethoxy]-phenyl}-1,2,3,6-tetrahydro-pyridine



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1: 1-(1-Trifluoromethyl-cyclopropanecarbonyl)-piperidine-4-carboxylic acid ethyl ester

1,1'-Carbonyldiimidazole (77.36 g; 467.52 mmol) is added to a solution of 1-(trifluoromethyl)cyclopropanecarboxylic acid (72.04 g; 467.52 mmol) in tetrahydrofuran
5 (600 mL) while keeping the internal temperature below 30°C. Piperidine-4-carboxylic acid ethyl ester (50 g; 311.68 mmol) is added after 10 min and the reaction is stirred under nitrogen atmosphere at room temperature for 16 h. The solvent is removed under controlled vacuum and the residue is partitioned between 2 M aqueous solution of sodium hydroxide (200 mL) and dichloromethane (300 mL). The organic layer is washed with
10 brine (100 mL), dried over magnesium sulphate, filtered and concentrated to obtain 93.45 g of the title compound. MS (m/z) 294 (M+1).

2: [1-(1-Trifluoromethyl-cyclopropylmethyl)-piperidin-4-yl]-methanol

1-(1-Trifluoromethyl-cyclopropanecarbonyl)-piperidine-4-carboxylic acid ethyl ester (50 g; 170.48 mmol) in tetrahydrofuran (350 mL) is added to a solution of 1 M
15 lithium aluminum hydride (170.48 mL; 170.48 mmol) in tetrahydrofuran. The reaction mixture is allowed to warm to room temperature and stirred for 1 h. The reaction mixture is cooled at 0°C and water/2 M aqueous solution of sodium hydroxide/water (1:3:1) are added sequentially (8.5 mL : 12 mL: 8.5 mL). The resulting slurry is filtered over a celite® pad and washed with tetrahydrofuran (200 mL). The organic layer is concentrated
20 under controlled vacuum to afford 17 g of the volatile title compound as colorless oil. The crude material is used without further purification. MS (m/z) 238 (M+1).

3: 1-Methanesulfonyl-4-{4-[1-(1-trifluoromethyl-cyclopropylmethyl)-piperidin-4-ylmethoxy]-phenyl}-1,2,3,6-tetrahydro-pyridine

Diisopropyl azodicarboxylate (27.43 g; 128.87 mmol) is added to a solution of
25 triphenylphosphine (33.80 g; 128.87 mmol) in dry tetrahydrofuran (330 mL) at 0°C. The reaction is stirred for 20 min. A suspension of [1-(1-trifluoromethyl-cyclopropylmethyl)-piperidin-4-yl]-methanol (24 g; 99.13 mmol), Preparation 1 (25.89 g; 99.13 mmol) in dry tetrahydrofuran (200 mL) is added dropwise. The reaction is stirred at 0°C for 10 min and it is allowed to warm to room temperature and reacted overnight. The solvent is
30 evaporated and the resulting slurry is diluted with dichloromethane (350 mL) and washed with 2 M aqueous solution of sodium hydroxide (2 x 30 mL) and brine (2 x 30 mL), dried over magnesium sulfate, filtered and concentrated. The pink solid is purified over silica

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gel eluting with hexane/acetone: 100%; 95:5; 90:10; 80:20 and 70:30, to afford 16 g of title compound, around 80% pure. The solid is treated with 2N aqueous hydrogen chloride. A white solid precipitates and is filtered and dried. The solid is dissolved in water (150 mL) and is basified to pH 12 with sodium hydroxide pellets. The resulting
5 solid is filtered, dried and crystallized with methyl *t*-butyl ether (100 mL) filtered and dried in the oven at 50°C to obtain 8 g of the title compound. MS (m/z) 473 (M+1).

An alternative method for the preparation of Example 10 is as follows:

1: 1-(1-Trifluoromethyl-cyclopropanecarbonyl)-piperidine-4-carboxylic acid ethyl ester

10 1-(Trifluoromethyl)cyclopropanecarboxylic acid (400 g, 2.6 mol) is dissolved in 3.2 L of tetrahydrofuran and cooled to 10~20 °C. Carbonyldiimidazole (462.4 g, 1.1 eq) is added in portions. The mixture is stirred at 25-30 °C for 20 min. Then piperidine-4-carboxylic acid methyl ester (445.6 g, 1.2 eq) is added dropwise at < 30 °C. The mixture is stirred at 25-30 °C for 18~20 h. 3.2 L of water are added dropwise at < 30 °C and the
15 solution is concentrated to ~ 1 L of volume to remove most of tetrahydrofuran. The resulting solution is extracted with dichloromethane (2x). The combined organic layers are washed with 3 volumes of 0.5 M hydrochloric acid and concentrated. 500 mL of methyl *tert*-butyl ether is added and the solution is concentrated. This process is run twice. The organic layer is concentrated to provide 567g of the title compound in 95%
20 purity.

2: [1-(1-Trifluoromethyl-cyclopropylmethyl)-piperidin-4-yl]-methanol

Lithium aluminum hydride (208 g, 5.0 eq) is suspended in 3.9 L of methyl *tert*-butyl ether and the suspension is stirred for 10 min. A solution of 1-(1-trifluoromethyl-cyclopropanecarbonyl)-piperidine-4-carboxylic acid ethyl ester (260 g, 0.93 mol) in 1.3 L of
25 methyl *tert*-butyl ether is added dropwise at < 30 °C. The mixture is refluxed for 20 h and cooled to 0~10 °C. 500 mL of water are added, at 0~10 °C and the mixture is stirred for 30 min. The suspension is filtered and the cake is washed with 1.8 L of methyl *tert*-butyl ether. The filtrate is concentrated to ~ 3 L of volume at <35 °C under vacuum. The solvent is displaced with tetrahydrofuran (1.0 L x 2) and concentrated to provide 212 g of
30 the title compound in 96.8% purity.

3: 1-Methanesulfonyl-4-{4-[1-(1-trifluoromethyl-cyclopropylmethyl)-piperidin-4-ylmethoxy]-phenyl}-1,2,3,6-tetrahydro-pyridine

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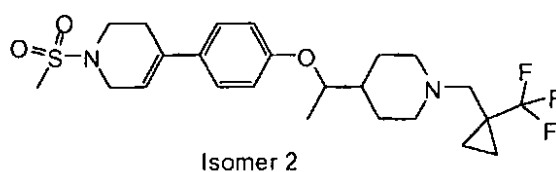
-29-

[1-(1-Trifluoromethyl-cyclopropylmethyl)-piperidin-4-yl]-methanol (371 g, 1.56 mol) is dissolved in 1.85 L of dichloromethane and triethylamine (237.3 g, 2.34 mol) and the mixture is cooled to 0~10 °C. Methanesulfonyl chloride (215 g, 1.2 eq) is added dropwise. The reaction is warmed to 20~25 °C and stirred for 1 h. 1.85 L of water are added dropwise. Layers are separated and the aqueous layer is extracted with 1 L of dichloromethane. The combined organic layers are washed with 1.85 L of water, dried over anhydrous sodium sulfate and concentrated to provide 491 g of an oil that is used for the next step in two batches.

Preparation 1 (197.8 g, 0.781 mol) is dissolved in 1.8 L of dimethylformamide and cooled to 0~10 °C. A solution of potassium tert-butoxide (87.6 g, 0.781 mol) dissolved in 1.6 L of dimethylformamide is added dropwise to the solution and the mixture is stirred at 20~30 °C for 30 min. A solution of [1-(1-trifluoromethyl-cyclopropylmethyl)-piperidin-4-yl]-methanol (246 g, 0.781 mol) in 0.5 L of dimethylformamide is added dropwise to the solution. The mixture is heated at ~60 °C and stirred for 1.5 h. It is cooled to 30~40 °C, and 4.4 L of water are added dropwise. The mixture is stirred at 30 °C for 1 h and filtered. This process is done with the two batches of [1-(1-trifluoromethyl-cyclopropylmethyl)-piperidin-4-yl]-methanol and the resulting cakes are combined for purification. The cake is washed with 800 mL of a 1:1 mixture of dimethylformamide and water. The solid is stirred with 4 L of dichloromethane and filtered. The filtrate is concentrated and purified by chromatography eluting with dichloromethane to obtain 180 g of the title compound in 99% purity. (CDCl₃, 400MHz), δ = 7.31 (d, 2H, J=8.8 Hz), 6.88 (d, 2H, J= 8.8 Hz), 6.00-5.98 (m, 1H), 3.97 (s, 2H), 3.82 (s, 2H), 3.55-3.52 (m, 2H), 3.04-3.01 (m, 2H), 2.87 (s, 3H), 2.70-2.60 (m, 4H), 2.06-2.03 (m, 2H), 1.85-1.82 (m, 3H), 1.48-1.45 (m, 2H), 1.03-1.01 (m, 2H), 0.74-0.71 (m, 2H) ppm.

Example 11

1-(Methylsulfonyl)-4-(4-(1-(1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)ethoxy)phenyl)-1,2,3,6-tetrahydropyridine



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1. (1-(Trifluoromethyl)cyclopropyl)methanol

To an ice-cold suspension of lithium aluminum hydride (33.91 mmol; 1.29 g) in diethyl ether (90 mL) is added dropwise over 25 minutes methyl 1-(trifluoromethyl)cyclopropanecarboxylate (16.95 mmol; 3.00 g) in 30 mL of

diethylether. The reaction is stirred at 0°C for 2 hours. The mixture is quenched by slow addition of 7.5 mL of water, then 15 mL of 5 M sodium hydroxide and 9 mL of water. The thick slurry is vigorously stirred at room temperature for 3 hours. The mixture is transferred to a separatory funnel, diluted with water and extracted with diethylether. The combined organic layers are washed with brine, dried over magnesium sulfate, filtered and concentrated to dryness. 2.37 g of the title compound as a colorless oil are obtained. 2.37 g, ¹H NMR (CDCl₃) δ (ppm): 0.762-0.807 (m, 2H), 1.018-1.055 (m, 2H), 3.732 (s, 2H).

2. (1-(Trifluoromethyl)cyclopropyl)methyl methanesulfonate

Prepared essentially as Preparation 2 (step 1) using (1-trifluoromethyl)cyclopropyl)-methanol as starting material. ¹H NMR (CDCl₃) δ (ppm): 0.921-0.975 (m, 2H), 1.182-1.223 (m, 2H), 3.057 (s, 3H), 4.296 (s, 2H).

3. 1-(Methylsulfonyl)-4-(4-(1-(1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)ethoxy)phenyl)-1,2,3,6-tetrahydropyridine

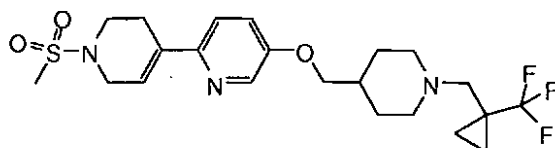
To Preparation 5 (isomer 2) (62 mg, 0.169 mmol), potassium carbonate (70 mg, 0.506 mmol) and acetonitrile (1.12 mL, 21.46 mmol) in a vial is added (1-(trifluoromethyl)cyclopropyl)methyl methanesulfonate (147 mg, 0.675 mmol). The vial is sealed and heated at 110 °C for 16 h. The reaction is diluted with dichloromethane and water. The organic layer is separated and washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo to afford an off-white solid. The solid is purified by flash chromatography over silica gel to obtain 0.057 g of a white solid. MS (m/z) 487.2 (M+1).

Example 12

2-(1-(Methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-((1-(1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)pyridine

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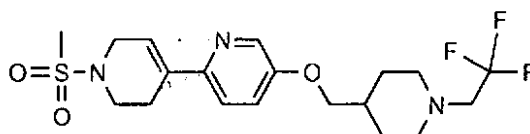
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To Preparation 6 (206 mg, 0.586 mmol), potassium carbonate (243 mg, 1.76 mmol) and acetonitrile (2.93 mL, 56 mmol) in a microwave vial is added (1-(trifluoromethyl)cyclopropyl)methyl methanesulfonate (256 mg, 1.17 mmol). The microwave vial is sealed and heated at 140 °C for 2 h then 150 °C for 30 min in the Biotage microwave. The reaction is diluted with dichloromethane and water. The organic layer is separated and washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue is triturated with diethylether and the title product is collected via vacuum filtration to obtain 0.181 g of the title compound. MS (m/z) 474 (M+1).

Example 13

2-(1-(Methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-((1-(2,2,2-trifluoroethyl)piperidin-4-yl)methoxy)pyridine



To a solution of Preparation 6 (0.05 g, 0.14 mmol) in acetonitrile (1.50 mL) are added potassium carbonate (0.07 g, 0.56 mmol) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (0.06 g, 0.28 mmol). The reaction mixture is heated at 85 °C for 1 h in a microwave, cooled to room temperature and diluted with water. The mixture is extracted with ethyl acetate and the combined organic extracts are dried over sodium sulfate, filtered, and concentrated. The residue is purified by flash column chromatography over silica gel to obtain 30 mg of the title compound as an off-white solid. MS (m/z) 433 (M+1).

Human GPR119 Activity Assay

A stable cell line expressing human GPR119 off an inducible promoter is generated in 293 T-REx™ cells (Invitrogen). T-REx™ (Tetracycline-Regulated Expression) cell line stably expresses the tetracycline repressor protein and, therefore,

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allow for inducible expression of the gene of interest (GPR119) with doxycycline. Agonists to the human GPR119 receptor are characterized by measuring increases in the cAMP levels in 293 T-REx™ cells expressing hGPR119. 10,000 cells/well are seeded into a 96-well plate and cultured for 24h in DMEM supplemented with 10% fetal bovine serum, 15µg/mL Blasticidin and 200µg/mL Hygromycin B. Next day, cells are stimulated with 1 ng/mL Doxycycline in DMEM with no further addition of Hygromycin B and Blasticidin. cAMP assay is performed after 18 h incubation with doxycycline. cAMP is determined using the cAMP HiRange HTRF assay (Cisbo International). Cells are washed with PBS and pre-incubated for 15 min with PBS supplemented with 2 mM glucose, 0.25 mM IBMX and 0.1% BSA. Test compounds diluted in the pre-incubation buffer are added and cells are further incubated at room temperature for 1h. Incubation is stopped by addition of HTRF reagents diluted in the lysis buffer, followed by incubation for 1h and measurements of fluorescence at 620 and 655 nm. The potency of the agonists is determined as the agonist concentration that gives 50% activation of the hGPR119 mediated cAMP increase (EC50).

All of the exemplified compounds were tested essentially as described above and each were found to have an EC50 value of <10 nM. Example 1 has an EC50 value of 4.61 nM; Example 6 has an EC50 value of 0.95 nM; Example 7 has an EC50 value of 2.13 nM; Example 8 has an EC50 value of 1.10 nM; and Example 10 has an EC50 value of 0.95 nM.

Thus, certain compounds of the present invention are shown to act as agonists of GPR119 *in vitro*.

Glucagon-like peptide 1 secretion in GLUTag cells

Effects of GPR119 agonists on glucagon-like peptide 1 (GLP-1) secretion are determined in vitro in GLUTag cells. GLUTag cells are an immortalized murine intestinal enteroendocrine cell line that express the preproglucagon gene and secrete GLP-1 in a regulated manner (Brubaker PL, Schloos J, Drucker DJ. Regulation of glucagon-like peptide-1 synthesis and secretion in the GLUTag enteroendocrine cell line. Endocrinology. 1998 139:4108-14). To measure GLP-1 secretion, 15,000 cells/well are seeded in 96-well-plate and incubated for 3 days in DMEM supplemented with 10% FBS and 1% Glutamine. On the day of the experiment, cells are washed twice with the incubation buffer, EBSS supplemented with 5 mM glucose and 0.1% BSA. 150 µL of the

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incubation buffer containing test compounds is added to each well and cells are incubated at 37°C for 2 h. After incubation, the supernatant is collected and filtered using 96-well-filter-plates. GLP-1 content in the filtrate is determined with the Mouse/Rat Total GLP-1 Assay (Meso Scale Discovery). The potency of the GPR119 agonists to stimulate GLP-1 secretion is determined as the agonist concentration that gives 50% increase in GLP-1 (EC50).

Examples 6 and 9 were tested essentially as described above and found to have respective EC50 value of 62.7 and 36.8 nM.

Thus, certain compounds of the present invention are shown to have functional activity as agonists of GPR119 *in vitro*.

Bioavailability

Methods for accessing oral bioavailability are well appreciated in the art. One such reference is *Medicinal Research Reviews* Vol 21 No. 5 382-396 (2001). The oral bioavailability of compounds of the present invention may be estimated essentially as follows.

Cohorts of three 250-400 gram male Sprague-Dawley rats or approximately 10 kg Beagle dogs (female or male) are used. Animals do not need to be fasted for the intravenous (IV) portion of the study. Dogs are IV administered the compounds by cannulated cephalic vein and blood collections are by jugular vein. Animals are first IV dosed at 1 mg/kg and blood samples (0.1 to 0.2 mL) are then collected using EDTA as an anticoagulant at 0.0830, 0.25, 0.50, 1, 2, 4, 8, 12, and 24 h. After at least two days and overnight fasting, the animals are dosed at 3 mg/kg by oral gavage. Blood samples (0.1 to 0.2 mL) are then collected using EDTA as an anticoagulant at 0.25, 0.50, 1, 2, 4, 6, 8, 12, and 24 h. During the course of a study the total of blood (mL) collected is not to exceed 1% of total body weight in grams.

Compound plasma concentrations are measured by LC/MS/MS assays. Data are then analyzed using standard non-compartmental pharmacokinetic analysis. Oral bioavailability is calculated as:

$$(AUC_{0-\infty, \text{ oral}} / AUC_{0-\infty, \text{ IV}}) \times (\text{Dose, IV.} / \text{Dose, oral}) \times 100\%$$

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Example 6 was tested essentially as described above and found to have oral bioavailability of 90 % in Beagle dogs. Example 10 was tested essentially as described above and found to have oral bioavailability of 53 % in Sprague Dawley rats.

Thus, certain compounds of the present invention have been shown to have good oral bioavailability.

Mouse Gastric Inhibitory Polypeptide (GIP) Assay

Male C57BL/6 mice (8-10 weeks of age, n=20/dose level, n=5/time point) are fasted overnight (16 hr), weighed the following morning, and then orally dosed with vehicle (1% HEC) or various doses of test article at 5 mL/kg. Animals are euthanized by CO₂ asphyxiation for 1 minute, and then blood is collected by cardiac puncture at various times (0.5, 1.5, 3, and 6 h post compound dose) into EDTA plasma tubes containing 10 µL/mL DPP4 inhibitor (Millipore, DPP4-010) and 1.1x10⁵ KIU/mL aprotinin. Blood samples are kept on ice until plasma is separated by centrifugation at 3000xg for 5 min. Resulting plasma samples are placed into 96-well plates and stored at -20°C until analyzed. Measurements of total GIP (measured by Millipore kit EZRMGIP-55K) are performed for each time-point. For each treatment group, the AUC for GIP is determined by applying the trapezoid rule to the timepoint-specific average GIP levels. Potencies were estimated using piecewise linear interpolation across the collection of calculated GIP AUCs above vehicle from a dose response study. Compound potency is defined as the dose and/or concentration of compound that yielded an increase of 350 pg*hr/mL above the vehicle group GIP AUC over the timecourse of the experiment.

Using the procedure essentially as described above, a 10 mg/kg dose of Example 3 resulted in an increase in GIP AUC over vehicle of 762 pg*h/mL; a 10 mg/kg dose of Example 10 resulted in an increase in GIP AUC over vehicle of 762 pg*h/mL; and a 1.6 mg/kg dose of Example 6 resulted in an increase in GIP AUC over vehicle of 422 pg*h/mL.

Certain compounds of the present invention have been shown to stimulate GIP secretion in vivo, which induces insulin secretion, such data indicates potential for use of compounds of the present invention in the treatment of diabetes.

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Mouse Oral Glucose Tolerance Test (OGTT)

Normal C57BL/6 mice are fasted overnight, randomized into groups (n=6) and orally dosed with vehicle (1% HEC, 0.25% tween 80, 0.05% antifoam) or 0.9, 2, 6 and 18 mg/kg GPR119 agonist suspended in vehicle. 30 minutes after the compound is
5 administered, mice are dosed orally with a 50% dextrose solution at 3 g/kg. At various times (0, 20, 40, or 60 minutes post glucose), the mice are restrained in cotton gloves or paper towels and 1 mm or less of the tail is cut. A small drop of blood is placed onto Accu-Chek® glucometers (Roche model 22-044217) for glucose measurements. Three
10 glucometers are used to read glucose in each collected sample, with the median value being reported as the final glucose value. Area under the plasma glucose curve (glucose AUC) is calculated for each group and the percentage decrease in the glucose AUC versus the control group is used as a measure of efficacy of the compound to decrease plasma glucose.

Example 6 was tested essentially as described above and found to demonstrate
15 improved glucose tolerance. Example 6 did not influence fasting plasma glucose but significantly decreased postprandial plasma glucose. The data shows that the dose of Example 6 which produces a 50% decrease in glucose area under the curve (ED50) is equal to 0.4 mg/kg.

Thus, a compound of the present invention has been shown to decrease plasma
20 glucose levels in vivo, indicating potential for use of the compounds of the present invention in the treatment of diabetes.

Chronic treatment of diet-induced obese (DIO) mice

DIO male C57/BL6 mice are maintained on a calorie-rich diet and have free
25 access to food and water for at least 2 weeks before randomization into groups by weight (n=8) and treatment. Animals are individually housed in a temperature-controlled (24°C) facility with 12 hour light, 12 hour dark cycle. Body weights range from 34–40 g. Mice are administrated once daily vehicle (1% HEC), 30 mg/kg GPR119 agonist, 30 mg/kg DPPIV inhibitor or a combination of 30 mg/kg GPR119 agonist and 30 mg/kg DPPIV
30 inhibitor. Treatment continues for 3 weeks. Food and body weights are recorded daily before dark photoperiod. Cumulative body weight change is calculated as the daily body weight minus body weight before treatment for each animal and presented as an average

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for the group. Food intake is measured daily for each animal and combined with the total amount of food consumed by that animal from all previous days to yield cumulative food intake, which is then averaged for the group. At the end of the study OGTT is performed after overnight fasting.

5 Example 6 was tested essentially as described above where the DPPIV inhibitor is sitagliptin. Sitagliptin alone did not alter body weight or food intake in the study.

Example 6 alone produced a mild decrease in both food intake and body weight observed only during the first week of treatment. Combination of sitagliptin and Example 6 produced profound decreases in body weight and food intake that were sustained

10 throughout the course of the study. Example 6 alone or in combination with sitagliptin did not significantly modify plasma glucose levels in this model.

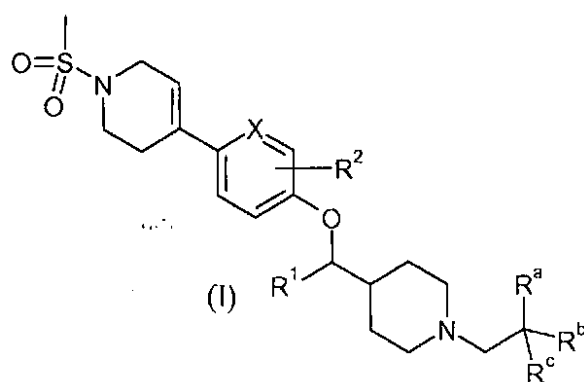
Thus, a compound of the present invention has been shown to decrease food intake and body weight, indicating potential for use of the compounds of the present invention in the treatment of obesity.

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WE CLAIM:

1. A compound of the formula:



5 wherein;

X is selected from N and CH;

R^a is selected from F and CF₃;

R^b and R^c are independently selected from F and methyl or combine to form a C₃₋₅ cycloalkyl ring;

10 R¹ is selected from H and methyl;

R² is selected from H and F;

or a pharmaceutically acceptable salt thereof.

- 15 2. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R^b and R^c are independently selected from F and methyl or combine to form C₃ cycloalkyl.

- 20 3. A compound according to any one of claims 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^b and R^c are methyl or combine to form C₃ cycloalkyl.

4. A compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein R^a is CF₃.

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5. A compound according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R² is H.

6. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, selected from 5-[1-(2-Fluoro-2-methyl-propyl)-piperidin-4-ylmethoxy]-1'-methanesulfonyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl; and 1-Methanesulfonyl-4-{4-[1-(1-trifluoromethyl-cyclopropylmethyl)-piperidin-4-ylmethoxy]-phenyl}-1,2,3,6-tetrahydro-pyridine.

7. A pharmaceutical composition comprising a compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier.

8. A pharmaceutical composition according to claim 7 additionally comprising one or more other therapeutic ingredients.

9. A pharmaceutical composition according to claim 8 wherein sitagliptin is an additional therapeutic ingredient.

10. A compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, for use in therapy.

11. A compound according to any of claims 1 to 6, or a pharmaceutically acceptable salt thereof, for use in the treatment of diabetes or obesity.

12. A compound according to claim 11 for use in the treatment of type II diabetes.

13. A method for the treatment of diabetes or obesity, which comprises administering an effective amount of a compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, to a human being or animal in need thereof.

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2010/041645

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/12 C07D401/14 A61K31/4427 A61P3/10
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/038974 A1 (IRM LLC; ALPER PHILLIP [US]; AZIMIOARA MIHAI [US]; COW CHRISTOPHER [US]) 26 March 2009 (2009-03-26) cited in the application See compounds J1-J9, pages 84-88. -----	1-14
A	WO 2008/025798 A1 (BIOVITRUM AB PUBL [SE]; BRANDT PETER [SE]; EMOND RIKARD [SE]; JOHANSSON) 6 March 2008 (2008-03-06) the whole document -----	1-14

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

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

7 October 2010

Date of mailing of the international search report

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Authorized officer

Menchaca, Roberto

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2010/041645

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009038974 A1	26-03-2009	AR 068496 A1	18-11-2009
		AU 2008302570 A1	26-03-2009
		CA 2697551 A1	26-03-2009
		CN 101801954 A	11-08-2010
		CR 11292 A	22-03-2010
		EC SP100042 A	30-04-2010
		EP 2197873 A1	23-06-2010
		KR 20100055536 A	26-05-2010
		PE 07082009 A1	15-07-2009
		US 2009270409 A1	29-10-2009
WO 2008025798 A1	06-03-2008	AU 2007291252 A1	06-03-2008
		AU 2007291254 A1	06-03-2008
		CA 2660699 A1	06-03-2008
		CA 2661371 A1	06-03-2008
		EP 2059516 A1	20-05-2009
		EP 2059517 A1	20-05-2009
		WO 2008025799 A1	06-03-2008
		WO 2008025800 A1	06-03-2008
		JP 2010501629 T	21-01-2010
		JP 2010501630 T	21-01-2010
		US 2008058339 A1	06-03-2008
		US 2008103141 A1	01-05-2008
		US 2008103123 A1	01-05-2008

AGONISTAS DE GPR119

DESCRIPCIÓN DE LA INVENCION

GPR119 es un receptor acoplado a la proteína G
5 grandemente confinado en humanos a tejidos pancreáticos
(células β) e intestinales (células enteroendocrinas) y se ha
estudiado y descrito usando varios sinónimos incluyendo
SNORF25, RUP3, GPCR2, 19AJ, OSGPR116 y receptor
insulinotrópico dependiente de la glucosa.

10 La farmacología y potencial terapéutico para GPR119
se ha revisado recientemente (Br. J. Pharmacol. 2008, 153,
S76-S81), que describe a GPR119 como un objetivo interesante
para el tratamiento de diabetes y obesidad.

Un número de agonistas sintéticos de GPR119 se ha
15 descrito para el tratamiento de diabetes y obesidad, por
ejemplo aquéllos descritos en WO 09/038974. Permanece una
necesidad de agonistas de GPR119 alternativos como terapias
antidiabéticas y antiobesidad.

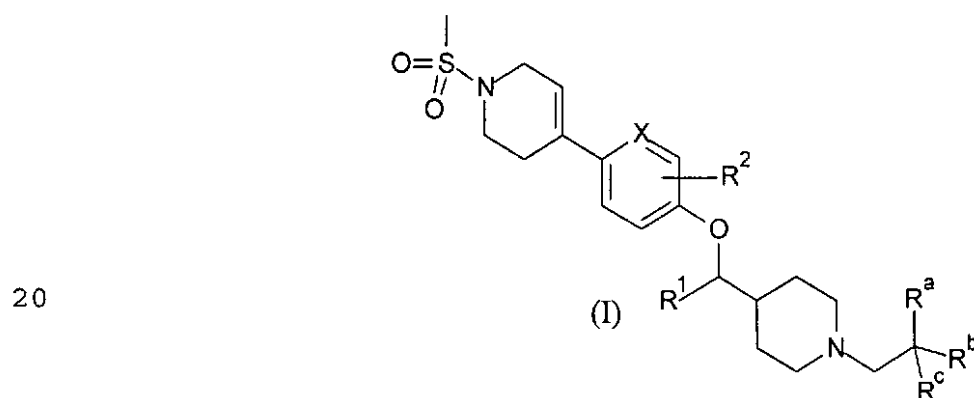
La administración oral típicamente es la ruta de
20 administración preferida para terapias antidiabéticas y
antiobesidad. Para compuestos que exhiben buena
biodisponibilidad oral, típicamente deben tener suficiente
solubilidad acuosa para permitir la absorción, y suficiente
estabilidad metabólica para minimizar la degradación de
25 primer pasado en el hígado.

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Se ha encontrado que los compuestos de Fórmula I son agonistas de GPR119 *in vitro*. Se ha mostrado que ciertos compuestos de la presente invención estimulan la secreción GIP *in vivo*. Ciertos compuestos de la presente invención exhiben mayor potencia que los agonistas existentes. Ciertos compuestos de la presente invención tienen buena biodisponibilidad oral.

La presente invención se dirige a compuestos de Fórmula I los cuales son agonistas del receptor acoplado a la proteína G GPR119, composiciones farmacéuticas que los contienen como ingrediente activo, y a su uso en el tratamiento o prevención de diabetes u obesidad, en particular diabetes Tipo II.

La presente invención proporciona un compuesto de la fórmula:



en donde;

X se selecciona de N y CH;

R^a se selecciona de F y CF₃;

25 R^b y R^c se seleccionan independientemente de F y

metilo o se combinan para formar un anillo cicloalquilo de C₃-
5;

R¹ se selecciona de H y metilo;

R² se selecciona de H y F;

5 o una sal del mismo farmacéuticamente aceptable.

La presente invención proporciona una composición farmacéutica que comprende un compuesto de Fórmula I, o una sal del mismo farmacéuticamente aceptable, y un diluyente o portador farmacéuticamente aceptable.

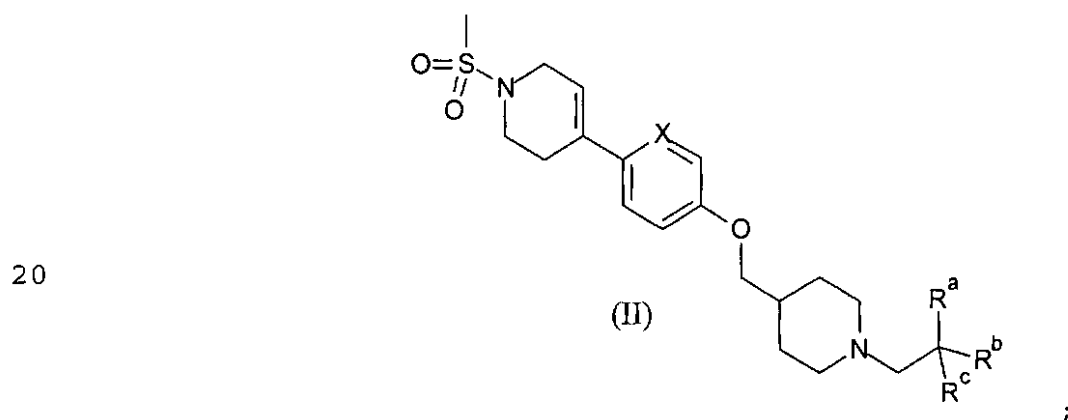
10 La presente invención proporciona un compuesto de Fórmula I, o una sal del mismo farmacéuticamente aceptable, para uso en terapia. La presente invención también proporciona un compuesto de Fórmula I, o una sal del mismo farmacéuticamente aceptable para uso en el tratamiento de
15 diabetes y obesidad. La presente invención adicionalmente proporciona un compuesto de Fórmula I, o una sal del mismo farmacéuticamente aceptable para uso en el tratamiento de diabetes u obesidad. En otro aspecto de la presente invención, se proporciona el uso de un compuesto de Fórmula
20 I, o una sal del mismo farmacéuticamente aceptable, para la manufactura de un medicamento para el tratamiento de diabetes y obesidad. La presente invención adicionalmente proporciona el uso de un compuesto de Fórmula I, o una sal del mismo farmacéuticamente aceptable, para la manufactura de un
25 medicamento para el tratamiento de diabetes u obesidad.

27

La presente invención también proporciona un método para el tratamiento de diabetes y obesidad, el cual comprende administrar una cantidad efectiva de un compuesto de Fórmula I, o una sal del mismo farmacéuticamente aceptable, a un ser humano o animal en necesidad del mismo. La presente invención adicionalmente proporciona un método para el tratamiento de diabetes u obesidad, el cual comprende administrar una cantidad efectiva de un compuesto de Fórmula I, o una sal del mismo farmacéuticamente aceptable, a un ser humano o animal en necesidad del mismo.

Es preferido que los compuestos de la presente invención sean usados en el tratamiento de diabetes u obesidad, en particular diabetes tipo II.

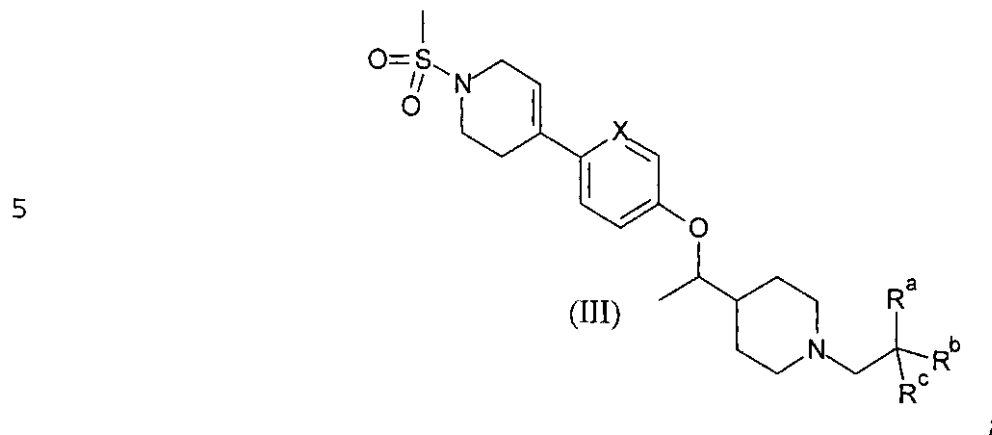
Una especie preferida de los compuestos de Fórmula I son compuestos de la fórmula:



o una sal del mismo farmacéuticamente aceptable, en donde X, R^a, R^b, y R^c son como se definen en la presente.

25 Una especie preferida de los compuestos de Fórmula

I son compuestos de la fórmula:



o una sal del mismo farmacéuticamente aceptable, en
10 donde X, R^a, R^b, y R^c son como se definen en la presente.

Ciertas clases de compuestos de Fórmula I, II o III
son preferidas. Las siguientes selecciones numeradas
describen tales clases preferidas:

- 1) X es N;
- 15 2) X es CH;
- 3) R² es H;
- 4) R^a es F;
- 5) R^a es CF₃;
- 6) R^b y R^c se seleccionan independientemente de F
y metilo o se combinan para formar cicloalquilo
20 de C₃;
- 7) R^b y R^c son metilo o se combinan para formar
cicloalquilo de C₃;
- 8) X es N y R^b y R^c son metilo o se combinan para
25 formar cicloalquilo de C₃;

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9) X es CH y R^b y R^c son metilo o se combinan para formar cicloalquilo de C₃;

10) R^b y R^c son metilo y R^a es F;

11) R^b y R^c se combinan para formar cicloalquilo de C₃ y R^a es CF₃.

5

Las sales farmacéuticamente aceptables de cada uno de los compuestos de la presente invención se contemplan dentro del alcance de la presente solicitud.

Los compuestos preferidos de la presente invención incluyen 5-[1-(2-Fluoro-2-metil-propil)-piperidin-4-ilmetoxi]-1'-metansulfonil-1',2',3',6'-tetrahidro-[2,4']bipiridinilo; y 1-Metansulfonil-4-{4-[1-(1-trifluorometil-ciclopropilmetil)-piperidin-4-ilmetoxi]-fenil}-1,2,3,6-tetrahidro-piridina.

15 Como se usa en toda esta especificación, se entenderá que donde un grupo es calificado por "aquí definido" o "definido aquí", el grupo abarca la primera definición más amplia y que ocurra así como también todas y cada una de las definiciones particulares de este grupo.

20 Como se utilizó anteriormente y en toda la descripción de la invención, los siguientes términos, a menos que se indique de otra forma, tendrán el siguiente significado:

Como se usa en la presente, el término 25 "cicloalquilo de C₃-C₅" se toma para significar ciclopropilo,

ciclobutilo y ciclopentilo. Los grupos cicloalquilo de C₃-C₅ preferidos incluyen ciclopropilo y ciclobutilo; otro grupo preferido es ciclopropilo.

Como se usa en la presente los términos "isómero 1" e "isómero 2" se refieren a los enantiómeros específicos de los intermediarios o compuestos finales, "isómero 1" se refiere al primer compuesto que se eluye del proceso cromatográfico descrito e "isómero 2" el segundo. En donde el término "isómero 1" o "isómero 2" es atribuido primero a un intermediario, el término es retenido hasta el compuesto final.

Como se usa en la presente el término "sales farmacéuticamente aceptables" se refiere a sales de los compuestos de la presente invención las cuales son sustancialmente no tóxicas para organismos vivos. Tales sales y metodología común para prepararlas son bien conocidas en la técnica. Véase, por ejemplo, P. Stahl, et al., Handbook of Pharmaceutical Salts: Properties Selection and Use, (VCHA/Wiley-VCH, 2002); y J. Pharm. Sci. 66, 2-19 (1977). Las sales farmacéuticamente aceptables preferidas incluyen clorhidrato, mesilato y fumarato; las sales más preferidas son clorhidrato y mesilato.

Los compuestos de la presente invención son formulados preferiblemente como composiciones farmacéuticas administradas por una variedad de vías. En forma más

preferible, tales composiciones son para administración oral. Tales composiciones farmacéuticas y procesos para preparar las mismas son bien conocidas en la técnica. Véase, por ejemplo, Remington: The Science and Practice of Pharmacy (A, Gennaro, et al., eds., 19th ed., Mack Publishing Co., 1995). Las composiciones farmacéuticas preferidas incluyen un compuesto de la presente invención mezcladas con vehículo seleccionado del grupo que consiste de ácido fosfórico 0.5 M (concentración máxima de 100 mg/ml); hidroxietilcelulosa (1% p/v), polisorbato 80 (0.25% v/v), antiespuma (0.05% v/v) y agua desionizada (concentración máxima de 110 mg/ml); y vitamina E TPGS (d-alfa-tocoferil polietilenglicol 1000 succinato) (10% v/v), antiespuma (0.05% v/v) y agua desionizada (concentración máxima de 250 mg/ml).

En un aspecto adicional de la invención, los presentes compuestos son administrados en combinación con uno o más ingredientes terapéuticos. Tales ingredientes terapéuticos incluyen por ejemplo metformina o un inhibidor de DPPIV, por ejemplo, sitagliptina.

La administración en combinación incluye administración simultánea, separada o secuencial.

Para la administración en combinación para el tratamiento de diabetes es preferido que los compuestos de la presente invención sean administrados simultáneamente, en forma separada o secuencialmente con metformina. Para la

administración en combinación para el tratamiento de obesidad es preferible que los compuestos de la presente invención sean administrados simultáneamente, en forma separada o secuencialmente con sitagliptina.

5 Los siguientes Esquemas de Reacción, Preparaciones y Ejemplos se proporcionan para aclarar mejor la práctica de la presente invención. Las condiciones de reacción adecuadas para las etapas de estos Esquemas de Reacción, Preparaciones y Ejemplos son bien conocidas en la técnica y la modificación
10 apropiada de condiciones de reacción, incluyendo la sustitución de solventes y co-reactivos está dentro de la capacidad de los artesanos expertos. Las temperaturas indicadas en las siguientes Preparaciones y Ejemplos corresponden a temperatura de baño externo, a menos que se
15 indique de otra forma.

Además, el artesano experto apreciará que en algunas circunstancias, el orden en el que se introducen las porciones no es crítico. El orden particular de etapas requeridas para producir los compuestos de la Fórmula I es
20 dependiente del compuesto particular que es sintetizado, el compuesto de partida, y la labilidad relativa de las porciones sustituidas, como es bien apreciado por el químico experto. El artesano experto apreciará que no todos los sustituyentes son compatibles con todas las condiciones de
25 reacción. Estos compuestos pueden ser protegidos o

20

modificados en un punto conveniente en la síntesis por métodos bien conocidos en la técnica.

Los grupos protectores adecuados incluyen aquéllos descritos en T.W. Greene, "Protective Groups in Organic
5 Synthesis", John Wiley and Sons, New York, N.Y., 1991, de aquí en adelante referido como "Greene". Greene indica las condiciones apropiadas para la "protección y "desprotección" de grupos protectores adecuados a ser usados por el artesano experto.

10 Los productos finales e intermediarios de la presente invención se pueden purificar, si se desea por técnicas comunes tales como recristalización o cromatografía sobre soportes sólidos tales como gel de sílice o alúmina.

Los nombres de compuestos para los Ejemplos de la
15 presente invención son generados usando AutoNom 2000.

Las abreviaturas usadas en la presente se definen como sigue:

"h" significa horas; "min" significa minutos; "cAMP" significa Monofosfato de Adenosina Cíclica; "DMEM" significa
20 Medio de Eagle Modificado de Dulbecco; "HTRF" significa Fluorescencia Resuelta con el Tiempo Homogénea; "PBS" significa Solución Salina Amortiguada de Fosfato; "IBMX" significa Isobutilmetilxantina; "BSA" significa Albúmina de Suero Bovino; "FBS" significa Suero de Bovino Fetal; "EBSS"
25 significa Solución de Sal Equilibrada de Earle; "EDTA"

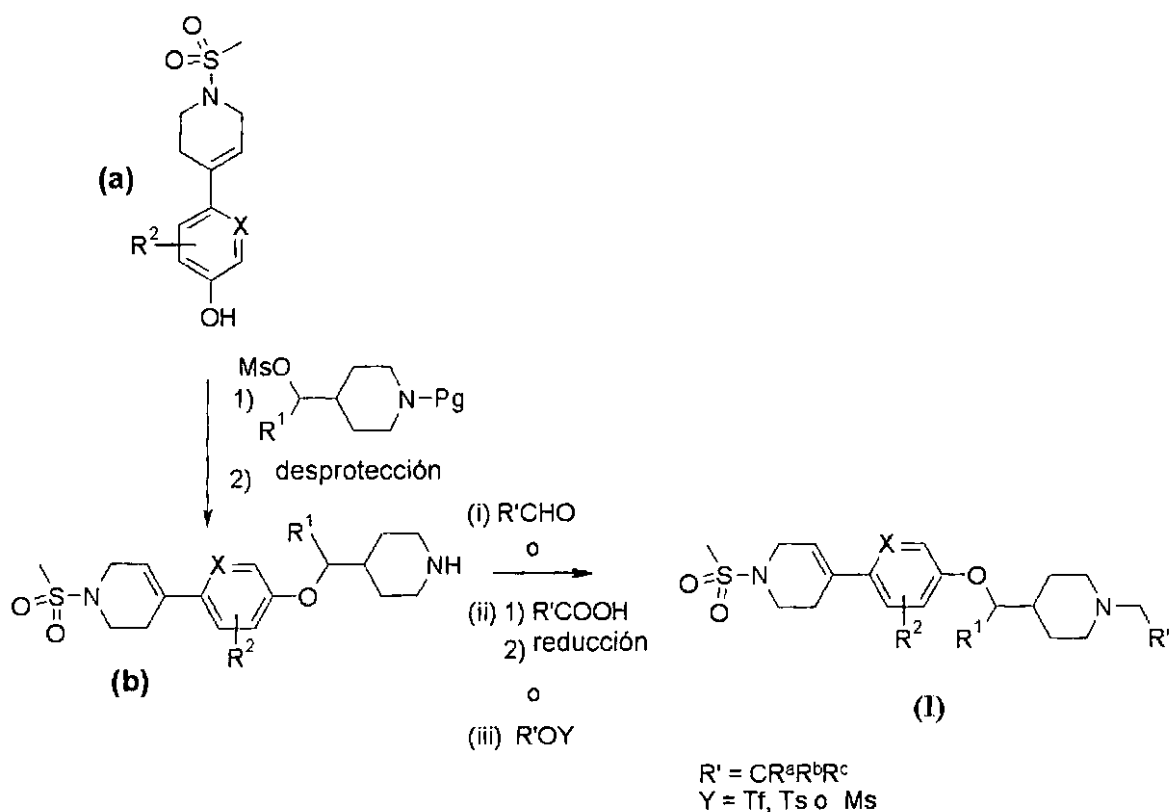
significa Ácido Tetraacético de Etilen Diamina; "NADPH" significa Fosfato de Dinucleótido de Nicotinamida Adenosina; "HEC" significa Hidroxietyl Celulosa; LC-ESI/MS" significa Cromatografía Líquida-Ionización por Electrorrocío/Espectrometría de Masa; "Pg" significa Grupo Protector; "Tf" significa trifluorometil sulfonilo; "Ts" significa para-toluen sulfonilo, y "Ms" significa metil sulfonilo.

Esquema de Reacción A

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El hidroxilo de partida (a) se hace reaccionar con un mesilato que lleva una piperidina con un grupo protector

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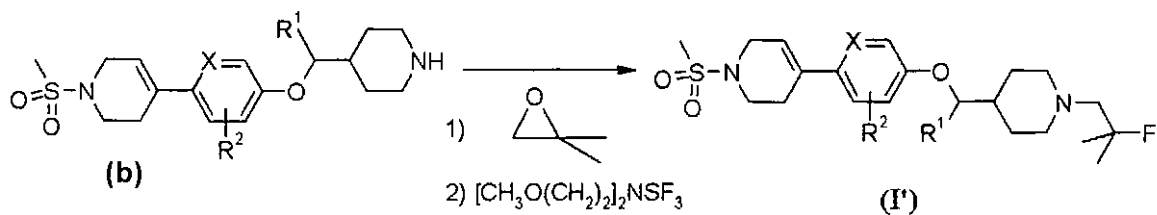
apropiado tal como éster terc-butílico del ácido carboxílico y una base adecuada tal como carbonato de potasio en un solvente adecuado tal como acetonitrilo a temperatura elevada. El producto aislado es desprotegido bajo condiciones bien conocidas para el artesano experto para proporcionar el compuesto (b). El compuesto (b) se hace reaccionar con un aldehído bajo condiciones de aminación reductiva estándar, con un agente reductor adecuado tal como triacetoxiborohidruro de sodio en un solvente adecuado tal como diclorometano para proporcionar el compuesto (I) final. Alternativamente, el compuesto (b) se hace reaccionar con un ácido sustituido apropiadamente usando un reactivo de acoplamiento tal como tetrafluoroborato de o-benzotriazol-1-il-*N,N,N',N'*-tetrametiluronio y una base adecuada tal como diisopropiletilamina en un solvente adecuado tal como dimetilformamida a temperatura elevada. El producto aislado se hace reaccionar con un agente reductor adecuado tal como hidruro de litio y aluminio en un solvente adecuado tal como tetrahidrofurano a temperatura elevada para proporcionar el compuesto (I) final. Alternativamente, el compuesto (b) se hace reaccionar con $R'OY$ y una base adecuada tal como carbonato de potasio en un solvente adecuado tal como acetonitrilo a temperatura elevada para proporcionar el compuesto (I) final.

Alternativamente, donde R^a es F y tanto R^b como R^c

son metilo los compuestos I' se pueden preparar como se describe posteriormente en el Esquema de Reacción B.

Esquema de Reacción B

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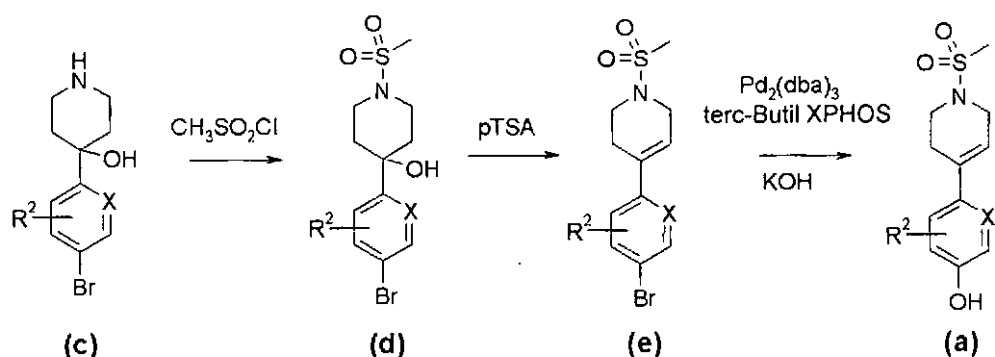


La piperidina (b) de partida se hace reaccionar con 2,2-dimetiloxirano bajo una atmósfera inerte tal como nitrógeno en un solvente adecuado tal como metanol. El producto aislado se hace reaccionar con un agente de fluoración adecuado tal como trifluoruro de bis(2-metoxietil)aminoazufre en un solvente adecuado tal como diclorometano para proporcionar el compuesto (I') final.

El hidroxilo (a) indispensable se puede preparar como se describe posteriormente en el Esquema C.

Esquema de Reacción C

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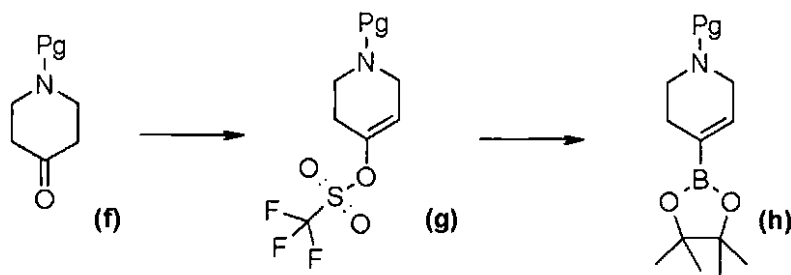
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La piperidin-4-ol (c) de partida se hace reaccionar con cloruro de metansulfonilo y una base adecuada tal como trietilamina o piridina en un solvente adecuado tal como diclorometano o tetrahidrofurano para proporcionar el compuesto (d). El compuesto (d) se hace reaccionar con ácido p-toluensulfónico en un solvente adecuado tal como tolueno a temperatura elevada para proporcionar la tetrahidro-piridina (e). El compuesto (e) se hace reaccionar por el método descrito en J. Am. Chem. Soc 2006, 128, 10694-10695 usando hidróxido de potasio, 2-di-terc-butilfosfino-2',4',6'-tri-i-propil-1,1'-bifenil y tris(dibencilidenacetona)dipaladio en un solvente adecuado tal como dioxano/agua a temperatura elevada para proporcionar el compuesto tetrahidro-piridina (a).

Alternativamente, el bromo (e) indispensable e hidroxilo (a) se pueden preparar como se describe en los Esquemas de Reacción D y E.

Esquema de Reacción D

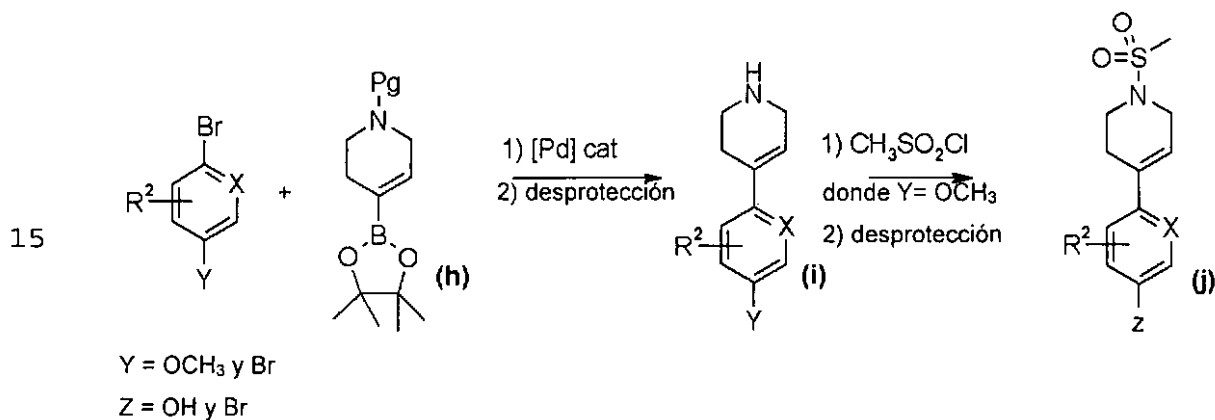


La piperidona (f) de partida se mezcla con una base

adecuada tal como diisopropilamida de litio en un solvente adecuado tal como tetrahidrofurano a temperatura reducida y se hace reaccionar con *N*-fenilbis(trifluorometansulfonimida) para proporcionar el compuesto (g). El compuesto tetrahidro-
 5 piridina (g) se hace reaccionar con bis-(pinacolato)diboro, cloruro de 1,1'-bis(difenilfosfino)ferroceno)paladio(II), 1,1'-bis(difenilfosfino)ferroceno, y acetato de potasio en un solvente adecuado tal como 1,4-dioxano a temperatura elevada para proporcionar el compuesto (h).

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Esquema de Reacción E



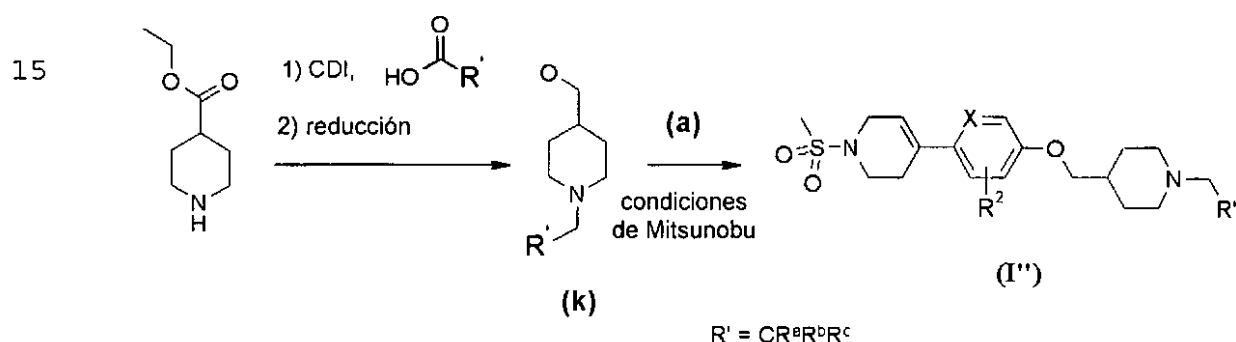
El bromuro de partida se hace reaccionar con un
 20 compuesto de boronato (h) que lleva un grupo protector apropiado tal como éster terc-butílico del ácido carboxílico, un catalizador de paladio adecuado tal como tetraquis(trifenil)fosfina)paladio y una base adecuada tal como carbonato de cesio en un solvente adecuado tal como
 25 dioxano/agua a temperatura elevada. El producto aislado es

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desprotegido bajo condiciones bien conocidas por el artesano experto para proporcionar el compuesto (i). El compuesto (i) se hace reaccionar con cloruro de metansulfonilo y una base adecuada tal como trietilamina en un solvente adecuado tal como diclorometano para proporcionar el compuesto (j). Donde el sustituyente Y es OCH₃, se requiere una etapa de desprotección adicional, usando condiciones bien conocidas para el artesano experto, para proporcionar el compuesto (j).

Alternativamente, los compuestos donde R¹ es H se pueden preparar como se describe posteriormente en el Esquema de Reacción F.

Esquema de Reacción F



20 Un ácido apropiadamente sustituido se hace reaccionar con 1,1'-Carbonildiimidazol en un solvente adecuado tal como tetrahidrofurano, al cual se adiciona éster etílico del ácido piperidin-4-carboxílico. El producto aislado se hace reaccionar con un agente reductor adecuado tal como hidruro de litio y aluminio en un solvente adecuado tal como

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tetrahidrofurano para proporcionar el compuesto (k). El compuesto (k) se hace reaccionar con el compuesto (a) usando condiciones de Mitsunobu estándar tales como azodicarboxilato de diisopropilo y trifenilfosfina, a temperatura reducida, en un solvente adecuado tal como tetrahidrofurano para proporcionar el compuesto final (I'').

Preparación 1

4-(1-Metansulfonil-1,2,3,6-tetrahidro-piridin-4-il)-fenol

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1: 4-(4-Bromo-fenil)-1-metansulfonil-piperidin-4-ol.

El cloruro de metansulfonilo (21.91 g, 14.81 mL, 191.30 mmol) se adiciona lentamente (10 min) a una solución 4-(4-bromofenil)-4-piperidinol (50.00 g, 191.30 mmol) y trietilamina (29.04 g, 40.00 mL, 286.95 mmol) en tetrahidrofurano (575 mL) a 23°C (temperatura interna) bajo atmósfera de nitrógeno. La mezcla se agitó a 23°C por 30 min. 500 mL de ácido clorhídrico ac. 1 M se adicionan y la mezcla se agita por 10 min. La mezcla se extrae con acetato de etilo (2 x 500 mL) las capas orgánicas se combinan, se secan sobre sulfato de sodio anhidro, se filtran y el solvente se remueve para obtener 60.0 g del compuesto del título como un sólido blanco. MS *m/e* (⁷⁹Br/⁸¹Br) 333, 335 (M+1).

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2: 4-(4-Bromo-fenil)-1-metansulfonil-1,2,3,6-tetrahidro-piridina.

Una mezcla de 4-(4-bromo-fenil)-1-metansulfonil-piperidin-4-ol (60.00 g, 179.51 mmol) y ácido p-toluensulfónico (9.37 g, 53.85 mmol) en tolueno (1.08 L) se agita a 100°C por 16 h. La reacción se enfría a 23°C y sucesivamente se lava con hidróxido de sodio ac. 2 M a pH 10, y agua. Las fases se separan y la capa orgánica se seca sobre sulfato de sodio anhidro, se filtran y el solvente se remueve. Se adiciona éter metil terc-butílico (200 mL) y el sólido se filtra y lava con éter metil terc-butílico para obtener 35.0 g del compuesto del título como un sólido café pálido. MS m/e ($^{79}\text{Br}/^{81}\text{Br}$) 315, 317 (M+1).

3: 4-(1-Metansulfonil-1,2,3,6-tetrahidro-piridin-4-il)-fenol.

Una mezcla de 4-(4-bromo-fenil)-1-metansulfonil-1,2,3,6-tetrahidro-piridina (23.50 g, 74.32 mmol), hidróxido de potasio (14.72 g, 222.95 mmol), 2-di-terc-butilfosfino-2',4',6'-tri-*i*-propil-1,1'-bifenil (2.52 g, 5.95 mmol) y tris(dibencilidenacetona)dipaladio (0) (1.36 g, 1.49 mmol) se purga con nitrógeno, y después se adicionan 1,4-dioxano desoxigenado (150 ml) y agua desoxigenada (150 ml). La mezcla se agita a 100°C por 1 h. La mezcla se enfría a 23°C y se adiciona ácido clorhídrico ac. 1 M hasta pH 2-3. La capa

acuosa se extrae con acetato de etilo. Las capas orgánicas se combinan, se secan sobre sulfato de sodio anhidro, se filtran, y el solvente se remueve para obtener un sólido rojo. Se adiciona éter dietílico y el sólido se filtra para
5 obtener 16 g del compuesto del título como un sólido descolorido. MS (m/z) 254 (M+1).

Preparación 2

1-Metansulfonil-4-[4-(piperidin-4-ilmetoxi)-fenil]-1,2,3,6-
10 tetrahidro-piridina

1: Éster terc-butílico del ácido 4-metansulfoniloximetil-piperidin-1-carboxílico.

El cloruro de metansulfonilo (29.26 g, 19.77 mL, 255.47 mmol) se adiciona lentamente (10 min) bajo atmósfera
15 de nitrógeno a una solución de 4-(hidroximetil)piperidin-1-carboxilato de terc-butilo (50.00 g, 232.24 mmol) y trietilamina (35.25 g, 48.56 mL, 348.36 mmol) en diclorometano anhidro (700 mL) a 9°C (temperatura interna).
20 La mezcla se agita a 23°C por 16 h. La mezcla de reacción se lava sucesivamente con ácido clorhídrico ac. 1 M, agua, y salmuera. La capa orgánica se seca sobre sulfato de sodio anhidro, se filtra, y el solvente se remueve para obtener 60 g del compuesto del título como un sólido blanco. MS (m/z)
25 316 (M+23).

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2: Éster terc-butílico del ácido 4-[4-(1-Metansulfonil-1,2,3,6-tetrahidro-piridin-4-il)-fenoximetil]-piperidin-1-carboxílico.

Una mezcla de éster terc-butílico del ácido 4-
5 metansulfoniloximetil-piperidin-1-carboxílico (17.95 g, 61.19 mmol), Preparación 1 (15.50 g, 61.19 mmol) y carbonato de potasio (16.91 g, 122.37 mmol) en acetonitrilo (120 mL) se calienta bajo reflujo por 18 h. La reacción se enfría a 23°C y el solvente se remueve. El residuo se disuelve con una
10 mezcla de 1 L de diclorometano y 500 mL de agua y las fases se separan. La capa orgánica se lava con salmuera, se seca sobre sulfato de sodio, se filtra y evapora. El sólido obtenido se trata con 250 mL de éter metil terc-butílico para producir 22.0 g del producto del título. MS (m/z) 473 (M+23).

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3: 1-Metansulfonil-4-[4-(piperidin-4-ilmetoxi)-fenil]-1,2,3,6-tetrahidro-piridina.

El ácido trifluoroacético (2.98 g, 1.97 mL, 26.10 mmol) se adiciona a una solución de éster terc-butílico del
20 ácido 4-[4-(1-metansulfonil-1,2,3,6-tetrahidro-piridin-4-il)-fenoximetil]-piperidina-1-carboxílico (1.20 g, 2.61 mmol) en diclorometano (13 mL). La mezcla se agita a 23°C por 30 min., se adiciona hidróxido de sodio ac. 2 M. El precipitado blanco resultante se filtra y se lava con agua. El licor madre se
25 extrae con diclorometano. Las capas orgánicas combinadas se

secan sobre sulfato de sodio anhidro, se filtran, y el
solvente se remueve para obtener un sólido blanco el cual se
combina con el precipitado inicial y se seca bajo alto vacío
por 16 h. Se adiciona éter dietílico y el sólido se filtra y
5 lava con acetato de etilo para obtener 0.810 g de un sólido
descolorido. MS (m/z) 351 (M+1).

Preparación 3

Éster terc-butílico del ácido 4-(4,4,5,5-Tetrametil-
10 [1,3,2]dioxaborolan-2-il)-3,6-dihidro-2*H*-piridina-1-
carboxílico

1: Éster terc-butílico del ácido 4-trifluorometansulfoniloxi-
3,6-dihidro-2*H*-piridin-1-carboxílico.

15 En un matraz de 3 cuellos con embudo adicional,
sonda de temperatura y agitador magnético, una solución de
diisopropilamina (32.30 g, 44.93 mL, 319.20 mmol) en
tetrahidrofurano (160 mL) se enfría a -10°C (temperatura
interna). El n-butil litio (133.0 mL, 332.50 mmol, 2.5 M en
20 hexanos) se adiciona por goteo (10 min, cambia la temperatura
de -10°C hasta 1°C). La mezcla se agita a -10°C por 10 min, y
luego se enfría a -60°C (temperatura interna, baño a -75°C).
Una solución de *N*-terc-butoxicarbonil-4-piperidona (53.00 g,
266.00 mmol) en tetrahidrofurano (160 mL) se adiciona por
25 goteo (10 min). La mezcla se agita a -60°C por 1.5 h, una

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solución de *N*-fenilbis(trifluorometansulfonimida) (99.78 g, 279.30 mmol) en tetrahidrofurano (160 mL) se adiciona por goteo a -60°C (5 min). Se adiciona más tetrahidrofurano (40 mL) y la mezcla se deja calentar a 23°C por 16 h. Se adiciona
5 a la mezcla bicarbonato de sodio ac. saturado (400 mL), la cual después se extrae con acetato de etilo (3 x 400 mL). Las capas orgánicas combinadas se lavan con salmuera, se secan sobre sulfato de magnesio anhidro, se filtran y se concentran. La mezcla resultante se hace pasar a través de un
10 tapón de gel de sílice, eluyendo con hexano:acetato de etilo 4:1 para producir 78.00 g del compuesto del título como un aceite amarillo. El material se usa en la siguiente etapa sin purificación adicional. ¹H NMR (CDCl₃) δ (ppm): 1.47 (s, 9H), 2.43-2.47 (m, 2H), 3.63 (t, 2H), 4.03-4.11 (m, 2H), 5.76 (s,
15 1H).

2. Éster terc-butílico del ácido 4-(4,4,5,5-Tetrametil-[1,3,2]dioxaborolan-2-il)-3,6-dihidro-2*H*-piridina-1-carboxílico.

20 El éster terc-butílico del ácido 4-trifluorometansulfonilo-3,6-dihidro-2*H*-piridin-1-carboxílico (235.43 mmol; 78.00 g) se disuelve en 1,4-dioxano (1170 mL) y la solución se desgasifica por 5 min. Se adicionan Bis(pinacolato)diboro (65.76 g, 258.97 mmol), 1,1'-
25 bis(difenilfosfino)ferroceno (6.53 g, 11.77 mmol), cloruro de

(1,1'-bis(difenilfosfino)ferroceno)paladio(II) (9.61 g, 11.77 mmol) y acetato de potasio (69.32 g, 706.28 mmol), y la mezcla se agita bajo nitrógeno a 85°C por 3 h. La mezcla se enfría a 23°C y se agita por 16 h. La mezcla se filtra a través de tierra diatomácea, se lava con acetato de etilo, y se concentra in vacuo. El producto crudo se purifica por cromatografía instantánea sobre gel de sílice, eluyente hexano:acetato de etilo (12:1 a 4:1) para producir 72.00 g del compuesto del título, el cual se usa en la siguiente etapa sin purificación adicional. MS (m/z) 254 (M-55).

Preparación 4

Éster terc-butílico del ácido 4-(1-Metansulfoniloxi-etil)-piperidin-1-carboxílico

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1: Éster terc-butílico del ácido 4-(1-Hidroxi-etil)-piperidin-1-carboxílico.

A una solución de *N*-terc-butoxicarbonil-4-piperidincarboxaldehído (32.20 g, 151.45 mmol) en tetrahidrofurano a -78°C se adiciona bromuro de metil magnesio (2 M en éter dietílico, 100.96 mL, 302.89 mmol). La reacción se agita a -78 °C por 4.5 h, y después se calienta a -50°C por 30 min. La reacción se apaga con agua a -50°C y se deja calentar a temperatura ambiente por 16 h. Los solventes se remueven y el material se divide entre éter dietílico y

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ácido clorhídrico 0.1 M. La mezcla se extrae con éter dietílico. Las capas orgánicas combinadas se lavan con ácido clorhídrico 0.1 M, bicarbonato de sodio acuoso saturado y salmuera, se secan sobre sulfato de magnesio, se filtran y se
5 concentran a sequedad. El producto crudo se purifica por cromatografía instantánea sobre gel de sílice para producir 16.90 g del compuesto del título como un aceite incoloro. MS (m/z) 229 (M+1).

10 2: Éster *terc*-butílico del ácido 4-(1-metansulfonilo-*etil*)-piperidin-1-carboxílico.

A una solución de éster *terc*-butílico del ácido 4-(1-hidroxio-*etil*)-piperidin-1-carboxílico (18.24 g, 79.54 mmol) en diclorometano (400 mL) y trietilamina (12.20 mL, 87.49 mmol) a 0°C se adiciona cloruro de metansulfonilo (9.23 mL, 119.30 mmol). La reacción se deja calentar a temperatura ambiente por 16 h. La mezcla se calienta con ácido clorhídrico 0.1 M, bicarbonato de sodio acuoso saturado, agua, y salmuera. El material se seca sobre
20 sulfato de magnesio, se filtra, y se concentra a sequedad. El material crudo se purifica por cromatografía instantánea sobre gel de sílice para producir 22.65 g del compuesto del título como aceite incoloro. ¹H NMR (CDCl₃) δ (ppm): 1.19-1.30 (m, 2H), 1.39 (d, 3H), 1.44 (s, 9H), 1.6-
25 1.8 (m, 3H), 2.66 (m, 2H), 2.99 (s, 3H), 4.16 (m, 2H), 4.62

(t, 1H).

Preparación 5

4-{1-[4-(1-Metansulfonil-1,2,3,6-tetrahidro-piridin-4-il)-
5 fenoxi]-etil}-piperidina

1: Éster terc-butílico del ácido 4-{1-[4-(1-Metansulfonil-1,2,3,6-tetrahidro-piridin-4-il)-fenoxi]-etil}-piperidin-1-carboxílico.

10 A una solución de la Preparación 1 (2.35 g, 9.27 mmol) y Preparación 4 (2.85 g, 9.27 mmol) en acetonitrilo (93.00 mL) se adiciona carbonato de cesio (3.02 g, 9.27 mmol) y 18-corona-6 (0.49 g, 1.85 mmol). La mezcla se calienta a 80°C por 72 h. La mezcla se concentra in vacuo y el material
15 remanente se divide entre acetato de etilo y agua. La capa orgánica se lava con hidróxido de sodio 1 M y salmuera. El material se seca sobre sulfato de magnesio, se filtra, y se concentra a sequedad. El material resultante se diluye con 10 mL de éter dietílico, es sonificado por 3 min, y el sólido
20 remanente se filtra, y se seca bajo vacío para producir 2.02 g del producto del título como un sólido blanco. MS (m/z) 487 (M+32), 365 (M-55).

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2: 4-{1-[4-(1-Metansulfonil-1,2,3,6-tetrahidro-piridin-4-il)-fenoxi]-etil}-piperidina.

A una solución de éster *terc*-butílico del ácido 4-{1-[4-(1-metansulfonil-1,2,3,6-tetrahidro-piridin-4-il)-fenoxi]-etil}-piperidin-1-carboxílico (1.16 g, 2.50 mmol) en diclorometano (25 mL) se adiciona ácido trifluoroacético (1.32 mL, 17.48 mmol). La reacción se agita a temperatura ambiente por 18 h. La mezcla se concentra in vacuo y se diluye con 3 mL de acetato de etilo. Se adiciona hidróxido de sodio acuoso 2 M para producir un sólido blanco. El sólido se filtra y se seca para producir 0.86 g del compuesto del título. MS (m/z) 365 (M+1). El compuesto del título (0.320 g, 0.88 mmol) se separa en sus enantiómeros usando un eluyente de 0.2% dimetiletilamina en 2:3 acetonitrilo:metanol sobre una columna de 4.6 x 150 mm Chiralcel AD-H a 1mL/min para producir 0.115 g del isómero 1 (100%ee, RT = 5.27 min). MS (m/z) 365 (M+1) y 0.112 g del isómero 2 (100%ee, RT = 8.59 min). MS (m/z) 365 (M+1).

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Preparación 6

Sal de diclorhidrato de 4-(1'-Metansulfonil-1',2',3',6'-tetrahidro-[2,4']bipiridinil-5-iloximetil)-piperidinio

1: Éster *terc*-butílico del ácido 5-Bromo-3',6'-dihidro-2'H-[2,4']bipiridinil-1'-carboxílico.

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Una mezcla de 2,5-dibromopiridina (50.00 g, 211.07

mmol), Preparación 3 (71.79 g, 232.17 mmol), carbonato de sodio acuoso 2 M (158.30 mL, 316.60 mmol) y tetrakis(trifenilfosfina)paladio (0) (7.32 g, 6.33 mmol) en 1,4-dioxano (633 mL) se calienta a 100°C bajo una atmósfera de nitrógeno durante la noche. La reacción se deja enfriar a temperatura ambiente, se filtra a través de tierra diatomácea y se lava con acetato de etilo. La capa orgánica se lava con 500 mL de agua, se seca sobre sulfato de magnesio, se filtra y se evapora. El material crudo se purifica por cromatografía de gel de sílice eluyendo con hexano:acetato de etilo 6:1 para producir 55 g de un sólido blanco. MS m/e ($^{79}\text{Br}/^{81}\text{Br}$) 339, 341 (M+1 de ambos isótopos).

2: Sal de diclorhidrato de 5-Bromo-1',2',3',6'-tetrahidro-[2,4']bipiridinil-1'-o.

Se adiciona cloruro de hidrógeno 4 M (170.24 g, 162.13 mL, 648.52 mmol) en 1,4-dioxano a una solución de éster *terc*-butílico del ácido 5-bromo-3',6'-dihidro-2'*H*-[2,4']bipiridinil-1'-carboxílico (55.00 g, 162.13 mmol) en diclorometano (810 mL). La mezcla se agita a temperatura ambiente por 12 h y se calienta a 40°C por 6 h. La mezcla se evapora y el sólido se filtra y se lava con éter metil *t*-butílico. El sólido se seca en un horno a 40°C por 12 h para proporcionar 50 g del compuesto del título. MS m/e ($^{79}\text{Br}/^{81}\text{Br}$) 238/240 (M+1).

3: 5-Bromo-1'-metansulfonil-1',2',3',6'-tetrahidro-[2,4']bipiridinilo.

El compuesto del título se prepara esencialmente por el método de Preparación 1 (etapa 1) usando sal de
5 diclorhidrato de 5-bromo-1',2',3',6'-tetrahidro-[2,4']bipiridinil-1'-o como el material de partida. MS m/e ($^{79}\text{Br}/^{81}\text{Br}$) 316/318 (M+1).

4: 1'-Metansulfonil-1',2',3',6'-tetrahidro-[2,4']bipiridinil-
10 5-ol.

El compuesto del título se prepara esencialmente por el método de Preparación 1 (etapa 3) usando 5-bromo-1'-metansulfonil-1',2',3',6'-tetrahidro-[2,4']bipiridinilo como el material de partida. MS (m/z) 255 (M+1).
15

5: Éster terc-butílico del ácido 4-(1'-Metansulfonil-1',2',3',6'-tetrahidro-[2,4']bipiridinil-5-iloximetil)-piperidin-1-carboxílico.

El compuesto del título se prepara esencialmente por el método de Preparación 2 (etapa 2) usando 1'-metansulfonil-1',2',3',6'-tetrahidro-[2,4']bipiridinil-5-ol como el material de partida. MS (m/z) 452 (M+1).
20

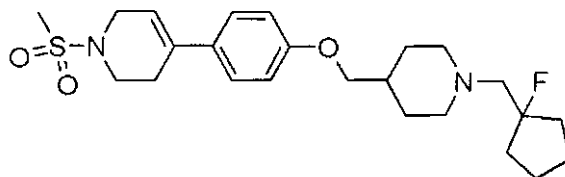
6: Sal de diclorhidrato de 4-(1'-Metansulfonil-1',2',3',6'-tetrahidro-[2,4']bipiridinil-5-iloximetil)-piperidinio.

25 El compuesto del título se prepara esencialmente

como en la etapa 2 de esta Preparación. MS (m/z) 352 (M+1)

Ejemplo 1

4-{4-[1-(1-Fluoro-ciclopentilmetil)-piperidin-4-ilmetoxi]-
5 fenil}-1-metansulfonil-1,2,3,6-tetrahidro-piridina



10 1: 1-Oxa-espiro[2.4]heptan-2-carbonitrilo.

Una solución 1 M de *tert*-butóxido de potassium en alcohol *tert*-butílico (184.4 mL, 184.4 mmol) se adiciona lentamente a una solución de cloroacetonitrilo (10.8 mL, 167.6 mmol) y ciclopentanona (15.0 mL, 167.6 mmol) en alcohol
15 *t*-butílico anhidro (33 mL). La reacción se agita a temperatura ambiente por 16 h. La mezcla se filtra a través de tierra diatomácea, el solvente se remueve, y el residuo es diluido con agua. La mezcla se neutraliza con solución de fosfato diácido de sodio ac. al 30% y se extrae con éter
20 dietílico. Las capas orgánicas se combinan, se secan sobre sulfato de sodio anhidro, se filtran, y el solvente se remueve. El residuo se purifica por cromatografía instantánea sobre gel de sílice para obtener 14.1 g del compuesto del título como aceite incoloro. ¹H NMR (CDCl₃) δ (ppm): 3.46 (s,
25 1H), 1.65-2.20 (m, 8H).

2: (1-Fluoro-ciclopentil)-hidroxi-acetonitrilo.

El diclorometano anhidro (3 mL) y una solución al 70% p/p de fluoruro de hidrógeno (2.68 mL, 20.44 mmol) en piridina se mezclan en una botella de polietileno a 0°C bajo una atmósfera de nitrógeno. Se adiciona lentamente una solución de 1-oxa-espiro[2.4]heptan-2-carbonitrilo (3.30 g, 26.76 mmol) en diclorometano anhidro (3.2 mL). La reacción se agita a 0°C por 1h y a temperatura ambiente por 1h. La mezcla se enfría a 0°C y se adiciona cuidadosamente una solución saturada de carbonato de sodio. La capa acuosa se extrae con éter dietílico. Las capas orgánicas se combinan, se lavan con agua y salmuera, se secan sobre sulfato de sodio anhidro, se filtran, y el solvente se remueve. El residuo se purifica por cromatografía en un cartucho con 20 g de gel de sílice eluyendo con hexano:éter dietílico (100:0 a 80:20) para obtener 1.7 g del compuesto deseado como aceite incoloro. ¹H NMR (CDCl₃) δ (ppm): 4.47 (d, 1H), 3.50 (bs, 1H), 2.12-1.67 (m, 8H).

3: 1-Fluoro-ciclopentancarbaldehído.

Una solución al 25% de hidróxido de sodio (7.00 mL, 72.8 mmol) en agua se adiciona a una solución de (1-fluoro-ciclopentil)-hidroxi-acetonitrilo (0.50 g, 3.5 mmol) en etanol (10 mL) y la reacción se agita a temperatura ambiente por 15 min. La mezcla se diluye con agua y éter dietílico y

la capa acuosa se extrae con éter dietílico. Las capas orgánicas se combinan, se lavan con agua y salmuera, se secan sobre sulfato de sodio anhidro, se filtran, y el solvente se remueve bajo vacío para obtener 430 mg de un aceite amarillo que es usado sin purificación adicional.

4: 4-{4-[1-(1-Fluoro-ciclopentilmetil)-piperidin-4-ilmetoxi]-fenil}-1-metansulfonil-1,2,3,6-tetrahidro-piridina.

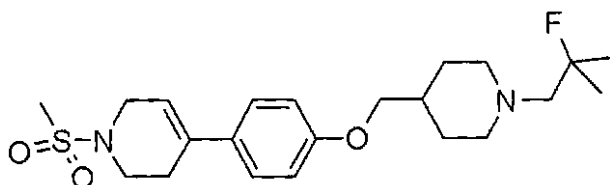
Se adicionan ácido acético (0.024 mL, 0.42 mmol) y 1-fluoro-ciclopentancarbaldehído (0.367 mL, 3.70 mmol) a una suspensión de la Preparación 2 (150 mg, 0.427 mmol) en diclorometano (4 mL) y la mezcla se agita a 40°C por 45 min. Se adiciona triacetoxiborohidruro (236.22 mg, 1.07 mmol) y la mezcla se agita a 40°C por 1.5 h. Se adiciona la solución acuosa saturada de bicarbonato de sodio y la mezcla se extrea con acetato de etilo. Las capas orgánicas se combinan, se lavan con agua y salmuera, se secan sobre sulfato de sodio anhidro, se filtran, y el solvente se remueve. El residuo se somete a cromatografía sobre un cartucho con 10 g de gel de sílice eluyendo con diclorometano:acetato de etilo 20%, 50%, y 100% para obtener un sólido amarillo pálido. El compuesto se tritura con éter dietílico y se filtra para obtener 25 mg del compuesto del título como un sólido blanco. MS (m/z) 451 (M+1).

51

Ejemplo 2

4-{4-[1-(2-Fluoro-2-metil-propil)-piperidin-4-ilmetoxi] -
fenil}-1-metansulfonil-1,2,3,6-tetrahidro-piridina

5



1: 2-Fluoro-1-{4-[4-(1-metansulfonil-1,2,3,6-tetrahidro-
piridin-4-il)-fenoximetil]-piperidin-1-il}-2-metil-propan-1-
10 ona.

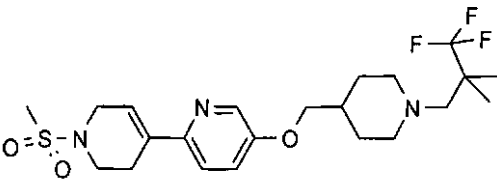
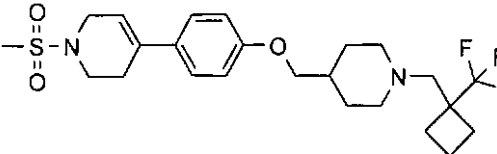
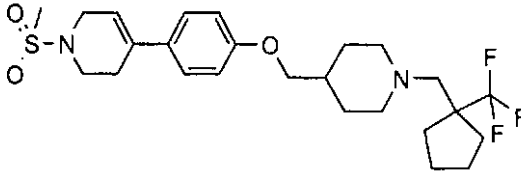
Se adiciona diisopropiletilamina (1.60 g, 2.16 mL,
12.40 mmol) a una suspensión de la Preparación 2 (1.60 g,
4.13 mmol), tetrafluoroborato de o-benzotriazol-1-il-
N,N,N',N'-tetrametiluronio (1.99 g, 6.20 mmol) y ácido 2-
15 fluoro-2-metil-propiónico (0.48 g, 0.54 mL, 4.55 mmol) en
dimetilformamida anhidra (20 mL) y la mezcla se agita a 40°C
por 1 h. La mezcla de reacción se diluye con acetato de
etilo y se lava sucesivamente con ácido clorhídrico
acuoso 1 M, agua, e hidróxido de sodio acuoso 2 M. La
20 capa orgánica se seca sobre sulfato de sodio anhidro,
se filtra, y el solvente se remueve. El residuo se
purifica por cromatografía de gel de sílice sobre un
cartucho de gel de sílice eluyendo con
diclorometano:acetato de etilo 0%, 5% después 10% para
25 obtener 1.0 g del compuesto del título como un sólido café

pálido. MS (m/z) 439 (M+1).

2: 4-{4-[1-(2-Fluoro-2-metil-propil)-piperidin-4-ilmetoxi]-fenil}-1-metansulfonil-1,2,3,6-tetrahidro-piridina.

5 A una solución de 2-fluoro-1-{4-[4-(1-metansulfonil-1,2,3,6-tetrahidro-piridin-4-il)-fenoximetil]-piperidin-1-il}-2-metil-propan-1-ona (1.00 g, 2.28 mmol) en tetrahidrofurano (23 mL) a temperatura ambiente se adiciona vía cánula una solución 1 M de hidruro de litio y aluminio en
10 tetrahidrofurano (7.18 g, 7.98 mL, 7.98 mmol). Después de 1 h, se adiciona cuidadosamente decahidrato de sulfato de sodio. La mezcla se agita por 15 min y el sólido se filtra y se lava con diclorometano. El solvente se remueve y el residuo se purifica por cromatografía de gel de sílice,
15 eluyendo con diclorometano:acetato de etilo 5.6:1 a 2:1 para obtener un sólido. Se adiciona éter dietílico y el sólido se filtra y se lava con éter dietílico y acetato de etilo para obtener 0.245 g del compuesto del título como un sólido blanco. MS (m/z) 425 (M+1).

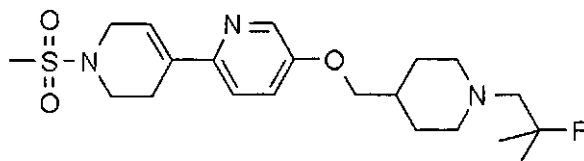
20 Los siguientes compuestos se preparan esencialmente por los mismos métodos como se indican en el Ejemplo 2.

Ejemplo	Nombre químico / estructura	MS (m/z)
3	 1'-Metansulfonil-5-[1-(3,3,3-trifluoro-2,2-dimetil-propil)-piperidin-4-ilmetoxi]-1',2',3',6'-tetrahidro-[2,4']bipiridinilo	476 (M+1)
4	 1-Metansulfonil-4-{4-[1-(1-trifluorometil-ciclobutilmetil)-piperidin-4-ilmetoxi]-fenil}-1,2,3,6-tetrahidro-piridina	487 (M+1)
5	 1-Metansulfonil-4-{4-[1-(1-trifluorometil-ciclopentilmetil)-piperidin-4-ilmetoxi]-fenil}-1,2,3,6-tetrahidro-piridina	501 (M+1)

Ejemplo 6

5-[1-(2-Fluoro-2-metil-propil)-piperidin-4-ilmetoxi]-1'-metansulfonil-1',2',3',6'-tetrahidro-[2,4']bipiridinilo

5



1: 4-(1'-Metansulfonil-1',2',3',6'-tetrahidro-[2,4']bipiridinil-5-iloximetil)-piperida.

10 La Preparación 6 (47 g, 114.5 mmol) se disuelve en solución acuosa 2 M de hidróxido de sodio (500 mL) y se extrae con diclorometano (2 x 500 mL). La capa orgánica se seca sobre sulfato de magnesio, se filtra y se evapora para obtener 40 g del compuesto del título como un sólido amarillo
15 claro. MS (m/z) 352 (M+1).

2: 1-[4-(1'-Metansulfonil-1',2',3',6'-tetrahidro-[2,4']bipiridinil-5-iloximetil)-piperidin-1-il]-2-metilpropan-2-ol

20 A una solución de 4-(1'-metansulfonil-1',2',3',6'-tetrahidro-[2,4']bipiridinil-5-iloximetil)-piperida (40 g, 113.81 mmol) en metanol (230 mL) a 25°C bajo atmósfera de nitrógeno se adiciona 2,2-dimetiloxirano (15.18 mL; 170.71 mmol) en una porción y la reacción se agita a 25°C por 16 h.
25 Se adiciona agua (500 mL) y el precipitado se filtra, se lava

53

con éter metil *t*-butílico (250 mL) y se seca para obtener 33 g del compuesto del título como un sólido amarillo claro. MS (m/z) 424 (M+1).

5 **3:** 5-[1-(2-Fluoro-2-metil-propil)-piperidin-4-ilmetoxi]-1'-metansulfonil-1',2',3',6'-tetrahidro-[2,4']bipiridinilo

A una solución de 2-metil-1-[4-[[6-(1-metilsulfonil-3,6-dihidro-2H-piridin-4-il)-3-piridil]oximetil]-1-piperidil]propan-2-ol (33 g; 77.91
10 mmoles) en diclorometano (155 mL) se adiciona trifluoruro de bis(2-metoxietil)aminoazufre (16.63 mL; 85.70 mmoles) a una temperatura interna de 22-23°C. La reacción se agita a 25°C por 2 h. La solución saturada acuosa de bicarbonato de sodio se adiciona a pH 7. Las capas se separan, la capa acuosa se
15 extrae con diclorometano (2 x 500 mL), las capas orgánicas combinadas se secan sobre sulfato de magnesio, se filtran y se concentran. El material crudo se purifica por cromatografía sobre gel de sílice eluyendo con 98:2 diclorometano:metanol. El sólido se tritura con 500 mL de
20 éter metil *t*-butílico y se filtra. El sólido se seca en un horno a 40°C por 3 días para obtener 24 g del compuesto del título como un sólido blanco. MS (m/z) 426 (M+1).

Un método alternativo para la Preparación del Ejemplo 6 es como sigue:

1: Éster terc-butílico del ácido 4-[4-(1-metansulfonil-1,2,3,6-tetrahidro-piridin-4-il)-fenoximetil]-piperidin-1-carboxílico

A un matraz de 3 cuellos con un agitador mecánico se adiciona éster terc-butílico del ácido 4-(1-hidroximetil)-piperidin-1-carboxílico (350 g, 1.63 mol), trietilamina (247 g, 2.44 mol) y diclorometano (1750 mL). La solución se agita a 0°C por 30 min. El cloruro de metansulfonilo (223.5 g, 1.95 mol) se adiciona lentamente a 0~5°C. La mezcla se agita a ~5°C por 1.5h. 1050 mL de solución 0.5 N de clorhidrato ac. se adicionan a la mezcla por goteo a 0~15°C y la solución resultante se agita por 30 min. Las capas se separan y la capa orgánica se lava con 1050 mL de agua y se concentra a sequedad. 700 mL de éter metil terc-butílico se adicionan y la mezcla se somete a reflujo por 0.5 h. Después de que la mezcla se enfría lentamente a ~5°C, la suspensión se filtra. El sólido se agita con 500 mL de éter metil terc-butílico y se filtra a sequedad para proporcionar 434 g de un sólido blancuzco con 98.6% de pureza por HPLC.

2: Éster terc-butílico del ácido 4-(1'-metansulfonil-1',2',3',6'-tetrahidro-[2,4']bipiridinil-5-iloximetil)-piperidin-1-carboxílico

A un matraz de 3 cuellos se adiciona 1'-

SA

metansulfonil-1',2',3',6'-tetrahidro-[2,4']bipiridinil-5-ol
 (254.3 g, 1.0 mol) seguido por éster terc-butílico del ácido
 4-(1-metansulfoniloxi-etil)-piperidin-1-carboxílico (396.1
 g, 1.34 mol) y carbonato de potasio (248.8 g, 1.8 mol). Se
 5 adiciona dimetilformamida (3800 mL) y la mezcla se calienta a
 80~90°C por 6 h. 3810 mL de agua se adicionan por goteo a
 70~80°C. La mezcla se enfría lentamente 20~30°C y se filtra.
 La torta se hace pasta aguada con 1000 mL de agua, se
 concentra y se seca bajo vacío para proporcionar 407 g de un
 10 sólido con 97.13% de pureza por HPLC.

3: 4-(1'-Metansulfonil-1',2',3',6'-tetrahidro-
 [2,4']bipiridinil-5-iloximetil)-piperidina

A un matraz de 3 cuellos con un agitador mecánico
 15 se adiciona éster terc-butílico del ácido 4-(1'-
 metansulfonil-1',2',3',6'-tetrahidro-[2,4']bipiridinil-5-
 iloximetil)-piperidin-1-carboxílico (407 g, 0.90 mol) y
 cloruro de hidrógeno ac. 6N (2000 mL, 12.0 mol) se adiciona
 por goteo a 25°C. La mezcla se agita mecánicamente a 25°C por
 20 0.5 h. 1000 mL de diclorometano se adicionan a 25°C y la
 mezcla se agita por 20~30 min. Las capas se separan y NaOH
 acuoso (1500 mL, 11.6 mol) se adiciona por goteo a la
 solución acuosa a pH=9~10 a 25°C. 3200 mL de diclorometano se
 adicionan y la mezcla se agita a 25~30°C por 40 min. La
 25 solución acuosa de NaOH (300 mL, 2.3 mol) se adiciona por

goteo a pH >14, hasta que se completa la disolución del sólido, la solución se agita por 20 a 30 min y las capas se separan. La capa acuosa se extrae con 1700 mL de diclorometano. Las capas orgánicas combinadas se lavan con 5 900 mL de agua y se concentran. El residuo se usa para la siguiente etapa sin purificación adicional.

4: 1-[4-(1'-Metansulfonil-1',2',3',6'-tetrahidro-[2,4']bipiridinil-5-iloimetil)-piperidin-1-il]-2-metil-
10 propan-2-ol

La 4-(1'-Metansulfonil-1',2',3',6'-tetrahidro-[2,4']bipiridinil-5-iloimetil)-piperidina se suspende en 800 mL de metanol y se adiciona a un autoclave con un agitador mecánico. Se adicionan 1500 mL de metanol y después se
15 adiciona dimetiloóxirano (117 g, 1.62 mol). La mezcla se agita a 60~70°C por 88 h, se enfría a 25~30°C y se concentra a ~1000 mL. La mezcla se calienta a 60~70°C y se adicionan 4200 mL de agua. La mezcla resultante se agita a 60~70°C durante 30 min y se enfría lentamente a 0~5°C en 1.5~2h. La misma se
20 agita a esta temperatura por 30 minutos y se filtra. La torta se hace pasta aguada con H₂O: MeOH=3:1 (600 mL) preenfriada a 0~5°C y se concentra (2x). El producto se seca bajo vacío a 40~50°C para proporcionar 320 g de sólido blancuzco con 98.3% de pureza por HPLC.

S

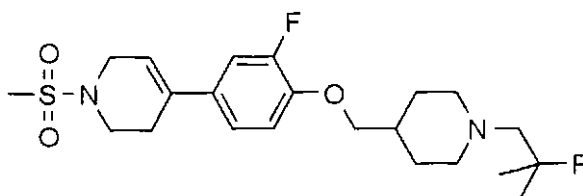
5: 5-[1-(2-Fluoro-2-metil-propil)-piperidin-4-ilmetoxi]-1'-metansulfonil-1',2',3',6'-tetrahidro-[2,4']bipiridinilo

El 1-[4-(1'-Metansulfonil-1',2',3',6'-tetrahidro-
 5 [2,4']bipiridinil-5-iloximetil)-piperidin-1-il]-2-metil-propan-2-ol (300 g, 0.58 mol) se disuelve en 3000 mL de diclorometano y la solución se concentra a volumen de 1 L a <35°C. Este proceso se repite con un volumen de 500 mL de diclorometano y después con un volumen de 1000 mL de
 10 diclorometano. Después de la concentración a volumen de 1 L a <35°C, la solución se diluye con 1000 mL de diclorometano. En otro matraz el desoxofluor (173 g, 0.74 mol) se disuelve en 1250 mL de diclorometano y se enfría a -30~-40°C. La solución de
 15 1-[4-(1'-metansulfonil-1',2',3',6'-tetrahidro-[2,4']bipiridinil-5-iloximetil)-piperidin-1-il]-2-metil-propan-2-ol en diclorometano se adiciona a esta solución mientras que se mantiene la mezcla a -30~-40°C. La reacción se calienta lentamente a 20~30°C y se agita a esta temperatura por 16 h. La mezcla se enfría a 0~10°C y la solución saturada de
 20 bicarbonato de sodio se adiciona por goteo a pH=6.0~6.5. La mezcla se agita por 30 30 min y las capas se separan. La capa acuosa se extrae con 1000 mL de diclorometano. Las capas orgánicas combinadas se lavan con 1000 mL de agua y se concentran a ~1L de mezcla a <50°C. 1750 mL de acetonitrilo
 25 se adicionan y la mezcla se concentra a ~1 L de mezcla a

<50°C. 500 mL de acetonitrilo se adicionan y la mezcla se calienta a 80~82°C por 30 min para obtener una solución clara. 1250 mL de agua se adicionan por goteo a 80~82°C y la mezcla se enfría lentamente a 20~30°C. La suspensión
 5 resultante se filtra. La torta se hace pasta aguada con 500 mL de una mezcla 1:1 de acetonitrilo y agua y se concentra. El residuo se seca bajo vacío para dar 210 g del sólido crudo. El crudo se purifica por cromatografía sobre gel de sílice eluyendo con diclorometano/metanol: 98/2 para
 10 proporcionar 165 g del compuesto del título en 98% de pureza. (DMSO-d₆, 400MHz), δ = 8.23 (dd, 1H, J=2.8 Hz), 7.49 (d, 1H, J=8.8Hz), 7.36 (dd, 1H, J=8.8, 2.8Hz), 6.56 (bs, 1H), 3.89-3.86 (m, 4H), 3.37-3.33 (m, 4H), 2.91 (s, 3H), 2.90-2.88 (m, 2H), 2.65-2.63 (m, 2H), 2.42-2.39 (m, 1H), 2.38-2.36 (m, 1H),
 15 2.08-2.03 (m, 2H), 1.71-1.67 (m, 3H), 1.31 (s, 3H), 1.25 (s, 3H) ppm.

Ejemplo 7

4-{3-Fluoro-4-[1-(2-fluoro-2-metil-propil)-piperidin-4-ilmetoxi]-fenil}-1-metansulfonil-1,2,3,6-tetrahidro-piridina
 20



1: Éster terc-butílico del ácido 4-(3-Fluoro-4-metoxi-fenil)-3,6-dihidro-2H-piridin-1-carboxílico.

El 4-Bromo-2-fluoroanisol (2.68 g, 12.94 mmol), Preparación 3 (4.40 g, 14.23 mmol) y cloruro (1,1'-bis(difenilfosfino)ferroceno)paladio(II) (528.40 mg, 0.647 mmol) se colocan en un tubo resellable y se purgan con nitrógeno. Se adicionan dimetilformamida (40 mL) y una solución acuosa 2 M de carbonato de sodio (23.71 mL, 38.82 mmol) y el tubo se sella y se agita a 90°C por 1h. La reacción se divide entre acetato de etilo y agua. La capa acuosa se extrae con acetato de etilo. Las capas orgánicas combinadas se lavan con agua y salmuera, se secan sobre sulfato de magnesio, se filtran, y se concentran a sequedad. El residuo se purifica por cromatografía usando un cartucho de 20 g de gel de sílice eluyendo con hexano:acetato de etilo (8:1) para proporcionar 2.6 g del compuesto del título como un aceite blanco. MS (m/z) 252 (M-55).

2: Sal de clorhidrato de 4-(3-Fluoro-4-metoxi-fenil)-1,2,3,6-tetrahidro-piridina.

Preparada esencialmente como la Preparación 6 (etapa 2) usando éster terc-butílico del ácido 4-(3-fluoro-4-metoxi-fenil)-3,6-dihidro-2H-piridina-1-carboxílico como material de partida. MS (m/z) 208 (M+1).

3: 4-(3-Fluoro-4-metoxi-fenil)-1-metansulfonil-1,2,3,6-tetrahidro-piridina.

La sal de clorhidrato de 4-(3-Fluoro-4-metoxi-fenil)-1,2,3,6-tetrahidro-piridina (462.00 mg, 1.90 mmol) se
5 suspende en diclorometano (10 mL). Se adicionan trietilamina (479.58 mg, 660.57 μ L, 4.74 mmol) y cloruro de metansulfonilo (260.59 mg, 176.07 μ L, 2.27 mmol) y la reacción se tapa y se
agita a temperatura ambiente por 16 h. La reacción se divide
entre diclorometano y agua. La capa acuosa se extrae con
10 diclorometano. Las capas orgánicas combinadas se lavan con
salmuera, se secan sobre sulfato de magnesio, se filtran, y
se concentran a sequedad. El material crudo se purifica por
cromatografía usando un cartucho con 5 g de gel de sílice
eluyendo con diclorometano para proporcionar 349 mg del
15 compuesto del título como un sólido blanco. MS (m/z) 286
(M+1).

4: 4-(3-Fluoro-4-hidroxi-fenil)-1-metansulfonil-piperidin-4-ol.

20 Se disuelve 4-(3-Fluoro-4-metoxi-fenil)-1-metansulfonil-1,2,3,6-tetrahidro-piridina (1.12 g, 3.93 mmol) en diclorometano seco (20 mL) bajo nitrógeno. La solución se
enfria a -78°C y se adiciona con jeringa tribromuro de boro (11.52 g, 7.85 mL, 7.85 mmol). La reacción se calienta a
25 temperatura ambiente y se agita por 1 h seguido por la

5X

adición de 5% de bicarbonato de sodio acuoso y diclorometano. Un sólido insoluble se forma y filtra para proporcionar 729 mg del compuesto del título como un sólido rosa. ^1H NMR (CDCl₃) δ (ppm): 7.21 (dd, 1H), 7.09 (m, 1H), 6.89 (t, 1H),
5 3.30 (m, 2H), 3.18 (td, 2H), 2.88 (m, 3H), 2.06 (m, 2H), 1.80 (m, 2H).

5: 2-Fluoro-4-(1-metansulfonil-1,2,3,6-tetrahidro-piridin-4-il)-fenol.

10 Se disuelve 4-(3-Fluoro-4-hidroxi-fenil)-1-metansulfonil-piperidin-4-ol (726.00 mg, 2.51 mmol) en 1,4-dioxano (10.36 g, 10.04 mL, 117.57 mmol). Se adiciona ácido p-toluensulfónico (43.65 mg, 250.93 μmol) y la mezcla se calienta a 60°C. Se adiciona carbonato de sodio sólido y se
15 concentra la reacción. El residuo se divide entre agua y acetato de etilo, el pH se ajusta a 7 con cloruro de hidrógeno 1 M y se extrae con acetato de etilo. La capa orgánica se lava con salmuera, se seca sobre sulfato de magnesio, se filtra, y se concentra a sequedad para
20 proporcionar 714 mg del compuesto del título como un sólido blanco. MS (m/z) 272 (M+1).

6: Éster terc-butílico del ácido 4-[2-Fluoro-4-(1-metansulfonil-1,2,3,6-tetrahidro-piridin-4-il)-fenoximetil]-piperidin-1-carboxílico.

25 Preparado esencialmente como la Preparación 2

(etapa 2) usando éster *terc*-butílico del ácido 4-metansulfoniloximetil-piperidin-1-carboxílico y 2-fluoro-4-(1-metansulfonil-1,2,3,6-tetrahidro-piridin-4-il)-fenol como materiales de partida. MS (m/z) 414 (M-55).

5

7: Sal de clorhidrato de 4-[3-Fluoro-4-(piperidin-4-ilmetoxi)-fenil]-1-metansulfonil-1,2,3,6-tetrahidro-piridina.

Preparada esencialmente como la Preparación 6 (etapa 2) usando éster *terc*-butílico del ácido 4-[2-fluoro-4-(1-metansulfonil-1,2,3,6-tetrahidro-piridin-4-il)-fenoximetil]-piperidina-1-carboxílico como el material de partida. MS (m/z) 369 (M+1).

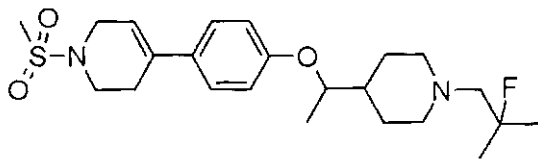
8: 4-{3-Fluoro-4-[1-(2-fluoro-2-metil-propil)-piperidin-4-ilmetoxi]-fenil}-1-metansulfonil-1,2,3,6-tetrahidro-piridina.

Preparada esencialmente como el Ejemplo 2 partiendo de sal de clorhidrato de 4-[3-fluoro-4-(piperidin-4-ilmetoxi)-fenil]-1-metansulfonil-1,2,3,6-tetrahidro-piridina y ácido 2-fluoro-2-metil-propiónico. MS (m/z) 443 (M+1).

20

Ejemplo 8

4-(4-{1-[1-(2-Fluoro-2-metil-propil)-piperidin-4-il]-etoxi}-fenil)-1-metansulfonil-1,2,3,6-tetrahidro-piridina



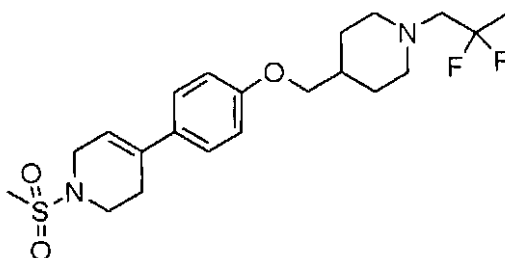
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Preparada esencialmente como el Ejemplo 2 usando la Preparación 5 (racémico) como material de partida para proporcionar el compuesto del título. El compuesto del título (0.194 g) se separa en sus enantiómeros usando un eluyente de 0.2% de dimetiletilamina en 100% de metanol sobre un Chiralpak OJ de 420 x 250 mm a 8 mL/min produciendo 77 mg del isómero 1 (96% ee, RT = 10.7min).

Ejemplo 9

4-{4-[1-(2,2-Difluoro-propil)-piperidin-4-ilmetoxi]-fenil}-1-metansulfonil-1,2,3,6-tetrahidro-piridina



1: Éster 2,2-difluoro-propílico del ácido toluen-4-sulfónico.

A una solución de 2,2-difluoropropanol (0.50 g, 5.20 mmol) in diclorometano (52.0 mL) y trietilamina (0.50 g, 0.73 mL, 5.20 mmol) a 0°C se adiciona cloruro de p-toluensulfonilo (0.99 g, 5.20 mmol). La mezcla se deja calentar lentamente a temperatura ambiente por 24 h. La mezcla se concentra y se divide entre éter dietílico y agua. La capa orgánica se lava con agua y salmuera, se seca sobre

sulfato de magnesio, se filtra, y se concentra a sequedad. El material se purifica sobre gel de sílice para obtener 1.0 g del compuesto del título como cristales claros. MS (m/z) 250 (M+1).

5

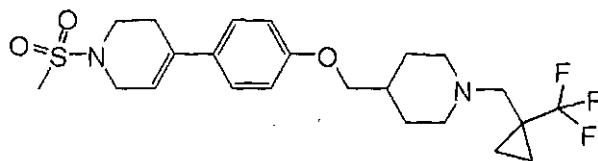
2: 4-{4-[1-(2,2-Difluoro-propil)-piperidin-4-ilmetoxi]-fenil}-1-metansulfonil-1,2,3,6-tetrahidro-piridina

A una mezcla de Preparación 2 (0.25 g, 0.71 mmol) y éster 2,2-difluoro-propílico del ácido toluen-4-sulfónico (0.25 g, 0.91 mmol) se adiciona 1,3-dimetil-2-imidazolidinona (7 mL). La mezcla se coloca en un reactor de microondas Biotage y se calienta a 175°C por 1 hora y después 180°C por 1 hora. La mezcla se divide entre acetato de etilo y agua. La capa orgánica se lava con agua y salmuera, se seca sobre sulfato de magnesio, se filtra, y se concentra a sequedad. El material crudo se purifica sobre gel de sílice para producir 0.03 g del compuesto del título como un sólido blanco. MS (m/z) 429 (M+1).

20

Ejemplo 10

1-Metansulfonil-4-{4-[1-(1-trifluorometil-ciclopropilmetil)-piperidin-4-ilmetoxi]-fenil}-1,2,3,6-tetrahidro-piridina



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1: Éster etílico del ácido 1-(1-trifluorometil-ciclopropancarbonil)-piperidin-4-carboxílico

Se adiciona 1,1'-carbonildiimidazol (77.36 g; 467.52 mmol) a una solución de ácido 1-(trifluorometil)ciclopropancarboxílico (72.04 g; 467.52 mmol) en tetrahidrofurano (600 mL) aunque se mantiene la temperatura interna por debajo de 30°C. El éster etílico del ácido piperidin-4-carboxílico (50 g; 311.68 mmol) se adiciona después de 10 min y la reacción se agita bajo atmósfera de nitrógeno a temperatura ambiente por 16 h. El solvente se remueve bajo vacío controlado y el residuo se coloca entre solución acuosa 2 M de hidróxido de sodio (200 mL) y diclorometano (300 mL). La capa orgánica se lava con salmuera (100 mL), se seca sobre sulfato de magnesio, se filtra y se concentra para obtener 93.45 g del compuesto del título. MS (m/z) 294 (M+1).

2: [1-(1-Trifluorometil-ciclopropilmetil)-piperidin-4-il]-metanol

El éster etílico del ácido 1-(1-Trifluorometil-ciclopropancarbonil)-piperidin-4-carboxílico (50 g; 170.48 mmol) en tetrahidrofurano (350 mL) se adiciona a una solución 1 M de hidruro de litio y aluminio (170.48 mL; 170.48 mmol) en tetrahidrofurano. La mezcla de reacción se deja calentar a temperatura ambiente y se agita por 1 h. La mezcla de

reacción se enfría a 0°C y se adiciona secuencialmente agua/solución acuosa 2 M de hidróxido de sodio/agua (1:3:1) (8.5 mL : 12 mL : 8.5 mL). La pasta aguada resultante se filtra sobre una almohadilla de celite® y se lava con tetrahydrofurano (200 mL). La capa orgánica se concentra bajo vacío controlado para producir 17 g del compuesto volátil del título como aceite incoloro. El material crudo se usa sin purificación adicional. MS (m/z) 238 (M+1).

10 3: 1-Metansulfonil-4-{4-[1-(1-trifluorometil-ciclopropil metil)-piperidin-4-ilmetoxi]-fenil}-1,2,3,6-tetrahydro-
piridina

El azodicarboxilato de diisopropilo (27.43 g; 128.87 mmol) se adiciona a una solución de trifenilfosfina (33.80 g; 128.87 mmol) en tetrahydrofurano seco (330 mL) a 0°C. La reacción se agita por 20 min. Se adiciona por goteo una suspensión de [1-(1-trifluorometil-ciclopropilmetil)-piperidin-4-il]-metanol (24 g; 99.13 mmol), Preparación 1 (25.89 g; 99.13 mmol) en tetrahydrofurano seco (200 mL). La reacción se agita a 0°C por 10 min y se deja calentar a temperatura ambiente y se hace reaccionar durante la noche. El solvente se evapora y la pasta aguada resultante se diluye con diclorometano (350 mL) y se lava con solución acuosa 2 M de hidróxido de sodio (2 x 30 mL) y salmuera (2 x 30 mL), se secan sobre sulfato de magnesio, se filtra y se concentra. El

sólido rosa se purifica sobre gel de sílice eluyendo con hexano/acetona: 100%; 95:5; 90:10; 80:20 y 70:30, para producir 16 g del compuesto del título, alrededor de 80% puro. El sólido se trata con cloruro de hidrógeno acuoso 2N.

5 Un sólido blanco se precipita y se filtra y se seca. El sólido se disuelve en agua (150 mL) y se basifica a pH 12 con pelotillas de hidróxido de sodio. El sólido resultante se filtra, se seca y se cristaliza con éter metil t-butílico (100 mL) se filtra y se seca en el horno a 50°C para obtener
10 8 g del compuesto del título. MS (m/z) 473 (M+1).

Un método alternativo para la Preparación del Ejemplo 10 es como sigue:

1: Éster etílico del ácido 1-(1-Trifluorometil-ciclopropancarbonil)-piperidin-4-carboxílico

15 El ácido 1-(Trifluorometil)ciclopropancarboxílico (400 g, 2.6 mol) se disuelve en 3.2 L de tetrahidrofurano y se enfría a 10~20°C. El carbonildiimidazol (462.4 g, 1.1 eq) se adiciona en porciones. La mezcla se agita a 25-30°C por 20 min. Después el éster metílico del ácido piperidin-4-
20 carboxílico (445.6 g, 1.2 eq) se adiciona por goteo a < 30°C. La mezcla se agita a 25-30°C por 18~20h. 3.2 L de agua se adicionan por goteo a < 30°C y la solución se concentra a ~ 1 L de volumen para remover la mayoría del tetrahidrofurano. La solución resultante se extrae con diclorometano (2x). Las
25 capas orgánicas combinadas se lavan con 3 volúmenes de ácido

clorhídrico 0.5 M y se concentran. 500 mL de éter metil terc-butílico se adicionan y la solución se concentra. Este proceso se realiza dos veces. La capa orgánica se concentra para proporcionar 567 g del compuesto del título en 95% de pureza.

2: [1-(1-Trifluorometil-ciclopropilmetil)-piperidin-4-il]-metanol

El hidruro de litio y aluminio (208 g, 5.0 eq) se suspende en 3.9 L de éter metil terc-butílico y la suspensión se agita por 10 min. Una solución de éster etílico del ácido 1-(1-trifluorometil-ciclopropancarboxílico) (260 g, 0.93 mol) en 1.3 L de éter metil terc-butílico se adiciona por goteo a < 30°C. La mezcla se somete a reflujo por 20 h y se enfría a 0~10°C. 500 mL de agua se adicionan a 0~10°C y la mezcla se agita por 30 min. La suspensión se filtra y la torta se lava con 1.8 L de éter metil terc-butílico. El filtrado se concentra a ~ 3 L de volumen a <35°C bajo vacío. El solvente se desplaza con tetrahidrofurano (1.0 L x 2) y se concentra para proporcionar 212 g del compuesto del título en 96.8% de pureza.

3: 1-Metansulfonil-4-{4-[1-(1-trifluorometil-ciclopropilmetil)-piperidin-4-ilmetoxi]-fenil}-1,2,3,6-tetrahidro-piridina

El [1-(1-Trifluorometil-ciclopropilmetil)-piperidin-4-il]-metanol (371 g, 1.56 mol) se disuelve en 1.85

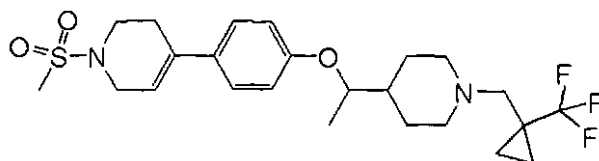
L de diclorometano y trietilamina (237.3 g, 2.34 mol) y la mezcla se enfría a 0~10°C. El cloruro de metansulfonilo (215 g, 1.2 eq) se adiciona por goteo. La reacción se calienta a 20~25°C y se agita por 1 h. 1.85 L de agua se adicionan por goteo. Las capas se separan y la capa acuosa se extrae con 1 L de diclorometano. Las capas orgánicas combinadas se lavan con 1.85 L de agua, se secan sobre sulfato de sodio anhidro y se concentran para proporcionar 491 g de un aceite que se usa para la siguiente etapa en dos lotes.

10 La Preparación 1 (197.8 g, 0.781 mol) se disuelve en 1.8 L de dimetilformamida y se enfría a 0~10°C. Una solución de terc-butoxido de potasio (87.6 g, 0.781 mol) disuelta en 1.6 L de dimetilformamida se adiciona por goteo a la solución y la mezcla se agita a 20~30°C por 30 min. Una
15 solución de [1-(1-trifluorometil-ciclopropilmetil)-piperidin-4-il]-metanol (246 g, 0.781 mol) en 0.5 L de dimetilformamida se adiciona por goteo a la solución. La mezcla se calienta a ~60°C y se agita por 1.5 h. La misma se enfría a 30~40°C, y se adicionan por goteo 4.4 L de agua. La mezcla se agita a
20 30°C por 1 h y se filtra. Este proceso se hace con los dos lotes de [1-(1-trifluorometil-ciclopropilmetil)-piperidin-4-il]-metanol y las tortas resultantes se combinan por purificación. La torta se lava con 800 mL de una mezcla 1:1 de dimetilformamida y agua. El sólido se agita con 4 L de
25 diclorometano y se filtra. El filtrado se concentra y se

purifica por cromatografía eluyendo con diclorometano para obtener 180 g del compuesto del título en 99% de pureza. (CDCl₃, 400MHz), δ = 7.31 (d, 2H, J=8.8 Hz), 6.88 (d, 2H, J=8.8 Hz), 6.00-5.98 (m, 1H), 3.97 (s, 2H), 3.82 (s, 2H), 3.55-3.52 (m, 2H), 3.04-3.01 (m, 2H), 2.87 (s, 3H), 2.70-2.60 (m, 4H), 2.06-2.03 (m, 2H), 1.85-1.82 (m, 3H), 1.48-1.45 (m, 2H), 1.03-1.01 (m, 2H), 0.74-0.71 (m, 2H) ppm.

Ejemplo 11

10 1-(Metilsulfonil)-4-(4-(1-(1-(1-(trifluorometil)ciclopropil)metil)piperidin-4-il)etoxi)fenil)-
1,2,3,6-tetrahidropiridina



15

Isómero 2

1. 1-(1-(Trifluorometil)ciclopropil)metanol

A una suspensión enfriada con hielo de hidruro de litio y aluminio (33.91 mmoles; 1.29 g) en éter dietílico (90 mL) se adiciona por goteo en 25 minutos 1-(trifluorometil)ciclopropancarboxilato de metilo (16.95 mmoles; 3.00 g) en 30 mL de dietiléter. La reacción se agita a 0°C por 2 horas. La mezcla se apaga por adición lenta de 7.5 mL de agua, después 15 mL de hidróxido de sodio 5 M y 9 mL de agua. La pasta aguada se agita vigorosamente a

temperatura ambiente por 3 horas. La mezcla se transfiere a un embudo de separación, se diluye con agua y se extrae con dietiléter. Las capas orgánicas combinadas se lavan con salmuera, se secan sobre sulfato de magnesio, se filtran y se concentran a sequedad. Se obtienen 2.37 g del compuesto del título como aceite incoloro. ^1H NMR (CDCl_3) δ (ppm): 0.762-0.807 (m, 2H), 1.018-1.055 (m, 2H), 3.732 (s, 2H).

2. (1-(Trifluorometil)ciclopropil)metil
10 metansulfonato

Preparado esencialmente como la Preparación 2 (etapa 1) usando (1-trifluorometil-ciclopropil)-metanol como material de partida. ^1H NMR (CDCl_3) δ (ppm): 0.921-0.975 (m, 2H), 1.182-1.223 (m, 2H), 3.057 (s, 3H), 4.296 (s, 2H).

15 3. 1-(Metilsulfonil)-4-(4-(1-(1-((1-(trifluorometil)ciclopropil)metil)piperidin-4-il)etoxi)fenil)-1,2,3,6-tetrahidropiridina

A la Preparación 5 (isómero 2) (62 mg, 0.169 mmol), carbonato de potasio (70 mg, 0.506 mmol) y acetonitrilo (1.12 mL, 21.46 mmol) en un vial se adiciona metansulfonato de (1-(trifluorometil)ciclopropil)metilo (147 mg, 0.675 mmol). El vial se sella y calienta a 110°C por 16 h. La reacción se diluye con diclorometano y agua. La capa orgánica se separa y lava con salmuera, se seca sobre sulfato de sodio, se filtra, y se concentra in vacuo para producir un sólido blancuzco. El

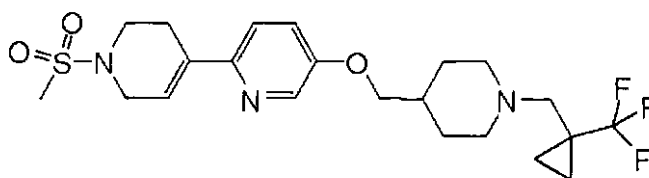
sólido se purifica por cromatografía instantánea sobre gel de sílice para obtener 0.057 g de un sólido blanco. MS (m/z) 487.2 (M+1).

5

Ejemplo 12

2-(1-(Metilsulfonil)-1,2,3,6-tetrahidropiridin-4-il)-5-((1-((1-(trifluorometil)ciclopropil)metil)piperidin-4-il)metoxi)piridina

10



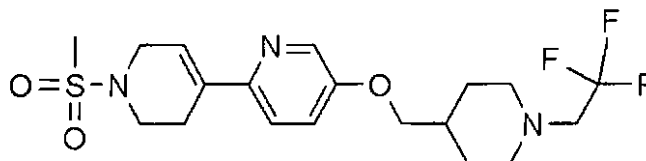
A la Preparación 6 (206 mg, 0.586 mmol), carbonato de potasio (243 mg, 1.76 mmol) y acetonitrilo (2.93 mL, 56 mmol) en un vial para microondas se adiciona metansulfonato de (1-(trifluorometil)ciclopropil)metilo (256 mg, 1.17 mmol). El vial para microondas se sella y calienta a 140°C por 2 h después a 150°C por 30 min en el microondas Biotage. La reacción se diluye con diclorometano y agua. La capa orgánica se separa y lava con salmuera, se seca sobre sulfato de sodio, se filtra, y se concentra in vacuo. El residuo se tritura con dietiléter y el producto del título se colecta vía filtración en vacío para obtener 0.181 g del compuesto del título. MS (m/z) 474 (M+1).

25

Ejemplo 13

2-(1-(Metilsulfonil)-1,2,3,6-tetrahidropiridin-4-il)-5-((1-(2,2,2-trifluoroetil)piperidin-4-il)metoxi)piridina

5



A una solución de la Preparación 6 (0.05 g, 0.14 mmol) en acetonitrilo (1.50 mL) se adiciona carbonato de potasio (0.07 g, 0.56 mmol) y trifluorometansulfonato de 2,2,2-trifluoroetilo (0.06 g, 0.28 mmol). La mezcla de reacción se calienta a 85°C por 1 h en un microondas, se enfría a temperatura ambiente y se diluye con agua. La mezcla se extrae con acetato de etilo y los extractos orgánicos combinados se secan sobre sulfato de sodio, se filtran, y se concentran. El residuo se purifica por cromatografía de columna instantánea sobre gel de sílice para obtener 30 mg del compuesto del título como un sólido blancuzco. MS (m/z) 433 (M+1).

20

Ensayo de Actividad GPR119 Humano

Una línea celular estable que expresa GPR119 humano fuera de un promotor inducible es generado en células 293 T-REx™ (Invitrogen). La línea celular T-REx™ (Expresión Regulada con tetraciclina) expresa de manera estable la

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proteína represora de tetraciclina y, por lo tanto, permite la expresión inducible del gen de interés (GPR119) con doxiciclina. Los agonistas para el receptor GPR119 humano se caracterizan por medir incrementos en los niveles de cAMP en 5 células 293 T-REx™ que expresan hGPR119. Se siembran 10,000 células/cavidad en una placa de 96 cavidades y se cultivan por 24h en DMEM suplementado con 10% de suero bovino fetal, 15µg/mL de Blastomicina y 200µg/mL Higromicina B. Al siguiente día, las células se estimulan con 1 ng/mL de 10 Doxiciclina en DMEM sin agregación adicional de Higromicina B y Blastomicina. El ensayo cAMP se realiza después de 18 h de incubación con doxiciclina. Se determina cAMP usando el ensayo cAMP HiRange HTRF (Cisbo International). Las células se lavan con PBS y se pre-incuban por 15 min con PBS 15 suplementado con 2 mM de glucosa, 0.25 mM IBMX y 0.1% BSA. Los compuestos de prueba diluidos en el amortiguador de pre-incubación se adicionan y las células se incuban adicionalmente a temperatura ambiente por 1h. La incubación se detiene por adición de reactivos HTRF diluidos en el 20 amortiguador de lisis, seguido por incubación por 1h y mediciones de fluorescencia de 620 y 655 nm. La potencia de los agonistas se determina como la concentración agonista que proporciona 50% de activación del incremento de cAMP mediado por hGPR119 (EC50).

25 Todos los compuestos ejemplificados se prueban

69

esencialmente como se describió anteriormente y cada uno se encuentra que tiene un valor EC50 de <10 nM. El Ejemplo 1 tiene un valor EC50 de 4.61 nM; el Ejemplo 6 tiene un valor EC50 de 0.95 nM; el Ejemplo 7 tiene un valor EC50 de 2.13 nM; 5 el Ejemplo 8 tiene un valor EC50 de 1.10 nM; y el Ejemplo 10 tiene un valor EC50 de 0.95 nM.

Por consiguiente, ciertos compuestos de la presente invención se muestra que actúan como agonistas de GPR119 *in vitro*.

10

Secreción del péptido 1 semejante a Glucagon en células
GLUTag

Los efectos de agonistas de GPR119 en la secreción del péptido 1 semejante a glucagon (GLP-1) se determinan in 15 vitro en células GLUTag. Las células GLUTag son una línea celular enteroendocrina intestinal inmortalizada que expresa el gen preproglucagon y secreta GLP-1 de una manera regulada (Brubaker PL, Schloos J, Drucker DJ. Regulation of glucagon-like peptide-1 synthesis and secretion in the GLUTag 20 enteroendocrine cell line. Endocrinology. 1998 139:4108-14). Para medir la secreción de GLP-1, 15,000 células/cavidad se siembran en placas de 96 cavidades y se incuban por 3 días en DMEM suplementado con 10% FBS y 1% Glutamina. En el día del experimento, las células se lavan dos veces con el 25 amortiguador de incubación, EBSS suplementado con 5 mM de

glucosa y 0.1% de BSA. 150 µL del amortiguador de incubación que contiene los compuestos de prueba se adicionan a cada cavidad y las células se incuban a 37°C por 2 h. Después de la incubación, el sobrenadante se colecta y filtra usando 5 placas de filtro de 96 cavidades. El contenido de GLP-1 en el filtrado se determina con el Ensayo de GLP-1 Total de Ratón/Rata (Meso Scale Discovery). La potencia de los agonistas de GPR119 para estimular la secreción de GLP-1 se determina como la concentración de agonista que produce 50% 10 de incremento en GLP-1 (EC50).

Los Ejemplos 6 y 9 se prueban esencialmente como se describió anteriormente y se encuentra que tienen valor de EC50 respectivo de 62.7 y 36.8 nM.

Por consiguiente, se ha demostrado que ciertos 15 compuestos de la presente invención tienen actividad funcional como agonistas de GPR119 *in vitro*.

Biodisponibilidad

Los métodos para acceder a la biodisponibilidad 20 oral son bien apreciados en la técnica. Una referencia es *Medicinal Research Reviews* Vol 21 No. 5 382-396 (2001). La biodisponibilidad oral de los compuestos de la presente invención se puede estimar esencialmente como sigue.

Los cohortes de tres ratas macho Sprague-Dawley de 25 250-400 gramos o perros Beagle de aproximadamente 10 kg

63

(hembra o macho) se usan. Los animales no necesitan estar en ayunas para la porción intravenosa (IV) del estudio. A los perros se administran IV los compuestos por la vena cefálica canulada y las colecciones de sangre son por la vena yugular.

5 Los animales primero son dosificados IV a 1 mg/kg y después se colectan las muestras de sangre (0.1 a 0.2 mL) usando EDTA como un anticoagulante a 0.0830, 0.25, 0.50, 1, 2, 4, 8, 12, y 24 h. Después de al menos dos días y ayuno durante la noche, los animales se dosifican a 3 mg/kg por sonda. Las
10 muestras de sangre (0.1 a 0.2 mL) después se colectaron usando EDTA como un anticoagulante a 0.25, 0.50, 1, 2, 4, 6, 8, 12, y 24 h. Durante el curso de un estudio el total de sangre (mL) colectada no excede 1% del peso corporal total en gramos.

15 Las concentraciones de plasma del compuesto se miden por ensayos LC/MS/MS. Después se analizan los datos usando análisis farmacocinético no compartimental estándar. La biodisponibilidad oral es calculada como:

$$\frac{(AUC_{0-\infty}, \text{ oral} / AUC_{0-\infty}, \text{ IV}) \times (\text{Dosis, IV.} / \text{Dosis, oral}) \times 100\%}{}$$

20

El Ejemplo 6 se prueba esencialmente como se describió anteriormente y se encuentra que tiene biodisponibilidad oral de 90 % en perros Beagle. El Ejemplo 10 se prueba esencialmente como se describió anteriormente y
25 se encuentra que tiene biodisponibilidad oral de 53% en ratas

Sprague Dawley.

Por consiguiente, ciertos compuestos de la presente invención han mostrado tener buena biodisponibilidad oral.

5 Ensayo de Polipéptido Inhibidor Gástrico de Ratón (GIP)

Los ratones macho C57BL/6 (8-10 semanas de edad, n=20/nivel de dosis, n=5/punto de tiempo) se dejan en ayunas durante la noche (16 hr), se pesan la mañana siguiente, y después se dosifican oralmente con vehículo (1% HEC) o varias
10 dosis del artículo de prueba a 5 mL/kg. Los animales se eutanizan por asfixia con CO₂ por 1 minuto, y después se colecta sangre por punción cardíaca en varias ocasiones (0.5, 1.5, 3, y 6 h post-dosis del compuesto) en tubos de plasma de EDTA que contienen 10 µL/mL de inhibidor DPP4 (Millipore,
15 DPP4-010) y 1.1x10⁵ KIU/mL aprotinina. Las muestras de sangre se mantienen en hielo hasta que se separa el plasma por centrifugación a 3000xg por 5 min. Las muestras de plasma resultantes se colocan en placas de 96 cavidades y se almacenan a -20°C hasta que se analizan. Las mediciones de
20 GIP total (medidas por kit Millipore EZRMGIP-55K) se realizan por cada punto de tiempo. Para cada grupo de tratamiento, el AUC para GIP se determina aplicando la regla trapezoidal a los niveles de GIP promedio de punto de tiempo específico. Las potencias se estiman usando interpolación lineal en
25 piezas a través de la colección GIP AUCs calculadas arriba

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del vehículo de un estudio de respuesta a la dosis. La potencia del compuesto se define como la dosis y/o concentración del compuesto que produce un incremento de 350 pg*hr/mL arriba del GIP AUC del grupo del vehículo en el transcurso del tiempo del experimento.

Usando el procedimiento esencialmente como se describió anteriormente, una dosis de 10 mg/kg del Ejemplo 3 resulta en un incremento en GIP AUC sobre vehículo de 762 pg*h/mL; una dosis de 10 mg/kg del Ejemplo 10 resulta en un incremento en GIP AUC sobre vehículo de 762 pg*h/mL; y una dosis de 1.6 mg/kg del Ejemplo 6 resulta en un incremento en GIP AUC sobre vehículo de 422 pg*h/mL.

Se ha mostrado que ciertos compuestos de la presente invención estimulan la secreción de GIP in vivo, lo que induce a la secreción de insulina, tales datos indican el potencial para uso de los compuestos de la presente invención en el tratamiento de diabetes.

Prueba Oral de Tolerancia a la Glucosa (OGTT) del Ratón

Los ratones C57BL/6 normales se dejan ayunar durante la noche, se aleatorizan en grupos (n=6) y se dosifican oralmente con vehículo (1% HEC, 0.25% tween 80, 0.05% antiespuma) ó 0.9, 2, 6 y 18 mg/kg de agonista GPR119 suspendido en vehículo. 30 minutos después de que el compuesto se administra, los ratones se dosifican oralmente

con una solución de dextrosa al 50% a 3 g/kg. En varios
tiempos (0, 20, 40, ó 60 minutos post-glucosa), los ratones
se retienen en guantes de algodón o toallas de papel y se
corta 1 mm o menos de la cola. Una gota pequeña de sangre se
5 coloca en glucómetros Accu-Chek® (Roche modelo 22-044217)
para mediciones de glucosa. Tres glucómetros se usan para
leer la glucosa en cada muestra colectada, con el valor
promedio que se reporta como el valor de glucosa final. El
área bajo la curva de glucosa de plasma (AUC de glucosa) se
10 calcula para cada grupo y la disminución del porcentaje en el
AUC de glucosa contra el grupo de control se usa como una
medición de eficacia del compuesto para disminuir la glucosa
en plasma.

El Ejemplo 6 se prueba esencialmente como se
15 describió anteriormente y se encuentra que demuestra la
tolerancia a la glucosa mejorada. El Ejemplo 6 no incluye en
la glucosa de plasma en ayunas pero disminuye
significativamente la glucosa en plasma postprandial. Los
datos muestran que la dosis del Ejemplo 6 que producen una
20 disminución del 50% en área de glucosa bajo la curva (ED50)
es igual a 0.4 mg/kg.

Por consiguiente, se ha demostrado que un compuesto
de la presente invención disminuye los niveles de glucosa en
plasma in vivo, indicando el potencial para uso de los
25 compuestos de la presente invención en el tratamiento de

6X

diabetes.

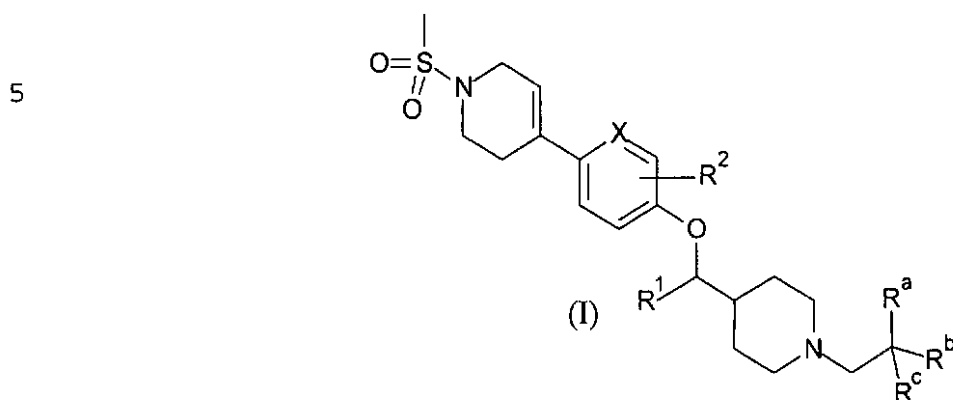
Tratamiento crónico de ratones obesos inducidos por dieta
(DIO)

5 Los ratones machos C57/BL6 DIO se mantienen con una
dieta rica en calorías y tienen libre acceso a comida y agua
por al menos 2 semanas antes de la aleatorización en grupos
por peso (n=8) y tratamiento. Los animales se alojan
individualmente en una instalación de temperatura controlada
10 (24°C) con ciclo de 12 horas de luz, 12 horas de oscuridad.
Los pesos corporales varían de 34-40 g. Los ratones se
administran el vehículo cada tercer día (1% HEC), 30 mg/kg de
agonista GPR119, 30 mg/kg de inhibidor de DPPIV o una
combinación de 30 mg/kg de agonista GPR119 y 30 mg/kg de
15 inhibidor de DPPIV. El tratamiento continúa por 3 semanas. El
alimento y pesos corporales se registran diario antes del
fotoperíodo oscuro. El cambio de peso corporal acumulativo se
calcula como el peso corporal diario menos peso corporal
antes del tratamiento para cada animal y se presenta como un
20 promedio para el grupo. La ingesta de alimentos se mide
diariamente para cada animal y se combina con la cantidad
total de alimento consumido por este animal de todos los días
previos para producir ingesta de alimentos acumulativa, que
después es promediada para el grupo. Al final del estudio se
25 realiza OGTT después del ayuno durante la noche.

El Ejemplo 6 se prueba esencialmente como se describió anteriormente donde el inhibidor de DPPIV es sitagliptina. La sitagliptina sola no altera el peso corporal o ingesta de alimentos en el estudio. El Ejemplo 6 solo produce una ligera disminución en tanto la ingesta de alimentos como en el peso corporal observado solamente durante la primera semana de tratamiento. La combinación de sitagliptina y el Ejemplo 6 produce disminuciones profundas en peso corporal e ingesta de alimentos que se mantienen en todo el transcurso del estudio. El Ejemplo 6 solo o en combinación con sitagliptina no modifican significativamente los niveles de glucosa en plasma en este modelo. Por consiguiente, se ha demostrado que un compuesto de la presente invención disminuye la ingesta de alimentos y peso corporal, indicando el potencial para uso de los compuestos de la presente invención en el tratamiento de obesidad.

REIVINDICACIONES

1. Un compuesto de la fórmula:



10 caracterizado porque;

X se selecciona de N y CH;

R^a se selecciona de F y CF₃;

R^b y R^c se seleccionan independientemente de F y metilo o se combinan para formar un anillo cicloalquilo de C₃₋₅;

15 R¹ se selecciona de H y metilo;

R² se selecciona de H y F;

o una sal del mismo farmacéuticamente aceptable.

2. Un compuesto de conformidad con la reivindicación 1, o una sal del mismo farmacéuticamente aceptable, caracterizado porque R^b y R^c se seleccionan independientemente de F y metilo o se combinan para formar un cicloalquilo de C₃.

20

3. Un compuesto de conformidad con cualquiera de las reivindicaciones 1 ó 2, o una sal del mismo farmacéuticamente aceptable, caracterizado porque R^b y R^c son

25

metilo o se combinan para formar un cicloalquilo de C_3 .

4. Un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 3, o una sal del mismo farmacéuticamente aceptable, caracterizado porque R^a es CF_3 .

5 5. Un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 4, o una sal del mismo farmacéuticamente aceptable, caracterizado porque R^2 es H.

6. Un compuesto de conformidad con la reivindicación 1, o una sal del mismo farmacéuticamente
10 aceptable, caracterizado porque se selecciona de 5-[1-(2-Fluoro-2-metil-propil)-piperidin-4-ilmetoxi]-1'-metansulfonil-1',2',3',6'-tetrahidro-[2,4']bipiridinilo; y 1-Metansulfonil-4-{4-[1-(1-trifluorometil-ciclopropilmetil)-piperidin-4-ilmetoxi]-fenil}-1,2,3,6-tetrahidro-piridina.

15 7. Una composición farmacéutica caracterizada porque comprende un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 6, o una sal del mismo farmacéuticamente aceptable, y un portador o diluyente farmacéuticamente aceptable.

20 8. Una composición farmacéutica de conformidad con la reivindicación 7, caracterizada porque adicionalmente comprende uno o más ingredientes terapéuticos diferentes.

9. Una composición farmacéutica de conformidad con la reivindicación 8, caracterizada porque la sitagliptina es
25 un ingrediente terapéutico adicional.

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10. Un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 6, o una sal del mismo farmacéuticamente aceptable, para uso en terapia.

5 11. Un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 6, o una sal del mismo farmacéuticamente aceptable, para uso en el tratamiento de diabetes u obesidad.

10 12. Un compuesto de conformidad con la reivindicación 11 para uso en el tratamiento de diabetes tipo II.

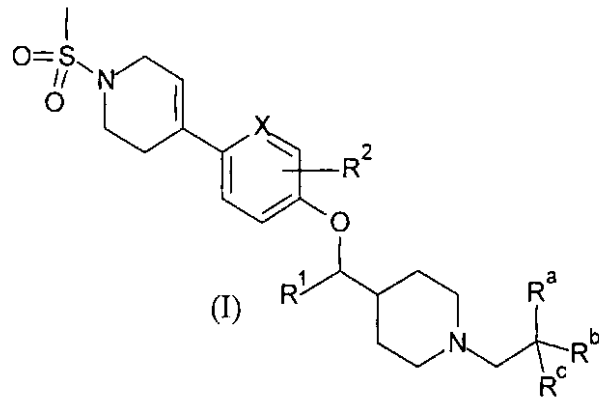
13. Un método para el tratamiento de diabetes u obesidad, caracterizado porque comprende administrar una cantidad efectiva de un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 6, o una sal del mismo
15 farmacéuticamente aceptable, a un ser humano o animal con necesidad del mismo.

14. Un método de conformidad con la reivindicación 13, caracterizado para el tratamiento de diabetes tipo II.

RESUMEN DE LA INVENCIÓN

Los compuestos agonistas de GPR119 de la fórmula:

5



10 y composiciones farmacéuticas para el tratamiento de diabetes y obesidad.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference X18674 WO	FOR FURTHER ACTION		See Form PCT/PEA416
International application No. PCT/US2010/041645	International filing date (day/month/year) 12.07.2010	Priority date (day/month/year) 15.07.2009	
International Patent Classification (IPC) or national classification and IPC INV. C07D401/12			
Applicant ELI LILLY AND COMPANY			
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u>5</u> sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☐ (sent to the applicant and to the International Bureau) a total of sheets, as follows: ☐ sheets of the description, claims and/or drawings which have been amended and/or sheets containing rectifications authorized by this Authority, unless those sheets were superseded or cancelled, and any accompanying letters (see Rules 46.5, 66.8, 70.16, 91.2, and Section 607 of the Administrative Instructions). ☐ sheets containing rectifications, where the decision was made by this Authority not to take them into account because they were not authorized by or notified to this Authority at the time when this Authority began to draw up this report, and any accompanying letters (Rules 66.4bis, 70.2(e), 70.16 and 91.2). ☐ superseded sheets and any accompanying letters, where this Authority either considers that the superseding sheets contain an amendment that goes beyond the disclosure in the international application as filed, or the superseding sheets were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in item 4 of Box No. I and the Supplemental Box (see Rule 70.16(b)). b. ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see paragraph 3bis of Annex C of the Administrative Instructions).			
4. This report contains indications relating to the following items: ☒ Box No. I Basis of the report ☐ Box No. II Priority ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability ☐ Box No. IV Lack of unity of invention ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement ☐ Box No. VI Certain documents cited ☐ Box No. VII Certain defects in the international application ☐ Box No. VIII Certain observations on the international application			
Date of submission of the demand		Date of completion of this report	
13.05.2011		19.10.2011	
Name and mailing address of the international preliminary examining authority:  European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016		Authorized officer Menchaca, Roberto Telephone No. +31 70 340-9524 	

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**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2010/041645

Box No. I Basis of the report

1. With regard to the **language**, this report is based on
- ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a) and (b))
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-36 as originally filed

Claims, Numbers

1-14 as originally filed

- ☐ a sequence listing - see Supplemental Box Relating to Sequence Listing.
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since either they are considered to go beyond the disclosure as filed, or they were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and (c-bis)):
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
5. ☐ This report has been established:
- ☐ taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rules 66.1(d-bis) and 70.2(e)).
 - ☐ without taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91(Rules 66.4bis and 70.2(e)).
6. ☐ Supplementary international search report(s) from Authority(ies) has/have been received and taken into account in establishing this report (Rule 45bis.8(b) and (c)).

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**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2010/041645

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-14</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-14</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-14</u>
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

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Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Document

Reference is made to the following document:

D1 WO 2009/038974 A1 (2009-03-26), cited in the application

2 Rule 39 PCT

Claims 13-14 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39(1)(iv) and Rule 67(1)(iv) PCT.

For the assessment of the present claims 13-14 on the question whether they are patentable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as patentable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first or further use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Consequently, and even if no opinion should be formulated with respect to the subject-matter of said claims 13-14 (Article 34(4)(a)(I) PCT), this authority has decided to carry out and base the search and present opinion on the alleged effects of the compounds and/or compositions.

3 Novelty

No prior art document discloses the compounds of formula (I) defined in present claim 1. The subject-matter of the present independent claims 1, 7 and 13, respectively disclosing the referred compounds, pharmaceutical compositions thereof and therapeutic use for the treatment of GPR119-related disorders, is therefore novel over the prior art in the sense of Article 33(2) PCT.

Dependent claims 2-6, 8-12 and 14 fulfill, as such, the requirements of the PCT with respect to novelty (Article 33(2) PCT).

4 Inventive step

D1 can be regarded as the closest prior art to the subject-matter of the present invention and discloses (see compounds J1-J9 on pages 84-88) structurally-related piperidine derivatives for the treatment of GPR119-related disorders.

The referred compounds J1-J9 defined in D1 always possess an isopropoxycarbonyl fragment attached to the nitrogen atom of the piperidine ring, while the presently claimed compounds of formula (I) possess a " $\text{CH}_2\text{C}(\text{R}^a\text{R}^b\text{R}^c)$ " moiety instead.

The problem to be solved may therefore be regarded as the provision of further piperidine derivatives for the treatment of GPR119-related disorders. The applicant solves this problem by using the compounds of formula (I) as defined in present claim 1.

Neither D1 nor any other prior art document suggests the fluorine-substitution of a substituted alkyl group at a position beta or gamma to the piperidine ring as defined in the presently claimed compounds of formula (I).

Even though D1 suggests the substitution of the piperidine ring in the compounds defined therein by a fluorine-containing group, it is noted that said groups are always nitrogenated aromatic rings; i.e. a pyridine group as in example J19 (see page 90) or a pyrimidine ring as in example J29 (see page 92).

Consequently, nothing in the prior art suggests the modification of the compounds defined in D1 upon the introduction of the fluorine-containing " $\text{CH}_2\text{C}(\text{R}^a\text{R}^b\text{R}^c)$ " moiety in order to arrive at the presently claimed compounds of formula (I).

The subject-matter of present claims 1-14 can therefore be regarded as involving an inventive step in the sense of Article 33(3) PCT.

From the INTERNATIONAL BUREAU

PCTNOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

MYERS, James B.
ELI LILLY AND COMPANY
Patent Division
P.O. Box 6288
Indianapolis, Indiana 46206-6288
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year)

08 December 2011 (08.12.2011)

Applicant's or agent's file reference

X18674

IMPORTANT NOTIFICATION

International application No.

PCT/US2010/041645

International filing date (day/month/year)

12 July 2010 (12.07.2010)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address

BUENO MELENDO, Ana, Belen
Lilly S.A.
Avenida de la Industria 30
28108 Alcobendas
Madrid
Spain

State of Nationality

ES

State of Residence

ES

Telephone No.

Facsimile No.

E-mail address

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address

BUENO MELENDO, Ana, Belen
Lilly S.A.
Avenida de la Industria 30
28108 Alcobendas
Madrid
Spain

State of Nationality

ES

State of Residence

ES

Telephone No.

Facsimile No.

E-mail address

☐ Notifications by e-mail authorized

3. Further observations, if necessary:

The person identified in Box 2 has been recorded as applicant for US only and inventor for all designated States.

4. A copy of this notification has been sent to:

☒ the receiving Office☐ the International Searching Authority☐ the Authority(ies) specified for supplementary search☐ the International Preliminary Examining Authority☐ the designated Offices concerned☒ the elected Offices concerned☐ other:The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Laniel David

e-mail pt04.pct@wipo.int

Telephone No. +41 22 338 74 04

Facsimile No. +41 22 338 89 95

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

see form PCT/ISA/220

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2010/041645

International filing date (day/month/year)
12.07.2010

Priority date (day/month/year)
24.09.2009

International Patent Classification (IPC) or both national classification and IPC
INV. C07D401/12 C07D401/14 A61K31/4427 A61P3/10

Applicant
ELI LILLY AND COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040
Fax +31 70 340 - 3016

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Menchaca, Roberto

Telephone No. +31 70 340-9524



7A

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2010/041645

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:
 - a. (means)
 - ☐ on paper
 - ☐ in electronic form
 - b. (time)
 - ☐ in the international application as filed
 - ☐ together with the international application in electronic form
 - ☐ subsequently to this Authority for the purposes of search
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-14</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-14</u>
Industrial applicability (IA)	Yes: Claims	<u>1-14</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Document

Reference is made to the following document:

D1 WO 2009/038974 A1 (2009-03-26)

Rule 39 PCT

Claims 13-14 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39(1)(iv) and Rule 67(1)(iv) PCT.

For the assessment of the present claims 13-14 on the question whether they are patentable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as patentable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first or further use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Consequently, and even if no opinion should be formulated with respect to the subject-matter of said claims 13-14 (Article 34(4)(a)(I) PCT), this authority has decided to carry out and base the search and present opinion on the alleged effects of the compounds and/or compositions.

Novelty

No prior art document discloses the compounds of formula (I) defined in present claim 1. The subject-matter of the present independent claims 1, 7 and 13, respectively disclosing the referred compounds, pharmaceutical compositions thereof and therapeutic use for the treatment of GPR119-related disorders, is therefore novel over the prior art in the sense of Article 33(2) PCT.

Dependent claims 2-6, 8-12 and 14 fulfill, as such, the requirements of the PCT with respect to novelty (Article 33(2) PCT).

Inventive step

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D1 can be regarded as the closest prior art to the subject-matter of the present invention and discloses (see compounds J1-J9 on pages 84-88) structurally-related piperidine derivatives for the treatment of GPR119-related disorders.

The referred compounds defined in D1 possess an isopropoxycarbonyl fragment attached to the nitrogen atom of the piperidine ring. However, other substituents are also possible (see list of substituents for "R4" in general formula (I), claim 1). The presently claimed compounds of formula (I) possess a "CH₂C(R^aR^bR^c)" moiety instead.

The problem to be solved may therefore be regarded as the provision of further piperidine derivatives for the treatment of GPR119-related disorders. The applicant solves this problem by using the compounds of formula (I) as defined in present claim 1.

Even though the structurally-related piperidine derivatives J1-J9 defined in D1 possess an isopropoxycarbonyl fragment attached to the nitrogen atom of the piperidine ring, other alternatives like an alkyl group substituted by halo- or by halosubstituted alkyl groups are also encompassed by the general formula (I) of D1 (see list of substituents for "R4" in general formula (I), claim 1). Hence, the presently claimed compounds are also suggested by the prior art.

In order for the presently claimed compounds to be regarded as an inventive selection of the compounds defined in D1, it is needed that an unexpected technical effect is demonstrated by means of comparative data, based on the structural difference mentioned above (i.e. the different substitution at the nitrogen of the piperidine ring).

It is noted that such comparative data is not present in the application as originally filed. In the absence of it, the solution proposed is to be regarded as merely one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed.

The subject-matter of present claims 1-14 cannot therefore be regarded as involving an inventive step in the sense of Article 33(3) PCT.

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO-ISA)

General information	For all international applications filed on or after 01/01/2004 the competent ISA will establish an ISR. It is accompanied by the WO-ISA. Unlike the former written opinion of the IPEA (Rule 66.2 PCT), the WO-ISA is not meant to be responded to, but to be taken into consideration for further procedural steps. This document explains about the possibilities.
Amending claims under Art. 19 PCT	Within 2 months after the date of mailing of the ISR and the WO-ISA the applicant may file amended claims under Art. 19 PCT directly with the International Bureau of WIPO. The PCT reform of 2004 did not change this procedure. For further information please see Rule 46 PCT as well as form PCT/ISA/220 and the corresponding Notes to form PCT/ISA/220.
Filing a demand for international preliminary examination	In principle, the WO-ISA will be considered as the written opinion of the IPEA. This should, in many cases, make it unnecessary to file a demand for international preliminary examination. If the applicant nevertheless wishes to file a demand this must be done before expiry of 3 months after the date of mailing of the ISR/ WO-ISA or 22 months after priority date, whichever expires later (Rule 54bis PCT). Amendments under Art. 34 PCT can be filed with the IPEA as before, normally at the same time as filing the demand (Rule 66.1 (b) PCT). If a demand for international preliminary examination is filed and no comments/amendments have been received the WO-ISA will be transformed by the IPEA into an IPRP (International Preliminary Report on Patentability) which would merely reflect the content of the WO-ISA. The demand can still be withdrawn (Art. 37 PCT).
Filing informal comments	After receipt of the ISR/WO-ISA the applicant may file informal comments on the WO-ISA directly with the International Bureau of WIPO. These will be communicated to the designated Offices together with the IPRP (International Preliminary Report on Patentability) at 30 months from the priority date. Please also refer to the next box.
End of the international phase	At the end of the international phase the International Bureau of WIPO will transform the WO-ISA or, if a demand was filed, the written opinion of the IPEA into the IPRP, which will then be transmitted together with possible informal comments to the designated Offices. The IPRP replaces the former IPER (international preliminary examination report).
Relevant PCT Rules and more information	Rule 43 PCT, Rule 43bis PCT, Rule 44 PCT, Rule 44bis PCT, PCT Newsletter 12/2003, OJ 11/2003, OJ 12/2003

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference X18674	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2010/041645	International filing date (day/month/year) 12/07/2010	(Earliest) Priority Date (day/month/year) 15/07/2009
Applicant ELI LILLY AND COMPANY		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ This international search report has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ Certain claims were found unsearchable (See Box No. II)

3. ☐ Unity of invention is lacking (see Box No. III)

4. With regard to the title,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. _____
☐ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
- b. ☐ none of the figures is to be published with the abstract

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2010/041645

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/12 C07D401/14 A61K31/4427 A61P3/10
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/038974 A1 (IRM LLC; ALPER PHILLIP [US]; AZIMIOARA MIHAI [US]; COW CHRISTOPHER [US]) 26 March 2009 (2009-03-26) cited in the application See compounds J1-J9, pages 84-88.	1-14
A	WO 2008/025798 A1 (BIOVITRUM AB PUBL [SE]; BRANDT PETER [SE]; EMOND RIKARD [SE]; JOHANSSO) 6 March 2008 (2008-03-06) the whole document	1-14

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

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

7 October 2010

Date of mailing of the international search report

14/10/2010

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Menchaca, Roberto

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2010/041645

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009038974 A1	26-03-2009	AR 068496 A1	18-11-2009
		AU 2008302570 A1	26-03-2009
		CA 2697551 A1	26-03-2009
		CN 101801954 A	11-08-2010
		CR 11292 A	22-03-2010
		EC SP100042 A	30-04-2010
		EP 2197873 A1	23-06-2010
		KR 20100055536 A	26-05-2010
		PE 07082009 A1	15-07-2009
		US 2009270409 A1	29-10-2009
WO 2008025798 A1	06-03-2008	AU 2007291252 A1	06-03-2008
		AU 2007291254 A1	06-03-2008
		CA 2660699 A1	06-03-2008
		CA 2661371 A1	06-03-2008
		EP 2059516 A1	20-05-2009
		EP 2059517 A1	20-05-2009
		WO 2008025799 A1	06-03-2008
		WO 2008025800 A1	06-03-2008
		JP 2010501629 T	21-01-2010
		JP 2010501630 T	21-01-2010
		US 2008058339 A1	06-03-2008
		US 2008103141 A1	01-05-2008
		US 2008103123 A1	01-05-2008

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Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 81

36/00

PATENTE DE INVENCION ☐

- ☐ Indicación que se solicita un
- ☐ 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 INVENCION 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 ☐