Industria y Comercio

SUPERINTENDENCIA

PCT

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-109309--00000-0000
Fecha: 2010-09-03 16:34:02 Dep:2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 1441

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 10-109309

54. **TÍTULO** DERÍVADO DE FENILPIRROL NOVEDOSA

51. **CLASIFICACIÓN INTERNACIONAL**

71. **SOLICITANTE** DAIICHI SANKYO COMPANY, LIMITED

DOMICILIO TOKYO,JAPON

74. **APODERADO** LUZ CLEMENCIA DE PAEZ
C.C. 35.456.344 de Usaquén

22. **BOGOTÁ, D.C.,** 06-09-2010

(FORMA P-10)

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-109309- -00000-0000
Fecha: 2010-09-03 16:34:02 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve. 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1441

FORMULARIO UNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.
☒ Capítulo I. ☐ Capítulo II.

2 SOLICITANTE (71)

Nombre: **DAIICHI SANKYO COMPANY, LIMITED**
Sociedad constituida y existente bajo las leyes de Japón.

Dirección: 3-531 Nihonbashi Honcho,
Chuo-ku,
Tokyo 103-8426,
Japón

Domicilio: Tokyo,
Japón

IDENTIFICACIÓN
C.C. ☐ NIT ☐
C.E. ☐ Otro ☐
Cual ____
Número ____

3 REPRESENTANTE O APODERADO

Nombre: LUZ CLEMENCIA DE PAEZ
Dirección: Carrera 4ª. No. 72-35
Teléfono: 347 36 11
Fax: 211 86 50
E-mail: clientes@cavelier.com
Domicilio: Bogotá, Colombia.

IDENTIFICACIÓN
C.C. ☒ NIT ☐
C.E. ☐ Otro ☐
Cual ____
Número 35.456.344 T.P 23.555

4 INVENTOR (ES) (72)

1. **Akihiro FURUKAWA**
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1-2-58, Hiromachi,
Shinagawa-ku,
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c/o Daiichi Sankyo Company, Limited
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Shinagawa-ku,
Tokyo 140-8710,
Japón

3. **Yukari ONISHI**
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1-2-58, Hiromachi,
Shinagawa-ku,
Tokyo 140-8710,
Japón

4. **Hideki KOBAYASHI**
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Shinagawa-ku,
Tokyo 140-8710,
Japón

5. **Takeshi HONDA**
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Shinagawa-ku,
Tokyo 140-8710,
Japón

6. **Yumi MATSUI**
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Japón

7. **Masahiro KONISHI**
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8. **Kenjiro UEDA**
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1-16-13, Kitakasai,
Edogawa-ku,
Tokyo 134-8630,
Japón

9. Tetsuyoshi MATSUFUJI
c/o Daiichi Sankyo Company, Limited
1-2-58, Hiromachi,
Shinagawa-ku,
Tokyo 140-8710,
Japón

(5) **PCT (86)**
Solicitud Internacional No. PCT/JP2009/051834 Fecha: 04 de febrero de 2009
Publicación Internacional No. WO 2009/099080 A1 Fecha: 13 de agosto de 2009

(6) **Título (54)**
DERIVADO DE FENILPIRROL NOVEDOSO

(7) **Clasificación Internacional (51)** C07D 207/333

(8) **Prioridad** SI ☒ NO ☐

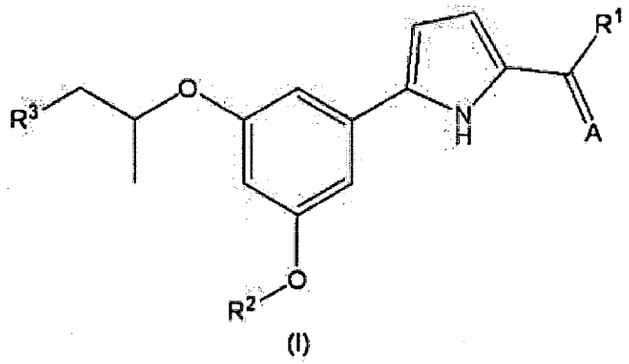
(33) País de Origen	(32) Fecha	(31) Número de Solicitud
JP	06 de febrero de 2008	2008-026519
JP	10 de diciembre de 2008	2008-314479

(9) **Comprobante de pago No.:** 10-67,890 **Fecha:** 18 de agosto de 2010

(10) **Anexos:**

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por $ 554.000.oo.
- ☒ Comprobante de pago por 7 reivindicaciones adicionales después de la décima reivindicación por$182.000.oo.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☒ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Formulario de modificaciones presentando capítulo descriptivo corregido y nuevo pliego reivindicatorio.
- ☒ Comprobante de pago de la tasa por concepto de la modificación
- ☐ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar 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 12x12
- ☐ 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.
- ☒ Otros: VER HOJA DE DOCUMENTOS ANEXOS

11 **FIGURA CARACTERÍSTICA**



(I)

12 Solicito la concesión de la patente,

NOMBRE: LUZ CLEMENCIA DE PAEZ

FIRMA : Luz Clemencia de Paez

C.C. 35.456.344 de Usaquén T.P. 23.555

DOCUMENTOS ANEXOS

1. ☒ Publicación Internacional WO 2009/099080 A1

   Descripción:

   Páginas 367 en el idioma original

   Páginas 491 en español

   Reivindicaciones: Número (s) 32

   Figuras: Número (s)

2. ☒ **Forma PCT/ISA/210.** Informe de Búsqueda Internacional.

3. ☒ Extracto de publicación.

NO SE REALIZARON MODIFICACIONES EN LA FASE INTERNACIONAL

Notaría Sexta 6 DEL CIRCULO DE BOGOTA, D.C.

COPIA NUMERO 4

DE LA ESCRITURA NUMERO: 1.035
FECHA: 25/Febrero/2010

ACTO O CONTRATO:
REVOCACION DE PODER,PODER ESPECIAL
OTORGANTES:
DAIICHI SANKYO COMPANY, LIMITED
CHAVARRO ARISTIZABAL JORGE y otros

ICONTEC
CERTIFICADO DE GESTION DE LA CALIDAD
CERTIFICADO SC 3980-1
PRESTACION DEL SERVICIO PUBLICO NOTARIAL
ISO 9001:2000
NTC-ISO 9001:2000

CERTIFIED IQNet MANAGEMENT SYSTEM

AMPARO QUINTERO ARTURO

NOTARIA SEXTA

CARRERA 9 No. 69-31 - PBX: 317 01 00 - FAX: 314 56 41
Correo Electrónico: notaria6debgta@etb.net.co

6

7 700004 335964

ESCRITURA PUBLICA NUMERO - - -1039 - - - - -

- - - - - - -MIL TREINTA Y NUEVE - - - - - - - - -

DE FECHA: FEBRERO VEINTICINCO (25) - - - - - - - -

DEL AÑO DOS MIL DIEZ (2.010) - - - - - - - - -

OTORGADA EN LA NOTARIA SEXTA (6a) DEL CIRCULO DE BOGOTA D.C. ----------

CLASE DE ACTO O CONTRATO: **PODER ESPECIAL** y **REVOCATORIA** ----------

DE: **CAVELIER ABOGADOS** ----------

A : **LUZ CLEMENCIA DE PÁEZ, NIDIA OSORIO LÓPEZ, OSCAR FERNANDO CORREA BARBOSA, EDNA DARMELY SARMIENTO CHARRY y JORGE CHAVARRO ARIZTIZABAL** ----------

En la ciudad de Bogotá D.C. República de Colombia, ante mí, AMPARO QUINTERO ARTURO Notaria sexta (6a.) —— de éste círculo notarial, se otorgó la presente escritura pública que se consigna en los siguientes términos: ----------

COMPARECENCIA: Con minuta escrita, compareció el señor **CARLOS ALBERTO GALLÓN GIRALDO**, mayor de edad, vecino de esta ciudad, casado, identificado con la cédula de ciudadanía No. 19.066.425 de Bogotá, y dijo:----------

ESTIPULACIONES: ----------

PRIMERA.- Que obra en su calidad de representante legal de la sociedad denominada **CAVELIER ABOGADOS** domiciliada en la **Carrera 4 No. 72-35, Bogotá, Colombia.** ----------

SEGUNDA: Que **DAIICHI SANKYO COMPANY, LIMITED,** sociedad constituida y existente bajo las leyes de Japón, domiciliada en 3-5-1, Nihonbashi Honcho, Chuo-ku, Tokio 103-8426, Japón, designó a **CAVELIER ABOGADOS** como su representante para la Propiedad Industrial en Colombia con facultades de nombrar apoderados tal como consta en la copia auténtica del documento de representación que se protocoliza. ----------

TERCERA.- Que en su carácter de representante legal de **CAVELIER ABOGADOS**, y en desarrollo de la facultad otorgada por **DAIICHI SANKYO COMPANY, LIMITED,** confiere poder a los abogados **LUZ CLEMENCIA DE PAEZ,** T.P.A. No. 23.555, identificada con cédula de ciudadanía número 35.456.344 de Usaquen, **NIDIA OSORIO LOPEZ**, T.P.A. No.73.366, identificada con cédula de ciudadanía número 39.787.682 de Bogotá, **OSCAR FERNANDO CORREA**

IMPRESO EN DICIEMBRE 1° DE 2009 POR POLYPRINT EDITORIAL LTDA - NIT 830.029.959-5

PAPEL DE USO EXCLUSIVO DEL PROTOCOLO NOTARIAL . NO TIENE COSTO PARA EL USUARIO

NOTARIA SEXTA DE BOGOTA

BARBOSA, T.P.A. No. 71.027 identificado con cédula de ciudadanía número 79.524.634 de Bogotá, **EDNA DARMELY SARMIENTO CHARRY**, T.P.A. 65.794 identificada con cédula de ciudadanía número 52.006.265 de Bogotá y **JORGE CHAVARRO ARIZTIZABAL**, T.P.A. No. 40.119, identificado con cédula de ciudadanía número 16.209.380 de Cartago (Valle), mayores de edad, vecinos de Bogotá, para que representen a la sociedad a cuyo nombre actúa, ante cualesquiera entidades o personas, ejerzan o no jurisdicción, incluyendo las del orden administrativo, contencioso administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos:----------

a) Obtención de patentes de invención, modelos de utilidad, diseños industriales, trazado de circuitos integrados, secretos industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, variedades vegetales, denominaciones de origen e indicaciones de procedencia, su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos ----------

b) Las acciones de competencia desleal, protección del consumidor, oposiciones, cancelación administrativa o judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la protección de secretos industriales y de nombres de dominio junto con su administración y pago; y en general los procesos civiles, penales, administrativos o contencioso- administrativos, de conciliación, arbitramento, tutela relacionados con estos derechos; acciones y procesos que promovamos o se nos promuevan. ----------

CUARTO.- Que los apoderados designados están facultados en todos los asuntos arriba determinados para sustituir este mandato, transigir, conciliar, arbitrar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar y ratificar los actos de agentes oficiosos. ----------

QUINTO- Que protocoliza con la presente escritura, un certificado expedido por la Cámara de Comercio de Bogotá, que acredita la constitución y personería de la sociedad **CAVELIER ABOGADOS,** igualmente protocoliza copia autenticada del documento de representación otorgado el día **02 de Noviembre de 2009** ---------- por **DAIICHI SANKYO COMPANY, LIMITED,** documento que está debidamente

1063

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4a Nº 72-35
BOGOTA, D. C. - COLOMBIA

REPRESENTACION

REPRESENTATION

Yo (nosotros), abajo firmado (s)/I (we), the undersigned

DAIICHI SANKYO COMPANY, LIMITED

domiciliado (s)
en/of 3-5-1, Nihonbashi Honcho, Chuo-ku, Tokyo103-8426, Japan

Por el presente nombramos a CAVELIER ABOGADOS, sociedad colectiva constituida de conformidad con las leyes de la República de Colombia, mediante Escritura Pública No. 6233 del 10 de septiembre de 1974, otorgada en la Notaría Sexta del Círculo de Bogotá, domiciliada en Bogotá D.C., con matrícula mercantil No. 00820237 y NIT 860041367-3, domiciliada en la Carrera 4a Nº 72-35, Bogotá, Colombia, como nuestra representante en todos los asuntos de Propiedad Industrial, con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales.

CAVELIER ABOGADOS también podrá representarnos, con las mismas facultades arriba indicadas, ante cualesquiera entidades o personas, ejerzan o no jurisdicción, autoridades administrativas o jurisdiccionales, tribunales de arbitramento, en asuntos de naturaleza civil, comercial, penal, constitucional, competencia, competencia desleal, administrativa, contencioso administrativa, protección del consumidor, variedades vegetales, nombres de dominio, oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, acciones de tutela, la protección de secretos industriales, derecho regulatorio y en general para que nos represente en cualesquiera acciones y procesos que promovamos o se nos promuevan.

La representante podrá, en nuestro nombre, designar apoderados para actuar ante autoridades administrativas y judiciales, por vía extrajudicial y también procesalmente en nuestro nombre, como demandantes, como demandados, como litisconsortes, como agentes oficiosos, como terceros, por llamamiento en garantía o como intervinientes ad excludendum. Dentro de esta autorización, la representante podrá facultar a los apoderados que ella designe para transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir,

Do hereby appoint CAVELIER ABOGADOS, a general partnership organized under the laws of the Republic of Colombia by means of Public Deed No. 6233 of September 10, 1974, granted at Notary Sixth of the Bogota Circuit, domiciled in Bogota D.C., with Mercantile Registration No. 00820237 and Taxpayer Identification Number 860041367-3, domiciled at Carrera 4a Nº 72-35, Bogota, Colombia, as our representative for all Industrial Property matters with faculty to receive notifications and appoint attorneys in and out of Court.

CAVELIER ABOGADOS may also represent us, with the same faculties stated above, before any entities or persons, with or without jurisdiction, administrative or jurisdictional authorities, courts of arbitration, in civil, commercial, criminal, constitutional, competition, unfair competition, administrative, administrative contentious, consumer protection, plant varieties, domain names, opposition or observation matters, administrative and Court cancellation, nullity, precautionary measures, licensing, action for writ mandamus, protection of trade secrets, regulatory law and in general represent us in any actions and suits instituted by us or against us.

The representative may, in our name, designate attorneys to act before administrative and judicial authorities, through out-of-court channels, and also procedurally in our name as plaintiff, defendant, joint litigant, representative without power of attorney, third party, when summoned to appear in court or as intervener ad excludendum. Under this authorization, the representative may empower the attorneys appointed thereby to compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign and substitute the

© CAVELIER ABOGADOS

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA, D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
17 DIC. 2009
AMPARO QUINTERO ARTURO
NOTARIA

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA, D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
25 FEB. 2010
AMPARO QUINTERO ARTURO
NOTARIA

NOTARIA SEXTA DE BOGOTA

renunciar y sustituir el poder que se le otorgue. Así mismo, la representante tendrá la facultad para revocar el poder así otorgado en el momento que considere pertinente. La representante en todo caso podrá ratificar los actos de agentes oficiosos.

power of attorney granted thereto. Likewise, the representative shall have the faculty of revoking the power of attorney thus granted at any time it may deem convenient. The representative may in any case ratify the acts of representatives without a power of attorney.

Dado y firmado hoy/Given and signed this 2nd day of November, 2009

En/in Tokyo

Por/by Kazuo Sato
General Manager, Intellectual Property

Firma/Signature

Nota:

PARA SOCIEDADES

El documento de Representación deberá ser firmado por el representante legal de la compañía, autenticado ante Notario Público y legalizado*.

El Notario deberá certificar: i) que la compañía existe; ii) que ejerce su objeto social; y iii) que la persona que firma está autorizada para otorgar este documento.

*La legalización podrá ser por Apostilla si el país del otorgante hace parte de la Convención de La Haya del 5 de octubre de 1961 o ante el Cónsul de Colombia en caso contrario.

PARA PERSONAS NATURALES

El documento de Representación deberá ser firmado por el otorgante: El Notario Público deberá certificar que la persona que firma es quien dice ser.

Posteriormente el documento de Representación deberá ser legalizado por Apostilla si el país del otorgante hace parte de la Convención de La Haya del 5 de octubre de 1961 o ante el Cónsul de Colombia en caso contrario.

Note:

FOR CORPORATIONS

The Representation document ought to be signed by the legal representative of the company, notarized and legalized*.

The Notary Public must certify: i) that the company legally exists; ii) that it is in exercise of its corporate purposes; and iii) that the person who signs the Representation document is authorized to do so.

* Legalization may be made by Apostille if the issuing country is a member of the The Hague Convention of October 5, 1961, or before the Colombian Consulate if otherwise.

FOR INDIVIDUALS

The Representation should be signed by the grantor. The Notary Public should certify that the person signing is who he/she purports to be.

Subsequently, the Representation document should be legalized by Apostille if the issuing country is a member of the The Hague Convention of October 5, 1961 or before the Colombian Consulate if otherwise.

© CAVELIER ABOGADOS

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C., HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
17 DIC. 2009
AMPARO QUINTERO ARTURO
NOTARIA

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C., HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
25 FEB. 2010
AMPARO QUINTERO ARTURO
NOTARIA

8

NOTARIAL CERTIFICATE Registration No 1755

This is to certify that the signature on the foregoing document is genuine and authentic signature of Kazuo Sato, General Manager, Intellectual Property of DAIICHI SANKYO COMPANY, LIMITED, a corporation existing and organized under the laws of Japan, who has produced sufficient proof of his power to execute the said instrument on behalf of the above-mentioned corporation.

NOV - 2 2009

TOKYO LEGAL AFFAIRS BUREAU
NOTARY
2-2-2, UCHISAIWAICHO
CHIYODA-KU
TOKYO JAPAN

TADAHIKO MITSUDA
NOTARY

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA, D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C., REPUBLICA DE COLOMBIA
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NOTARIA

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA, D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA
BOGOTA D.C., REPUBLICA DE COLOMBIA
25 FEB. 2010
AMPARO QUINTERO ARTURO
NOTARIA

NOTARIA SEXTA DE BOGOTA

平成２１年登簿第 1755号

認　　証

嘱託人第一三共株式会社知的財産部長佐藤一雄の代理人城野番は、本公証人に対し、嘱託人が別添文書に署名したことを自認している旨陳述した。

よって、これを認証する。

平成２１年　11　月　2　日、本公証人役場において

東京都千代田区内幸町２丁目２番２号

東京法務局所属

公証人

Notary

満田忠彦

TADAHIKO MITSUDA

証　　明

上記署名は、東京法務局所属公証人の署名に相違ないものであり、かつ、その押印は、真実のものであることを証明する。

平成２１年 11 月 2 日

東京法務局長　山浦 陟一郎

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: JAPAN
   This public document
2. has been signed by TADAHIKO MITSUDA
3. acting in the capacity of Notary of the Tokyo Legal Affairs Bureau
4. bears the seal/stamp of TADAHIKO MITSUDA, NOTARY

Certified

5. at Tokyo
6. NOV - 2 2009
7. by the Ministry of Foreign Affairs
8. 09- Nº 002049
9. Seal/stamp:
10. Signature

K. Oyabe

Kazutoyo OYABE

For the Minister for Foreign Affairs

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA, D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
25 FEB. 2010
AMPARO QUINTERO ARTURO
NOTARIA

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA, D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
17 DIC. 2009
AMPARO QUINTERO ARTURO
NOTARIA

TRADUCCIÓN OFICIAL 342/2009 DE UN DOCUMENTO EN IDIOMA INGLÉS REALIZADA POR EDUARDO CALADO NOGUERA, TRADUCTOR OFICIAL APROBADO POR RESOLUCION 541 DEL 27 DE FEBRERO DE 1976 EXPEDIDA POR EL MINISTERIO DE JUSTICIA DE COLOMBIA Y DEBIDAMENTE REGISTRADO ANTE EL MINISTERIO DE RELACIONES EXTERIORES DE COLOMBIA, POR EL CUAL **DAIICHI SANKYO COMPANY, LIMITED**. DOMICILIADA EN 3-5-1, NIHONBASHI HONCHO, CHUO-KU, TOKIO 103-8426, JAPÓN, OTORGA REPRESENTACIÓN EN ASUNTOS RELACIONADOS CON PROPIEDAD INDUSTRIAL A **CAVELIER ABOGADOS.**

DADO Y FIRMADO HOY 2 DE NOVIEMBRE DE 2009 EN TOKIO POR KAZUO SATO, GERENTE GENERAL, PROPIEDAD INTELECTUAL. FIRMA: ILEGIBLE.

CERTIFICACIÓN NOTARIAL

REGISTRO NO 1755

Por la presente certifico que la firma sobre el documento precedente es la firma genuina y auténtica de KAZUO SATO, gerente general, Propiedad Intelectual de DAIICHI SANKYO COMPANY, LIMITED, una sociedad constituida y existente de conformidad con las leyes del Japón, quien ha presentado prueba suficiente de su poder para firmar dicho documento a nombre de la sociedad arriba mencionada. 2009. Firmado: TADAHIKO MITSUDA, notario

SELLO: OFICINA DE ASUNTOS JURÍDICOS DE TOKIO

NOTARIO. 2-2-2, UCHISAIWAICHO, CHIYODA-KU, TOKIO, JAPÓN

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
17 DIC. 2009
AMPARO QUINTERO ARTURO
NOTARIA

APOSTILLA

(CONVENCION DE LA HAYA DEL 5 DE OCTUBRE DE 1961)

1. PAIS: JAPÓN

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C.
HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
25 FEB. 2010
AMPARO QUINTERO ARTURO
NOTARIA

NOTARIA SEXTA DE BOGOTA

2. Este documento público ha sido firmado por TADAHIKO MITSUDA

3. quien actúa en su calidad de notario de la oficina de asuntos jurídicos de TOKIO.

4. lleva el sello/estampilla de TADAHIKO MITSUDA, NOTARIO

CERTIFICADO

5. En TOKIO 6. el 2 de noviembre de 2009

7. Por el Ministerio de Relaciones Exteriores

8. 09- No. 002049

9. Sello/estampilla: MINISTERIO DE RELACIONES EXTERIORES, JAPÓN

10. Firma: KAZUTOYO OYABE, A NOMBRE DEL MINISTRO DE RELACIONES EXTERIORES

COLO-15869-841-017-8

ECN\ECN\ID-162614\WPCL002G

Bogotá, 14 de diciembre de 2009.

Eduardo Calvo M.

TRADUCTOR OFICIAL

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA BOGOTA D.C. REPUBLICA DE COLOMBIA
17 DIC. 2009
AMPARO QUINTERO ARTURO
NOTARIA

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA BOGOTA D.C. REPUBLICA DE COLOMBIA
25 FEB. 2010
AMPARO QUINTERO ARTURO
NOTARIA

ASUME RESPONSABILIDAD POR EL TEXTO

15 FEB 9:38

150539

Eduardo Calvo

EMBAJADA DE ESPAÑA

MINISTERIO DE RELACIONES EXTERIORES

01

86226885

CAMARA DE COMERCIO DE BOGOTA

SEDE CHAPINERO

17 DE DICIEMBRE DE 2009 HORA 11:11:00

R027136832 PAGINA: 1 de 3

* *

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O INSCRIPCION DE DOCUMENTOS

CERTIFICA:

NOMBRE : CAVELIER ABOGADOS
N.I.T. : 860041367-3
DOMICILIO : BOGOTA D.C.

CERTIFICA:

NO: 00820237

CERTIFICA:

CONSTITUCION : QUE POR ESCRITURA PUBLICA NO. 0006233 DE NOTARIA SEXTA DE BOGOTA D.C. DEL 10 DE SEPTIEMBRE DE 1974 , INSCRITA EL 26 DE SEPTIEMBRE DE 1974 BAJO EL NUMERO 00021234 DEL LIBRO IX, SE CONSTITUYO LA SOCIEDAD CIVIL DENOMINADA: CAVELIER PERDOMO Y CAVELIER.

CERTIFICA :

QUE POR ESCRITURA PUBLICA NO. 0001000 DE NOTARIA SEXTA DE BOGOTA D.C. DEL 10 DE MARZO DE 1983 , INSCRITA EL 5 DE ABRIL DE 1983 BAJO EL NUMERO 00130769 DEL LIBRO IX, LA SOCIEDAD CAMBIO SU NOMBRE DE : CAVELIER PERDOMO Y CAVELIER. POR EL DE : CAVELIER ABOGADOS

CERTIFICA:

QUE POR ESCRITURA PUBLICA NUMERO 1.000 OTORGADA EN LA NOTARIA 6A. DE BOGOTA EL 10 DE MARZO DE 1.983, INSCRITA EN ESTA CAMARA DE COMERCIO EL 5 DE ABRIL DE 1.983 BAJO EL NUMERO 130769 DEL LIBRO IX, LA SOCIEDAD CAMBIO SU NOMBRE DE: CAVELIER PERDOMO Y CAVELIER, POR EL DE: CAVELIER ABOGADOS, E INTRODUJO OTRAS REFORMAS.

CERTIFICA:

CERTIFICA

QUE POR E.P.NO. 2.034 DE LA NOTARIA 6 DE SANTAFE DE BOGOTA DEL 18 DE ABRIL DE 1.995, INSCRITA EL 27 DE ABRIL DE 1.995 BAJO EL NO. 5.937 DEL LIBRO XIII,LA SOCIEDAD TRASLADO SU DOMICILIO DE LA CIUDAD DE SANTAFE DE BOGOTA D.C. AL MUNICIPIO DE TABIO (CUNDINAMARCA).-.

CERTIFICA:

QUE POR ESCRITURA PUBLICA NO. 7710 DE LA NOTARIA SEXTA DE BOGOTA DEL 10 DE OCTUBRE DE 1984, INSCRITA EL 15 DE NOVIEMBRE DE 1984 BAJO EL NO. 1559 DEL LIBRO XIII, LA SOCIEDAD CAMBIO SU NATURALEZA JURIDICA DE SOCIEDAD COMERCIAL A SOCIEDAD CIVIL.

CERTIFICA:

REFORMAS:

ESCRITURAS NO.	FECHA	NOTARIA	INSCRIPCION
842	10-V-1.977	18. BTA.	27-V-1.977-NO. 46.204
3.430	1-VII-1.980	6A. BTA.	3-IX-1.980-NO. 89.582
4.844	10-IX-1.980	6A. BTA.	8-X-1.980-NO. 91.261
432	10-II-1.983	6A. BTA.	1-III-1.983-NO.129.337

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA BOGOTA D.C. REPUBLICA DE COLOMBIA

25 FEB. 2010

ARO QUINTERO ARTURO
NOTARIA

NOTARIA SEXTA BOGOTA D.C.

7.710	10-X-1.984	6A. BTA.	15-XI-1.984-NO.	1.559
7.305	21-X-1.985	6A. BTA.	18-XI-1.985-NO.	1.906
2.567	29-IV-1.987	6A. BTA.	7-V- 1.987-NO.	2.386
4.278	3-VII-1.987	6A. BTA.	23-VII-1987 NO.	215.652
2.657	25- IV-1.988	6A. BTA.	19- V -1988-NO.	2,740
9.033	21-XII-1.990	6A. BTA.	10- I - 1991-NO.	3.786
25	3- I -1.991	6A. BTA.	10- I - 1991-NO.	3.787
1.608	8-III-1.991	6A. BTA.	14-III- 1991-NO.	3.841
2.155	2-IV- 1.991	6A. BTA.	8-IV - 1991-NO.	3.862
797	7-II -1.991	6A. BTA.	7- V -1991-NO.	3.882
1.739	14-III-1.991	6A. BTA.	7- V -1991-NO.	3.881
5.886	21-VIII-1.991	6A. BTA	27-VIII-1991 NO.	4.019
8.596	4-XII -1.991	6A. BTA	16-III -1992 NO.	4.430
1.494	10-III -1.992	6A. BTA.	19-III -1992 NO.	4.436
4.205	8 -VII -1.992	6A. BTA.	15-VII -1992 NO.	4.554
8.829	16-XII -1.992	6A. BTA.	24-XII -1992 NO.	4.819
12	5-I -1.993	6 STAFE BTA	13-I -1993 NO.	4.850
4.877	29-VI -1.993	6 STAFE BTA	7-VII -1993 NO.	5.065
5.216	12-VII -1.993	6 STAFE BTA	16-VII -1993 NO.	5.077
ACTA NO.71	2-IX- 1.993	JUNTA DE SOCIOS	29-IX- 1993 NO.	5.174
2.034	18-IV- 1.995	6 STAFE BTA	27- IV -1995 NO.	5.937
2.227	25-IV-1.995	6 STAFE BTA	18-VIII-1.995 NO.	6.092
7.594	12-XII-1.995	6 STAFE BTA	19- XII-1.995 NO.	6.294
676	11- II-1.997	6 STAFE BTA	14- II -1.997 NO.	6.873

CERTIFICA:

REFORMAS:

E.P. NO.	FECHA	NOTARIA	CIUDAD	FECHA	NO.INSC.
0004506	1997/07/28	0006	BOGOTA D.C.	1997/09/02	00007115
0002103	1998/04/08	0006	BOGOTA D.C.	1998/04/21	00007426
0005326	1998/08/06	0006	BOGOTA D.C.	1998/08/13	00007544
0005538	1998/08/14	0006	BOGOTA D.C.	1998/08/27	00007564
0007760	1998/11/10	0006	BOGOTA D.C.	1998/11/12	00007644
0006709	1997/11/04	0006	BOGOTA D.C.	2000/12/04	00008481
0003034	2003/05/30	0006	BOGOTA D.C.	2003/06/04	00882729
0003786	2004/07/16	0006	BOGOTA D.C.	2004/07/28	00009703
0001432	2005/03/18	0006	BOGOTA D.C.	2005/04/07	00009917
0004818	2005/08/22	0006	BOGOTA D.C.	2005/08/26	00010008
0005506	2007/07/17	0006	BOGOTA D.C.	2007/07/24	00010841
5453	2009/10/19	0006	BOGOTA D.C.	2009/10/21	00012243

CERTIFICA:

LA SOCIEDAD NO SE HALLA DISUELTA. DURACION HASTA EL 10 DE SEPTIEMBRE DE 2024 .

CERTIFICA:

OBJETO SOCIAL: LA SOCIEDAD TENDRA POR OBJETO : EL EJERCICIO DE LA PROFESION LIBERAL DE ABOGADOS. EN DESARROLLO DE ESTE OBJETO SOCIAL PODRA ADQUIRIR, CONTRAER OBLIGACIONES Y CELEBRAR TODA CLASE DE CONTRATOS DIRECTAMENTE RELACIONADOS Y SUBORDINADOS AL MISMO, INCLUSIVE LOS DE ARRENDAMIENTO, HIPOTECA, MUTUO CON O SIN INTERES, MANDATO CIVIL Y COMERCIAL, Y SOCIEDAD, ASI COMO PARTICIPAR EN ASOCIACIONES CIENTIFICAS, GREMIALES O PROFESIONALES SIN ANIMO DE LUCRO.

CERTIFICA:

CAPITAL Y SOCIOS: $10,000.00 DIVIDIDO EN 10,000.00 CUOTAS CON VALOR NOMINAL DE $1.00 CADA UNA, DISTRIBUIDO ASI :

- SOCIO CAPITALISTA (S)

ASOCIACION CAVELIER DEL DERECHO N.I.T. 000008001722568

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE ME FUE PUESTO A LA VISTA BOGOTA D.C. REPUBLICA DE COLOMBIA
25 FEB. 2010
AMPARO QUINTERO ARTURO
NOTARIA

NO. CUOTAS: 8,800.00 VALOR: $8,800.00
GAUDEBERT DE CAVELIER AGNES JEANNE C.E. 000000000131100
NO. CUOTAS: 1,200.00 VALOR: $1,200.00
- SOCIO INDUSTRIAL (S)
CHAVARRO JORGE C.C. 000000016209380
NO. CUOTAS: 0.00 VALOR: $0.00
SUAREZ DE PAEZ LUZ CLEMENCIA C.C. 000000035456344
NO. CUOTAS: 0.00 VALOR: $0.00
PEÑA VALENZUELA DANIEL C.C. 000000079518915
NO. CUOTAS: 0.00 VALOR: $0.00
MARIN RUALES GERMAN HUMBERTO C.C. 000000079155665
NO. CUOTAS: 0.00 VALOR: $0.00
TOTALES
NO. CUOTAS: 10,000.00 VALOR: $10,000.00

CERTIFICA:

QUE POR ESCRITURAS PUBLICAS NO. 001431 Y 001432 DEL 18 DE MARZO DE 2005 DE LA NOTARIA 06 DE BOGOTA D.C., INSCRITA EL 07 DE ABRIL DE 2005 BAJO EL NO. 0009918 Y 0009917, RESPECTIVAMENTE DEL LIBRO XIII, DE LAS MIL DOSCIENTAS (1200) PARTES DE INTERES SOCIAL RADICADAS EN CABEZA DE AGNES GAUDEBERT DE CAVELIER, SEISCIENTAS (600) PARTES ESTAN GRAVADAS O AFECTADAS EN PROPIEDAD FIDUCIARIA A FAVOR DE LAS SIGUIENTES PERSONAS : GERMAN CAVELIER FRANCO, ERNESTO CAVELIER FRANCO, JORGE CAVELIER FRANCO, INES CAVELIER FRANCO, GUILLERMO CAVELIER FRANCO, ELENA CAVELIER FRANCO, ALEJANDRO CAVELIER FRANCO, BEATRIZ CAVELIER FRANCO, Y LUCIA CAVELIER FRANCO.

CERTIFICA:

REPRESENTACION LEGAL: EL REPRESENTANTE LEGAL ES EL DIRECTOR. EL SOCIO FUNDADOR GERMAN CAVELIER GAVIRIA TENDRA EL CARACTER DE PRESIDENTE DIRECTOR VITALICIO, PARTICIPARA POR DERECHO PROPIO EN EL CONSEJO SUPERIOR Y EN EL CONSEJO DIRECTIVO Y LLEVARA LA REPRESENTACION LEGAL DE LA SOCIEDAD CUANDO LO ESTIME PERTINENTE SIN LIMITACION ALGUNA. IGUAL PARTICIPACION Y ATRIBUCIONES TENDRA SU SUPLENTE AGNES GAUDEBERT DE CAVELIER CUANDO OCUPE EL CARGO, EN CASO DE FALTA ABSOLUTA DE GERMAN CAVELIER GAVIRIA. LOS SOCIOS COLECTIVOS ESTÁN AUTORIZADOS PARA EJERCER LA REPRESENTACIÓN DE LA SOCIEDAD EN CUALQUIER TIEMPO, SIN PERJUICIO DE LAS DELEGACIONS CONFERIDAS A LOS ORGANOS CREADOS POR LOS PRESENTES ESTATUTOS

CERTIFICA:

** NOMBRAMIENTOS **

QUE POR NO. 12 DE JUNTA DE SOCIOS DEL 14 DE AGOSTO DE 2009, INSCRITA EL 24 DE SEPTIEMBRE DE 2009 BAJO EL NUMERO 00012200 DEL LIBRO XIII, FUE (RON) NOMBRADO (S):

NOMBRE IDENTIFICACION

DIRECTOR (REPRESENTANTE LEGAL DE LA ASOCIACIÓN CAVELIER DEL DERECHO)

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
25 FEB. 2010
ARO QUINTERO ARTURO
NOTARIA

NOTARIA SEXTA DE BOGOTÁ

GALLON GIRALDO CARLOS C.C. 000000019066425

QUE POR ESCRITURA PUBLICA NO. 0004818 DE NOTARIA 6 DE BOGOTA D.C. DEL 22 DE AGOSTO DE 2005, INSCRITA EL 26 DE AGOSTO DE 2005 BAJO EL NUMERO 00010008 DEL LIBRO XIII, FUE (RON) NOMBRADO (S):

NOMBRE	IDENTIFICACION
PRESIDENTE DIRECTOR VITALICIO	
CAVELIER GAVIRIA GERMAN	C.C. 000000002877924
SUPLENTE DEL PRESIDENTE DIRECTOR VITALICIO	
GAUDEBERT DE CAVELIER AGNES JEANNE	C.E. 000000000131100

CERTIFICA:

FACULTADES DEL REPRESENTANTE LEGAL: APARTE DE LAS FACULTADES Y DEBERES QUE DE TIEMPO EN TIEMPO SE LE ASIGNEN POR EL CONSEJO SUPERIOR, EL DIRECTOR TENDRA LAS SIGUIENTES FUNCIONES : A) LA DE REPRESENTAR LEGALMENTE A LA SOCIEDAD ANTE LAS AUTORIDADES DE CUALQUIER ORDEN O NATURALEZA Y ANTE OTRAS PERSONAS NATURALES O JURIDICAS, CON FACULTADES PARA NOVAR, TRANSIGIR, COMPROMETER Y DESISTIR Y PARA COMPARECER EN JUICIOS INCLUSIVE EN AQUELLOS EN DONDE SE DISPUTE LA PROPIEDAD DE BIENES INMUEBLES; B) CUMPLIR Y HACER CUMPLIR LOS ESTATUTOS Y REGLAMENTOS DE LA SOCIEDAD; Y C) CREAR O SUPRIMIR TODOS LOS EMPLEOS QUE SEAN NECESARIOS DE ACUERDO CON EL CONSEJO SUPERIOR PARA EL BUEN FUNCIONAMIENTO DE LA SOCIEDAD, ASIGNARLES FUNCIONES, FIJAR SUS SALARIOS Y NOMBRAR LAS PERSONAS QUE DEBAN DESEMPEÑARLOS, ASI COMO RETIRARLOS Y REEMPLAZARLOS CUANDO HAYA LUGAR. CUANDO CUALQUIERA DE LOS ACTOS INDICADOS EN LA CLAUSULA ANTERIOR SE REFIERA A OPERACIONES CUYO MONTO EXCEDA DE LA SUMA EQUIVALENTE A CIENTO OCHENTA (180) SALARIOS MINIMOS MENSUALES, SU CELEBRACION REQUERIRA LA APROBACION PREVIA DEL CONSEJO SUPERIOR.

CERTIFICA:

** REVISOR FISCAL **

QUE POR ACTA NO. 0000071 DEL 2 DE SEPTIEMBRE DE 1993, INSCRITA EL 29 DE SEPTIEMBRE DE 1993 BAJO EL NUMERO 00005175 DEL LIBRO XIII, FUE (RON) NOMBRADO (S):

NOMBRE	IDENTIFICACION
REVISOR FISCAL	
RINCON FANDIÑO MIGUEL ALFONSO	C.C. 000000002877024

CERTIFICA:

DE CONFORMIDAD CON LO ESTABLECIDO POR LA LEY 962 DE 2005, LOS ACTOS DE REGISTRO AQUI CERTIFICADOS QUEDAN EN FIRME CINCO (5) DIAS HABILES DESPUES DE LA FECHA DE INSCRIPCION, SIEMPRE QUE NO SEAN OBJETO DE RECURSO EN LA VIA GUBERNATIVA.

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA BOGOTA D.C. REPUBLICA DE COLOMBIA
25 FEB. 2010
QUINTERO ARTURO
NOTARIA

* * * EL PRESENTE CERTIFICADO NO CONSTITUYE PERMISO DE * * *
* * * FUNCIONAMIENTO EN NINGUN CASO * * *

EL SECRETARIO DE LA CAMARA DE COMERCIO,

****

01

88226887

CAMARA DE COMERCIO DE BOGOTA

SEDE CHAPINERO

17 DE DICIEMBRE DE 2009 HORA 11:11:00

R027136832 PAGINA: 3 de 3

* *

VALOR : $ 3,500

DE CONFORMIDAD CON EL DECRETO 2150 DE 1995 Y LA AUTORIZACION IMPARTIDA POR LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, MEDIANTE EL OFICIO DEL 18 DE NOVIEMBRE DE 1996, LA FIRMA MECANICA QUE APARECE A CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES

COMO NOTARIA SEXTA DEL CÍRCULO DE BOGOTÁ D.C., HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTÁ D.C., REPÚBLICA DE COLOMBIA
25 FEB. 2010
AMPARO QUINTERO ARTURO
NOTARIA

NOTARÍA SEXTA DE BOGOTÁ

7700004335957

13

legalizado ----------

Presente el señor **CARLOS ALBERTO GALLÓN GIRALDO**, domiciliado en Bogotá, identificado como aparece al pie de su firma y manifestó que está conforme con el contenido de esta escritura pública y que en consecuencia revoca la escritura número seis mil setecientos noventa y seis (6796) del diecisiete (17) de Diciembre de dos mil nueve (2009) otorgada ante esta misma notaría. ----------

---------- **HASTA AQUÍ LA MINUTA PRESENTADA** ----------

OTORGAMIENTO Y AUTORIZACION: LEIDA la presente escritura por los comparecientes y habiéndoseles hecho las advertencias sobre los trámites y formalidades de rigor le impartieron su aprobación y para constancia la firman ante mí el NOTARIO QUE AUTORIZA ----------

DERECHOS NOTARIALES: $ 85.720.oo - - - - - - - - - - - - - - -

IVA 16% $ 22.486.oo -

PAPEL NOTARIAL: esta escritura ha quedado extendida en las hojas de papel sellado notarial números: ----------

7-700004-335964 - 7-700004-335957 - - - - - - - - - - - - - - - - -

EN BLANCO... EN BLANCO

OTORGANTE

CARLOS ALBERTO GALLÓN GIRALDO

C.C. 19.066.425 Bta

TEL 3473611

REPRESENTANTE LEGAL DE **CAVELIER ABOGADOS**

REPÚBLICA DE COLOMBIA
AMPARO QUINTERO ARTURO
NOTARIA
NOTARIA SEXTA DE BOGOTÁ

AMPARO QUINTERO ARTURO
NOTARIA SEXTA (6a) DE BOGOTA D.C.

NOTARIA SEXTA DE BOGOTÁ

T1063/10.PG.ANGELIK

IMPRESO EN DICIEMBRE 1° DE 2009 POR POLYPRINT EDITORIAL LTDA. - NIT 830.029.959-5

PAPEL DE USO EXCLUSIVO DEL PROTOCOLO NOTARIAL . NO TIENE COSTO PARA EL USUARIO

ES FIEL Y SEGUNDA COPIA (FOTOCOPIA) TOMADA DE LA ESCRITURA PUBLICA NUMERO 4558 DE FECHA 27 DE AGOSTO DE 2010 QUE EXPIDO EN 12 HOJAS RUBRICADAS EN SUS MARGENES SE EXPIDE CON DESTINO AL INTERESADO.

BOGOTA, D.C. 30 DE AGOSTO DE 2010

RESOLUCION 01 DE 2008

POR LA NOTARIA SEXTA DE BOGOTA



AMPARO OLIVA INTERCARTURO.
NOTARIA SEXTA DE BOGOTA.

AB 14

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4a N° 72-35
BOGOTA, 8 – COLOMBIA

374

D&W Dkt. No. 191248/CO

CESION

ASSIGNMENT

Yo, (nosotros) abajo firmado (s)		I (we), the undersigned
		1) FURUKAWA, Akihiro, 2) FUKUZAKI, Takehiro,
		3) ONISHI, Yukari, 4) KOBAYASHI, Hideki,
		5) HONDA, Takeshi, 6) MATSUI, Yumi,
		7) KONISHI, Masahiro, 8) UEDA, Kenjiro,
		9) MATSUFUJI, Tetsuyoshi,
domiciliado(s) en		of
		1)-7)& 9) c/o Daiichi Sankyo Company, Limited
		1-2-58, Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan
		8) c/o Daiichi Sankyo Company, Limited
		1-16-13, Kitakasai, Edogawa-ku, Tokyo 134-8630 Japan
declaro(amos) bajo juramento ser único(s) y verdadero(s) inventor(es)		state(s) under oath to be sole and true inventor(s) of the invention:
de la invención:		**NOVEL PHENYLPYRROLE DERIVATIVE**
declaro(amos) así mismo que cedo(emos) y transfiero(erimos), sin		state as well, that assign, without reservations or limitations in favour
limitación, a favor de la sociedad		of
		DAIICHI SANKYO COMPANY, LIMITED
constituida y existente de conformidad con las leyes de		a corporation constituted and existing in conformity with the laws of
		JAPAN
domiciliada en		domiciled in
		3-5-1, Nihonbashi Honcho, Chuo-ku, Tokyo 103-8426 Japan
todos los derechos inherentes a dicha invención y que la citada Compañía queda facultada para solicitar en su nombre la patente de invención correspondiente en la República de Colombia.		all rights inherent to said invention and that the above mentioned company hereby is enabled to apply, in its name, for the corresponding patent invention, in the Republic of Colombia

© CAVELIER ABOGADOS

Dado y firmado hoy/Given and signed this:

en/in: **Tokyo, Japan**

Firma/Signature:

Akihiro Furukawa	May 28, 2010	Takehiro Fukuzaki	May 28, 2010
1. FURUKAWA, Akihiro	(date)	2. FUKUZAKI, Takehiro	(date)
Yukari Onishi	MAY 28, 2010	Hideki Kobayashi	May 28, 2010
3. ONISHI, Yukari	(date)	4. KOBAYASHI, Hideki	(date)
Takeshi Honda	May 28, 2010	Yumi Matsui	May 28, 2010
5. HONDA, Takeshi	(date)	6. MATSUI, Yumi	(date)
Masahiro Konishi	May 28, 2010	Kenjiro Ueda	May 28, 2010
7. KONISHI, Masahiro	(date)	8. UEDA, Kenjiro	(date)
Tetsuyoshi Matsufuji	May 28, 2010		
9. MATSUFUJI, Tetsuyoshi	(date)		

© CAVELIER ABOGADOS

16

CERTIFICACIÓN NOTARIAL (INDIVIDUO)

A los _____ días del mes de _____

de 200 ___ Ante mí, Notario Público de

_____

compareció(eron) personalmente _____

_____

_____

_____

_____

_____

a quien(es) doy fe de conocer y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede, y quien(es) tiene(n) capacidad legal para otorgarlo

NOTARIAL CERTIFICATION (INDIVIDUAL)

On this _____ day of _____

200 ___ before me, a Notary Public of

_____

personally appeared _____

_____

_____

_____

_____

_____

to me known, and known to me to be the person(s) who executed that foregoing document, and who has(have) legal capacity to execute it.

_____ NOTARIO PÚBLICO-NOTARY PUBLIC _____

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: .....
   This public document
2. has been signed by .....
3. acting in the capacity of .....
4. bears the seal/stamp of .....

Certified

5. at ..... 6. the .....
7. by .....
8. No. .....
9. Seal/stamp 10. Signature

....

© CAVELIER ABOGADOS

17

NOTARIAL CERTIFICATE Registration No 965

This is to certify that the signature on the foregoing document is genuine and authentic signature of Akihiro FURUKAWA, Takehiro FUKUZAKI, Yukari ONISHI, Hideki KOBAYASHI, Takeshi HONDA, Yumi MATSUI, Masahiro KONISHI, Kenjiro UEDA and Tetsuyoshi MATSUFUJI.

MAY 28 2010

TOKYO LEGAL AFFAIRS BUREAU
NOTARY
2-2-2, UCHISAIWAICHO
CHIYODA-KU
TOKYO JAPAN

MAKAZU IKEDA
NOTARY

平成２２年登簿第　965 号

18

認　　証

嘱託人古川詔大、福崎剛広、大西由香利、小林英樹、本田雄、松井由美、小西正博、上田健二郎及び松藤哲義の代理人城野喬は、本公証人に対し、嘱託人が別添文書に署名したことを自認している旨陳述した。

よって、これを認証する。

平成２２年　5　月　28　日、本公証人役場において

東京都千代田区内幸町２丁目２番２号

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Notary　池田眞一

MAKAZU IKEDA

証　　明

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APOSTILLE

(Convention de La Haye du 5 octobre 1961)

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K. Oyabe

Kazutoyo OYABE
For the Minister for Foreign Affairs

TRADUCCIÓN OFICIAL 206/2010 DE UN DOCUMENTO EN INGLÉS Y ESPAÑOL POR EL CUAL LOS ABAJO FIRMANTES, 1) FURUKAWA, AKIHIRO; 2) FUKUZAKI, TAKEHIRO, 3) ONOSHI, YUKARI; 4) KOBAYASHI, HIDEKI; 5) HONDA, TAKESHI; 6) MATSUI, YUMI; 7) KONISHI, MASAHIRO; 8) UEDA, KENJIRO Y 9) MATSUFUJI, TETSUYOSHI, RESIDENTES EN 1 A 7 Y 9 C/O DAIICHI SANKYO COMPANY, LIMITED 1-2-58, HIROMACHI, SHINAGAWA-KU, TOKIO 140-8710, JAPÓN ; 8) C/O DAIICHI SANKYO COMPANY, LIMITED 1-16-13, KITAKASAI, EDOGAWA-KU, TOKIO 134-8630, JAPÓN, DECLARAN BAJO JURAMENTO SER LOS INVENTORES ÚNICOS Y VERDADEROS DEL INVENTO **NOVEDOSO DERIVADO DE FENILPIRROL** Y QUE CEDEN Y TRANSFIEREN SIN LIMITACIÓN A FAVOR DE LA SOCIEDAD **DAIICHI SANKYO COMPANY, LIMITED**, UNA SOCIEDAD CONSTITUIDA Y EXISTENTE DE CONFORMIDAD CON LAS LEYES DE JAPÓN, DOMICILIADA EN 3-5-1, NIHONBASHI HONCHO, CHUO-KU, TOKIO, 103-8426, JAPÓN TODOS LOS DERECHOS INHERENTES A DICHA INVENCIÓN Y QUE LA CITADA COMPAÑÍA QUEDA FACULTADA PARA SOLICITAR EN SU NOMBRE LA PATENTE DE INVENCIÓN CORRESPONDIENTE EN LA REPUBLICA DE COLOMBIA.

DADO Y FIRMADO HOY 28 DE MAYO DE 2010 EN TOKIO, JAPÓN

A CONTINUACIÓN APARECEN TODAS LAS FIRMAS DE LOS INVENTORES ARRIBA MENCIONADOS.

CERTIFICACIÓN NOTARIAL

REGISTRO NÚMERO 965

Por la presente certifico que las firmas sobre el documento precedente corresponden a las firmas de (aquí aparece la lista de todos los inventores arriba mencionados). 28 de mayo de 2010. Firmado: MAKAZU IKEDA, notario

Eduardo Calado N.

Eduardo Calado Noguera
TRADUCTOR OFICIAL
Inglés - Español - Inglés
Res. 541 Febrero de 1976

SELLO: OFICINA DE ASUNTOS JURÍDICOS DE TOKIO

NOTARIO. 2-2-2, UCHISAIWAICHO, CHIYODA-KU, TOKIO, JAPÓN.

APOSTILLA

(CONVENCION DE LA HAYA DEL 5 DE OCTUBRE DE 1961)

1. PAIS: JAPÓN

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CERTIFICADO

5. En TOKIO. 6. el 28 de mayo de 2010

7. Por el Ministerio de Asuntos Exteriores

8. 10- No 000320

9. Sello/estampilla: MINISTERIO DE ASUNTOS EXTERIORES, JAPÓN

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Eduardo Calado N.

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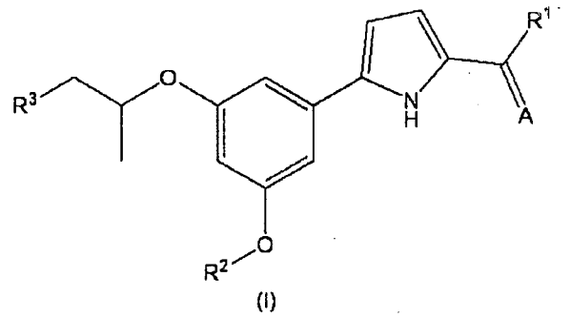
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[続葉有]

(54) **Title**: NOVEL PHENYLPYRROLE DERIVATIVE

(54) 発明の名称: 新規フェニルピロール誘導体



(I)

(57) **Abstract**: Disclosed is a compound having excellent glucokinase activating activity or a pharmacologically acceptable salt thereof. Specifically disclosed is a compound represented by general formula (I) or a pharmacologically acceptable salt thereof. [In the formula, A represents an oxygen atom, a sulfur atom or the like; R^1 represents a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a C_1-C_6 halogenated alkyl group or the like; A, R^1 and the carbon atom to which A and R^1 are bonded may combine together to form a heterocyclic ring group which may be mono- to tri-substituted independently by groups selected from a substituent group α; R^2 represents a phenyl group which may be mono- to penta-substituted independently by groups selected from the substituent group α or a heterocyclic ring group which may be mono- to tri-substituted independently by groups selected from the substituent group α; and R^3 represents a hydroxy group or a C_1-C_6 alkyl group. The substituent group α consists of halogen atoms, C_1-C_6 alkyl groups, C_1-C_6 alkyl groups substituted by one or two hydroxy groups, C_1-C_6 alkylsulfonyl groups and the like.]

(57) 要約:

[続葉有]

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DESCRIPTION

NOVEL PHENYLPYRROLE DERIVATIVE

TECHNICAL FIELD

The present invention relates to a phenylpyrrole compound, or a pharmacologically acceptable salt thereof, that has superior glucokinase activating activity and is useful as a therapeutic for diabetes and the like.

BACKGROUND ART

Glucokinase (abbreviated as GK in the present description; EC 2.7.1.1) is one of the four types of hexokinases (hexokinase IV) found in mammals. Hexokinases are enzymes that catalyze the conversion of glucose to glucose-6-phosphate in the first stage of the glycolysis system in cells, and the expression of GK is localized mainly in the liver and pancreatic beta cells. In pancreatic beta cells, GK functions as a detection mechanism of extracellular glucose concentration that regulates glucose-stimulated insulin secretion, while in the liver, the enzymatic reaction of GK serves as the rate-limiting step to regulate subsequent reactions such as glycolysis and glycogen synthesis. Although GK found in the liver and that found in pancreatic beta cells differ in the sequence consisting of 15 amino acids from the N-terminal due to a difference in splicing, their enzymatic properties are identical. In contrast to the enzymatic activities of the three types of hexokinases other than GK (types I, II and III) becoming saturated at a glucose concentration of 1 mM or less, GK exhibits low affinity for glucose, and the Km value thereof is near that of the physiological level of glucose in the blood at 8 to 15 mM. Thus, acceleration of GK-mediated intracellular glucose metabolism occurs in response to changes in blood glucose levels ranging from normal blood glucose levels (about 5 mM) to postprandial blood glucose levels (10 to 15 mM).

The hypothesis that GK functions as a glucose sensor in

the liver and pancreatic beta cells has long been advocated (Non-Patent Documents 1 to 3). Recent research findings have demonstrated that GK actually plays an important role in maintaining systemic glucose homeostasis, thereby verifying this hypothesis. For example, mice in which glucokinase gene had been disrupted exhibited prominent hyperglycemia symptoms and died soon after birth, while GK hetero-deficient mice were observed to have defective glucose tolerance and impaired glucose-stimulated insulin secretion (Non-Patent Document 4). On the other hand, normal mice excessively expressing GK were observed to demonstrate decreased blood glucose levels and increased glycogen content in the liver, and these phenomena were similar to those in mice in which diabetes was artificially induced (Non-Patent Document 5).

In addition, GK also functions as a glucose sensor in humans, and has been demonstrated by recent research to play an important role in maintaining glucose homeostasis. Abnormalities have been discovered in the GK genes of family lineages exhibiting a form of juvenile-onset diabetes referred to as maturity onset diabetes of the young (MODY2), and a correlation was clearly observed between these cases and GK activity (Non-Patent Document 6). On the other hand, family lineages have also been found that possess a mutation that increases GK activity, and symptoms of fasting hypoglycemia accompanied by elevated plasma insulin concentrations have been observed in such family lineages (Non-Patent Document 7). On the basis of these reports, GK plays an important role in blood glucose regulation by functioning as a glucose sensor in mammals, including humans. Thus, substances having GK activating activity are considered to be useful as drugs for treatment of glycometabolic diseases including type II diabetes mellitus. Since GK activating substances can be expected to simultaneously demonstrate glucose uptake promoting activity and glucose release inhibitory activity in the liver as well as insulin secretion promoting activity in pancreatic beta cells in particular, they are predicted to be able to demonstrate potent

therapeutic effects unable to be attained with existing drugs.

Pancreatic beta cell type GK has recently been determined to be expressed, being localized in the ventromedial hypothalamus (VMH) of the rat brain. The VMH has been conventionally known to be the site of neurons that respond to glucose concentration. In contrast to food intake decreasing when glucose is administered to rat ventricle, food intake is accelerated when glucose metabolism is inhibited by administration of the glucose analogue, glucosamine (Non-Patent Document 8). Electrophysiological experiments have demonstrated that glucose-responsive neurons are activated by responding to physiological changes in glucose concentrations (5 to 20 mM), and glucokinase has been determined to similarly function as a glucose sensor in peripheral tissue (Non-Patent Document 9). Thus, substances that give rise to glucokinase activation not only in the liver and pancreatic beta cells, but also in the VMH can be expected to demonstrate blood glucose lowering activity as well as activity that corrects obesity, which is considered to be a problem associated with numerous patients of type II diabetes mellitus.

On the basis of the aforementioned descriptions, substances having GK activating activity are useful as diabetes therapeutics and preventives, or as therapeutics and preventives of chronic complications of diabetes, including diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, ischemic heart disease and arteriosclerosis.

Furthermore, although a plurality of compounds having GK activating activity have been reported in the past, all of these have different structures from that of the compound of the present invention. For example, although Patent Document 1 describes a compound having an amide structure as an essential constituent thereof, the compound of the present invention has a pyrrole structure instead of an amide structure as an essential constituent thereof. In addition, although Patent Document 2 describes a compound having a condensed pyrrole, the compound of the present invention has a non-condensed pyrrole as an

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essential constituent thereof. Moreover, although Patent Document 3 describes a compound having a 3,5-di-substituted pyrazole or 1,2,4-triazole moiety, this differs from the 2,5-di-substituted pyrrole structure of the present invention. Although a plurality of compounds having GK activating activity have been reported in addition to those described in the above publications, all of these have different structures from that of the compound of the present invention (see, for example, Patent Documents 4 to 15 and Non-Patent Documents 10 and 11).

[Patent Document 1] International Publication No. WO2005/080359 Pamphlet

[Patent Document 2] International Publication No. WO2007/031739 Pamphlet

[Patent Document 3] International Publication No. WO2007/061923 Pamphlet

[Patent Document 4] International Publication No. WO2000/058293 Pamphlet

[Patent Document 5] International Publication No. WO2003/080585 Pamphlet

[Patent Document 6] International Publication No. WO2005/066145 Pamphlet

[Patent Document 7] International Publication No. WO2005/090332 Pamphlet

[Patent Document 8] International Publication No. WO2006/112549 Pamphlet

[Patent Document 9] International Publication No. WO2007/007886 Pamphlet

[Patent Document 10] International Publication No. WO2007/037534 Pamphlet

[Patent Document 11] International Publication No. WO2007/053765 Pamphlet

[Patent Document 12] International Publication No. WO2007/117381 Pamphlet

[Patent Document 13] International Publication No. WO2005/044801 Pamphlet

[Patent Document 14] International Publication No.

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WO2007/053662 Pamphlet
[Patent Document 15] International Publication No. WO2008/136428 Pamphlet
[Non-Patent Document 1] Am J Physiol. 1984 Sep; 247(3 Pt 2):R527-36.
[Non-Patent Document 2] Diabetes. 1986 Jan; 35(1):61-7.
[Non-Patent Document 3] Diabetes. 1986 Oct; 35(10):1163-73.
[Non-Patent Document 4] Cell. 1995 Oct 6; 83(1):69-78.
[Non-Patent Document 5] Proc Natl Acad Sci U S A. 1996 Jul 9; 93(14):7225-30.
[Non-Patent Document 6] Nature. 1992 Apr 23; 356(6371):721-2.
[Non-Patent Document 7] N Engl J Med. 1998 Jan 22; 338(4):226-30.
[Non-Patent Document 8] Life Sci. 1985 Dec 30; 37(26):2475-82.
[Non-Patent Document 9] Diabetes. 2006 Feb; 55(2):412-20. Erratum in: Diabetes. 2006 Mar; 55(3):862.
[Non-Patent Document 10] Science. 2003 Jul 18; 301(5631):370-3.
[Non-Patent Document 11] J Biol Chem. 2006 Dec 8; 281(49):37668-74. Epub 2006 Oct 6.

DISCLOSURE OF THE INVENTION

[Problems to be Solved by the Invention]

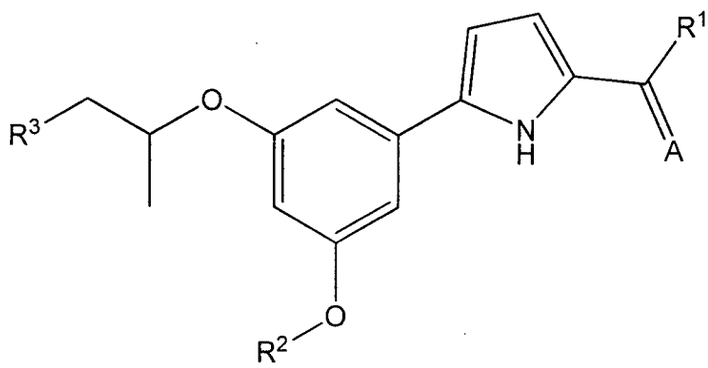
An object of the present invention is to provide a novel phenylpyrrole derivative and a GK activator that uses this novel phenylpyrrole derivative, and particularly to provide a therapeutic and preventive of diabetes and impaired glucose tolerance. As a result of conducting extensive studies on compounds having GK activating activity, the inventors of the present invention found that a phenylpyrrole compound having a specific chemical structure has superior GK activating activity. In addition, the compound of the present invention has superior GK selectivity, low toxicity and few adverse side effects. The inventors of the present invention also found that this phenylpyrrole compound is useful as an active ingredient of a pharmaceutical for the treatment and/or prevention of diseases selected from the group consisting of diabetes, impaired glucose

tolerance, gestational diabetes, chronic complications of diabetes (including diabetic peripheral neuropathy, diabetic nephropathy, diabetic retinopathy and diabetic macroangiopathy) and metabolic syndrome. The present invention was completed based on the aforementioned findings.

[Means for Solving the Problems]

The present invention relates to:

(1) a compound having the general formula (I):



(I)

[wherein,

A represents a group represented by the formula $=NOR^4$, an oxygen atom or a sulfur atom,

R^4 represents a hydrogen atom or a C_1-C_6 alkyl group,

R^1 represents a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a C_1-C_6 halogenated alkyl group, a C_1-C_6 halogenated alkoxy group, an amino group, a mono-C_1-C_6 alkylamino group, a mono-C_1-C_6 halogenated alkylamino group, a di(C_1-C_6 alkyl)amino group or a di-(C_1-C_6 halogenated alkyl)amino group, or

A and R^1 together with the carbon atom bonded thereto form a heterocyclic group that may be substituted with 1 to 3 group(s) independently selected from Substituent Group α,

R^2 represents a phenyl group that may be substituted with 1 to 5 group(s) independently selected from Substituent Group α or a heterocyclic group that may be substituted with 1 to 3 group(s) independently selected from Substituent Group α,

R^3 represents a hydroxy group or a C_1-C_6 alkoxy group, and

Substituent Group α represents the group of substituents

selected from a halogen atom, a C_1-C_6 alkyl group, a C_1-C_6 halogenated alkyl group, a C_2-C_6 alkenyl group, a C_2-C_6 alkynyl group, a hydroxy group, a C_1-C_6 alkyl group substituted with 1 or 2 hydroxy group(s), a C_1-C_6 alkoxy group, a C_1-C_6 halogenated alkoxy group, a (C_1-C_6 alkoxy)-(C_1-C_6 alkyl) group, a (C_1-C_6 alkoxy)-(C_1-C_6 alkoxy) group, a formyl group, a carboxyl group, a C_2-C_7 alkylcarbonyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 alkylcarbonyloxy group, a C_2-C_7 alkoxycarbonyloxy group, a nitro group, an amino group, a mono-C_1-C_6 alkylamino group, a di-(C_1-C_6 alkyl)amino group, a C_1-C_6 alkylthio group, a C_1-C_6 alkylsulfonyl group, a C_3-C_6 cycloalkylsulfonyl group, a C_1-C_6 hydroxyalkylsulfonyl group, a (C_1-C_6 alkoxy)-(C_1-C_6 alkylsulfonyl) group, a group represented by the formula -V-NR^5R^6 (wherein V represents a carbonyl group or a sulfonyl group, and R^5 and R^6 may be the same or different and respectively represent a hydrogen atom or a C_1-C_6 alkyl group, or R^5 and R^6 together with the nitrogen atom bonded thereto form a 4- to 6-membered saturated heterocycle that may be substituted with 1 or 2 group(s) independently selected from a C_1-C_6 alkyl group and a hydroxy group, and the 4- to 6-membered saturated heterocycle may further contain one oxygen atom or nitrogen atom), a mono-C_2-C_7 alkylcarbonylamino group, a mono-C_1-C_6 alkylaminocarbonyloxy group, a di-(C_1-C_6 alkyl)aminocarbonyloxy group, a mono-C_2-C_7 alkoxycarbonylamino group, a mono-C_1-C_6 alkylsulfonylamino group, a cyano group, a 1,3,4-oxadiazol-2-yl group optionally substituted with a C_1-C_6 alkyl group at the 5-position, a 1,3,4-thiadiazol-2-yl group optionally substituted with a C_1-C_6 alkyl group at the 5-position, and an oxo group] or a pharmacologically acceptable salt thereof;

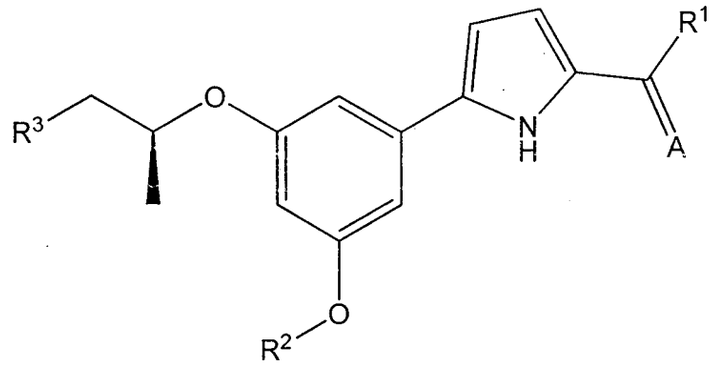
(2) the compound or pharmacologically acceptable salt thereof in (1) above, wherein

Substituent Group α represents the group of substituents selected from a halogen atom, a C_1-C_6 alkyl group, a C_1-C_6 halogenated alkyl group, a C_2-C_6 alkenyl group, a C_2-C_6 alkynyl group, a hydroxy group, a C_1-C_6 alkyl group substituted with 1 or 2 hydroxy group(s), a C_1-C_6 alkoxy group, a C_1-C_6 halogenated

alkoxy group, a (C_1-C_6 alkoxy)-(C_1-C_6 alkyl) group, a (C_1-C_6 alkoxy)-(C_1-C_6 alkoxy) group, a formyl group, a carboxyl group, a C_2-C_7 alkylcarbonyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 alkylcarbonyloxy group, a C_2-C_7 alkoxycarbonyloxy group, a nitro group, an amino group, a mono-C_1-C_6 alkylamino group, a di-(C_1-C_6 alkyl)amino group, a C_1-C_6 alkylthio group, a C_1-C_6 alkylsulfonyl group, a C_3-C_6 cycloalkylsulfonyl group, a C_1-C_6 hydroxyalkylsulfonyl group, a (C_1-C_6 alkoxy)-(C_1-C_6 alkylsulfonyl) group, a group represented by the formula -V-NR^5R^6 (wherein V represents a carbonyl group or a sulfonyl group, and R^5 and R^6 may be the same or different and respectively represent a hydrogen atom or a C_1-C_6 alkyl group, or R^5 and R^6 together with the nitrogen atom bonded thereto form a 4- to 6-membered saturated heterocycle that may be substituted with 1 or 2 group(s) independently selected from a C_1-C_6 alkyl group and a hydroxy group, and the 4- to 6-membered saturated heterocycle may further contain one oxygen atom or nitrogen atom), a mono-C_2-C_7 alkylcarbonylamino group, a mono-C_1-C_6 alkylaminocarbonyloxy group, a di-(C_1-C_6 alkyl)aminocarbonyloxy group, a mono-C_2-C_7 alkoxycarbonylamino group, a mono-C_1-C_6 alkylsulfonylamino group, a cyano group, a 1,3,4-oxadiazol-2-yl group optionally substituted with a C_1-C_6 alkyl group at the 5-position, and a 1,3,4-thiadiazol-2-yl group optionally substituted with a C_1-C_6 alkyl group at the 5-position;

(3) the compound or pharmacologically acceptable salt thereof in (1) or (2) above, wherein

the general formula (I) is a general formula (Ia);



(Ia)

(4) the compound or pharmacologically acceptable salt thereof in any one selected from (1) to (3) above, wherein A is an oxygen atom;

(5) the compound or pharmacologically acceptable salt thereof in any one selected from (1) to (4) above, wherein R^1 is a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group or a mono-C_1-C_6 halogenated alkylamino group;

(6) the compound or pharmacologically acceptable salt thereof in any one selected from (1) to (4) above, wherein R^1 is a methyl group or a 2-chloroethylamino group;

(7) the compound or pharmacologically acceptable salt thereof in any one selected from (1) to (4) above, wherein the heterocyclic group formed by A and R^1 together with the carbon atom bonded thereto and which may be substituted with 1 to 3 group(s) independently selected from Substituent Group α is a 2-pyridyl group, 5,6-dihydro-4H-1,3-oxazin-2-yl group, 1,3-thiazol-2-yl group, 1,3-oxazol-2-yl group, 1,3,4-oxadiazol-2-yl group, 1,3,4-thiadiazol-2-yl group, 4,5-dihydro-1,3-thiazol-2-yl group, 4,5-dihydro-1,3-oxazol-2-yl group or 4,5-dihydro-1,3-benzothiazol-2-yl group that may be substituted with 1 to 3 group(s) independently selected from Substituent Group γ, and

Substituent Group γ indicates the group consisting of a halogen atom, a C_1-C_6 alkyl group, a C_1-C_6 halogenated alkyl group, a C_1-C_6 alkyl group substituted with 1 or 2 hydroxy group(s), a C_1-C_6 alkoxy group, a carboxyl group, a mono-C_1-C_6 alkylaminocarbonyl group, a di-(C_1-C_6 alkyl)aminocarbonyl group and a hydroxy group;

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(8) the compound or pharmacologically acceptable salt thereof in any one selected from (1) to (3) above, wherein the heterocyclic group formed by A and R^1 together with the carbon atom bonded thereto and which may be substituted with 1 to 3 group(s) independently selected from Substituent Group α is a 1,3-thiazol-2-yl group, a 5-methyl-1,3-thiazol-2-yl group, a 5-methyl-1,3,4-oxadiazol-2-yl group, a 4,5-dihydro-1,3-thiazol-2-yl group, a 4,5-dihydro-1,3-oxazol-2-yl group, a (5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5R)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a 5-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5R)-5-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-ethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4S)-4-[(1R)-1-hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl group, a (4S)-4-[(1S)-1-hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5S)-4,5-dimethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5S)-4-hydroxy-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5S)-4-hydroxymethyl-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5R)-5-hydroxymethyl-4-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a 5-carboxyl-1,3-thiazol-2-yl group, a 5-dimethylaminocarbonyl-1,3-thiazol-2-yl group, a 5-methyl-1,3,4-thiadiazol-2-yl group or a 5,6-dihydro-4H-1,3-oxazin-2-yl group;

(9) the compound or pharmacologically acceptable salt thereof in any one selected from (1) to (3) above, wherein the heterocyclic group formed by A and R^1 together with the carbon atom bonded thereto and which may be substituted with 1 to 3 group(s) independently selected from Substituent Group α is a 4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-ethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5R)-5-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4S)-4-[(1R)-1-hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl group, a (4S)-4-[(1S)-1-hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5S)-4,5-dimethyl-4,5-dihydro-1,3-oxazol-2-yl group, a

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(4R,5S)-4-hydroxymethyl-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5R)-5-hydroxymethyl-4-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a 1,3-thiazol-2-yl group, a 5-carboxyl-1,3-thiazol-2-yl group, a 5-dimethylaminocarbonyl-1,3-thiazol-2-yl group, a 5-methyl-1,3,4-thiadiazol-2-yl group, a 5-methyl-1,3,4-oxadiazol-2-yl group, a 4,5-dihydro-1,3-thiazol-2-yl group or a 5,6-dihydro-4H-1,3-oxazin-2-yl group;

(10) the compound or pharmacologically acceptable salt thereof in any one selected from (1) to (3) above, wherein the heterocyclic group formed by A and R^1 together with the carbon atom bonded thereto and which may be substituted with 1 to 3 group(s) independently selected from Substituent Group α is a 4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-ethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5R)-5-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4S)-4-[(1R)-1-hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl group, a (4S)-4-[(1S)-1-hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5S)-4,5-dimethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5S)-4-hydroxymethyl-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group or a (4R,5R)-5-hydroxymethyl-4-methyl-4,5-dihydro-1,3-oxazol-2-yl group;

(11) the compound or pharmacologically acceptable salt thereof in any one selected from (1) to (10) above, wherein R^2 is a phenyl group that may be substituted with 1 to 5 group(s) independently selected from Substituent Group δ or a 2-pyridyl group, 3-pyridyl group or 2-pyrazinyl group that may be substituted with 1 to 3 group(s) independently selected from Substituent Group δ, and

Substituent Group δ indicates the group consisting of a halogen atom, a C_1-C_6 alkyl group, a C_1-C_6 halogenated alkyl group, a C_1-C_6 alkyl group substituted with 1 or 2 hydroxy group(s), a C_2-C_7 alkylcarbonyl group, a C_2-C_7 alkoxycarbonyl group, a C_1-C_6 alkylsulfonyl group, a group represented by the formula -V-NR^5R^6 (wherein V represents a carbonyl group or a

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sulfonyl group, and R^5 and R^6 may be the same or different and respectively represent a hydrogen atom or a C_1-C_6 alkyl group, or R^5 and R^6 together with the nitrogen atom bonded thereto form a 4- to 6-membered saturated heterocycle that may be substituted with 1 or 2 group(s) independently selected from a C_1-C_6 alkyl group and a hydroxy group, and the 4- to 6-membered saturated heterocycle may further contain one oxygen atom or nitrogen atom), a 1,3,4-oxadiazol-2-yl group optionally substituted with a C_1-C_6 alkyl group at the 5-position, and a 1,3,4-thiadiazol-2-yl group optionally substituted with a C_1-C_6 alkyl group at the 5-position;

(12) the compound or pharmacologically acceptable salt thereof in any one selected from (1) to (10) above, wherein R^2 is a 4-methylsulfonylphenyl group, a 4-(1-azetidinyl)carbonyl-2-fluorophenyl group, a 2-fluoro-4-(1-pyrrolidinyl)carbonylphenyl group, a 5-(1-azetidinyl)carbonyl-3-chloro-2-pyridyl group, a 2-methylsulfonyl-5-pyridyl group, a 5-(4-methyl-1-piperazinyl)carbonyl-2-pyrazinyl group, a 2-methylaminocarbonyl-5-pyridyl group, a 2-methylaminosulfonyl-5-pyridyl group or a 5-methylsulfonyl-2-pyrazinyl group;

(13) the compound or pharmacologically acceptable salt thereof selected from any of (1) to (10) above, wherein R^2 is a 4-methylsulfonylphenyl group, a 2-methylsulfonyl-5-pyridyl group, a 5-methylsulfonyl-2-pyrazinyl group or a 5-(1-azetidinyl)carbonyl-3-chloro-2-pyridyl group;

(14) the compound or pharmacologically acceptable salt thereof in any one selected from (1) to (13) above, wherein R^3 is a hydroxy group or a methoxy group;

(15) the compound or pharmacologically acceptable salt thereof in (1) above, wherein the general formula (I) is the general formula (Ia), A is an oxygen atom, R^1 is a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group or a mono-C_1-C_6 halogenated alkylamino group, R^2 is a phenyl group that may be substituted with 1 to 5 group(s) independently selected from Substituent Group δ or a 2-pyridyl group, 3-pyridyl group or 2-pyrazinyl group that may be substituted with 1 to 3 group(s) independently selected from

Substituent Group δ, and R^3 is a hydroxy group or a methoxy group;

(16) the compound or pharmacologically acceptable salt thereof in (1) above, wherein the general formula (I) is the general formula (Ia), A is an oxygen atom, R^1 is a methyl group or a 2-chloroethylamino group, R^2 is a 4-methylsulfonylphenyl group, a 4-(1-azetidinyl)carbonyl-2-fluorophenyl group, a 2-fluoro-4-(1-pyrrolidinyl)carbonylphenyl group, a 5-(1-azetidinyl)carbonyl-3-chloro-2-pyridyl group, a 2-methylsulfonyl-5-pyridyl group, a 5-(4-methyl-1-piperazinyl)carbonyl-2-pyrazinyl group, a 2-methylaminocarbonyl-5-pyridyl group, a 2-methylaminosulfonyl-5-pyridyl group or a 5-methylsulfonyl-2-pyrazinyl group, and R^3 is a hydroxy group or a methoxy group;

(17) the compound or pharmacologically acceptable salt thereof in (1) above, wherein the general formula (I) is the general formula (Ia), A is an oxygen atom, R^1 is a methyl group or a 2-chloroethylamino group, R^2 is a 4-methylsulfonylphenyl group, a 2-methylsulfonyl-5-pyridyl group, a 5-methylsulfonyl-2-pyrazinyl group or a 5-(1-azetidinyl)carbonyl-3-chloro-2-pyridyl group, and R^3 is a hydroxy group or a methoxy group;

(18) the compound or pharmacologically acceptable salt thereof in (1) above, wherein the general formula (I) is the general formula (Ia), the heterocyclic group formed by A and R^1 together with the carbon atom bonded thereto and which may be substituted with 1 to 3 group(s) independently selected from Substituent Group α is a 2-pyridyl group, 5,6-dihydro-4H-1,3-oxazin-2-yl group, 1,3-thiazol-2-yl group, 1,3-oxazol-2-yl group, 1,3,4-oxadiazol-2-yl group, 1,3,4-thiadiazol-2-yl group, 4,5-dihydro-1,3-thiazol-2-yl group, 4,5-dihydro-1,3-oxazol-2-yl group or 4,5-dihydro-1,3-benzothiazol-2-yl group that may be substituted with 1 to 3 group(s) independently selected from Substituent Group γ, R^2 is a phenyl group that may be substituted with 1 to 5 group(s) independently selected from Substituent Group δ or a 2-pyridyl group, 3-pyridyl group or 2-pyrazinyl group that may be substituted with 1 to 3 group(s) independently selected from Substituent Group δ, and R^3 is a hydroxy group or a methoxy

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group;

(19) the compound or pharmacologically acceptable salt thereof in (1) above, wherein the general formula (I) is the general formula (Ia), the heterocyclic group formed by A and R^1 together with the carbon atom bonded thereto and which may be substituted with 1 to 3 group(s) independently selected from Substituent Group α is a 1,3-thiazol-2-yl group, a 5-methyl-1,3-thiazol-2-yl group, a 5-methyl-1,3,4-oxadiazol-2-yl group, a 4,5-dihydro-1,3-thiazol-2-yl group, a 4,5-dihydro-1,3-oxazol-2-yl group, a (5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5R)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a 5-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5R)-5-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-ethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4S)-4-[(1R)-1-hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl group, a (4S)-4-[(1S)-1-hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5S)-4,5-dimethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5S)-4-hydroxy-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5S)-4-hydroxymethyl-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5R)-5-hydroxymethyl-4-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a 5-carboxyl-1,3-thiazol-2-yl group, a 5-dimethylaminocarbonyl-1,3-thiazol-2-yl group, a 5-methyl-1,3,4-thiadiazol-2-yl group or a 5,6-dihydro-4H-1,3-oxazin-2-yl group, R^2 is a 4-methylsulfonylphenyl group, a 4-(1-azetidinyl)carbonyl-2-fluorophenyl group, a 2-fluoro-4-(1-pyrrolidinyl)carbonylphenyl group, a 5-(1-azetidinyl)carbonyl-3-chloro-2-pyridyl group, a 2-methylsulfonyl-5-pyridyl group, a 5-(4-methyl-1-piperazinyl)carbonyl-2-pyrazinyl group, a 2-methylaminocarbonyl-5-pyridyl group, a 2-methylaminosulfonyl-5-pyridyl group or a 5-methylsulfonyl-2-pyrazinyl group, and R^3 is a hydroxy group or a methoxy group;

(20) the compound or pharmacologically acceptable salt thereof in (1) above, wherein the general formula (I) is the general formula (Ia), the heterocyclic group formed by A and R^1 together with the carbon atom bonded thereto and which may be substituted

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methylsulfonyl-5-pyridyl group, a 5-methylsulfonyl-2-pyrazinyl group or a 5-(1-azetidinyl)carbonyl-3-chloro-2-pyridyl group, and R^3 is a hydroxy group or a methoxy group;

(22) the compound or pharmacologically acceptable salt thereof described in (1) above, wherein the compound represented by the general formula (I) is:

2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole,

(2S)-2-{3-[4-(methylsulfonyl)phenoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl)phenoxy]propan-1-ol,

2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole-5-carboxylic acid,

2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-N,N-dimethyl-1,3-thiazole-5-carboxamide,

1-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)ethanone,

(2S)-2-{3-[5-(4,5-dihydro-1,3-oxazol-2-yl)-1H-pyrrol-2-yl]-5-[4-(methylsulfonyl)phenoxy]phenoxy}propan-1-ol,

2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-1,3,4-thiadiazole,

2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-thiazole,

(2S)-2-{3-[5-(4,5-dihydro-1,3-thiazol-2-yl)-1H-pyrrol-2-yl]-5-[4-(methylsulfonyl)phenoxy]phenoxy}propan-1-ol,

(2S)-2-(3-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-[4-(methylsulfonyl)phenoxy]phenoxy)propan-1-ol,

2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5,6-dihydro-4H-1,3-oxazine,

(2S)-2-(3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrrol-2-yl]phenoxy)propan-1-ol,

with 1 to 3 group(s) independently selected from Substituent Group α is a 4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-ethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5R)-5-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4S)-4-[(1R)-1-hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl group, a (4S)-4-[(1S)-1-hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5S)-4,5-dimethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5S)-4-hydroxymethyl-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5R)-5-hydroxymethyl-4-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a 1,3-thiazol-2-yl group, a 5-carboxyl-1,3-thiazol-2-yl group, a 5-dimethylaminocarbonyl-1,3-thiazol-2-yl group, a 5-methyl-1,3,4-thiadiazol-2-yl group, a 5-methyl-1,3,4-oxadiazol-2-yl group, a 4,5-dihydro-1,3-thiazol-2-yl group or a 5,6-dihydro-4H-1,3-oxazin-2-yl group, R^2 is a 4-methylsulfonylphenyl group, a 2-methylsulfonyl-5-pyridyl group, a 5-methylsulfonyl-2-pyrazinyl group or a 5-(1-azetidinyl)carbonyl-3-chloro-2-pyridyl group, and R^3 is a hydroxy group or a methoxy group;

(21) the compound or pharmacologically acceptable salt thereof in (1) above, wherein the general formula (I) is the general formula (Ia), the heterocyclic group formed by A and R^1 together with the carbon atom bonded thereto and which may be substituted with 1 to 3 group(s) independently selected from Substituent Group α is a 4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-ethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5R)-5-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4S)-4-[(1R)-1-hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl group, a (4S)-4-[(1S)-1-hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5S)-4,5-dimethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5S)-4-hydroxymethyl-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group or a (4R,5R)-5-hydroxymethyl-4-methyl-4,5-dihydro-1,3-oxazol-2-yl group, R^2 is a 4-methylsulfonylphenyl group, a 2-

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(2S)-2-(3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)propan-1-ol,

(2S)-2-(3-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol,

(2S)-2-(3-[5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrrol-2-yl]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol,

{(5R)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-5-yl}methanol,

(2S)-2-(3-{5-[(4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol,

(2S)-2-(3-{5-[(4R)-4-ethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol,

{(4R)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl}pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}methanol,

(2S)-2-(3-{5-[(4R,5S)-4,5-dimethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol,

{(4R,5R)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4-methyl-4,5-dihydro-1,3-oxazol-5-yl}methanol,

{(4R,5S)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazol-4-yl}methanol,

(1S)-1-{(4S)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol,

(1R)-1-{(4S)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol,

(2S)-2-(3-[5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrrol-2-yl]-5-

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{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol,
(2S)-2-(3-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol,
{(5R)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-5-yl}methanol,
(2S)-2-(3-{5-[(4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol,
(2S)-2-(3-{5-[(4R)-4-ethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol,
(2S)-2-(3-{5-[(4R,5S)-4,5-dimethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol,
{(4R,5S)-2-[5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazol-4-yl}methanol,
(1S)-1-{(4S)-2-[5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol, or
(1R)-1-{(4S)-2-[5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol.

(23) the compound or pharmacologically acceptable salt thereof described in (1) above, wherein the compound represented by the general formula (I) is:
(2S)-2-{3-[5-(4,5-dihydro-1,3-oxazol-2-yl)-1H-pyrrol-2-yl]-5-[4-(methylsulfonyl)phenoxy]phenoxy}propan-1-ol,
(2S)-2-(3-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-[4-(methylsulfonyl)phenoxy]phenoxy)propan-1-ol,
(2S)-2-(3-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol,
{(5R)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-

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(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-5-yl}methanol,
(2S)-2-(3-{5-[(4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol,
(2S)-2-(3-{5-[(4R)-4-ethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol,
{(4R)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}methanol,
(2S)-2-(3-{5-[(4R,5S)-4,5-dimethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol,
{(4R,5R)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4-methyl-4,5-dihydro-1,3-oxazol-5-yl}methanol,
{(4R,5S)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazol-4-yl}methanol,
(1S)-1-{(4S)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol,
(1R)-1-{(4S)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol,
(2S)-2-(3-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol,
{(5R)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-5-yl}methanol,
(2S)-2-(3-{5-[(4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol,
(2S)-2-(3-{5-[(4R)-4-ethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-

pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol,
(2S)-2-(3-{5-[(4R,5S)-4,5-dimethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol,
{(4R,5S)-2-[5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazol-4-yl}methanol,
(1S)-1-{(4S)-2-[5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol, or
(1R)-1-{(4S)-2-[5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol.

(24) the compound described in (1) above, wherein the compound represented by the general formula (I) is:
(2S)-2-{3-[5-(4,5-dihydro-1,3-oxazol-2-yl)-1H-pyrrol-2-yl]-5-[4-(methylsulfonyl)phenoxy]phenoxy}propan-1-ol,
(2S)-2-(3-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-[4-(methylsulfonyl)phenoxy]phenoxy}propan-1-ol,
(2S)-2-(3-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol,
{(5R)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-5-yl}methanol,
(2S)-2-(3-{5-[(4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol,
(2S)-2-(3-{5-[(4R)-4-ethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol,
{(4R)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}methanol,
(2S)-2-(3-{5-[(4R,5S)-4,5-dimethyl-4,5-dihydro-1,3-oxazol-2-yl]-

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1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol,
{(4R,5R)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4-methyl-4,5-dihydro-1,3-oxazol-5-yl}methanol,
{(4R,5S)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazol-4-yl}methanol,
(1S)-1-{(4S)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol,
(1R)-1-{(4S)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol,
(2S)-2-(3-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol,
{(5R)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-5-yl}methanol,
(2S)-2-(3-{5-[(4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol,
(2S)-2-(3-{5-[(4R)-4-ethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol,
(2S)-2-(3-{5-[(4R,5S)-4,5-dimethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol,
{(4R,5S)-2-[5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazol-4-yl}methanol,
(1S)-1-{(4S)-2-[5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol, or
(1R)-1-{(4S)-2-[5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-{[5-

(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol.

(25) the compound or pharmacologically acceptable salt thereof described in (1) above, wherein the compound represented by the general formula (I) is:

1-(4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}phenyl)ethanone,

1-(4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}phenyl)ethanol,

1-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)ethanone,

N-(2-chloroethyl)-5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-carboxamide,

6-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)nicotinic acid,

2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5,6-dihydro-4H-1,3-oxazine,

2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole,

2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-1,3-thiazole,

[2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazol-5-yl]methanol,

2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole-5-carboxylic acid,

2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-N,N-dimethyl-1,3-thiazol-5-carboxamide,

2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-1,3-oxazole,

5-methoxy-2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-1,3-oxazole,

2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-1,3,4-oxadiazole,
2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-1,3,4-thiadiazole,
2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-thiazole,
2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-oxazole,
(5S)-2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-4,5-dihydro-1,3-oxazole,
(5R)-2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-4,5-dihydro-1,3-oxazole,
2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5,5-dimethyl-4,5-dihydro-1,3-oxazole,
[2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-oxazol-5-yl]methanol,
2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-1,3-benzothiazole,
2-(5-{3-[4-(azetidin-1-ylsulfonyl)phenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole,
Methyl 3-fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy}-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}benzoate,
3-fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}benzamide,
3-fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}-N-methylbenzamide,
3-fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-

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2-yl)-1H-pyrrol-2-yl]phenoxy}-N,N-dimethylbenzamide,
2-(5-{3-[4-(azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl-1,3-thiazole,
2-(5-{3-[4-(azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-1,3,4-oxadiazole,
2-(5-{3-[4-(azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-oxazole,
(5S)-2-(5-{3-[4-(azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-4,5-dihydro-1,3-oxazole,
2-(5-{3-[2-fluoro-4-(pyrrolidin-1-ylcarbonyl)phenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole,
4-(3-fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}benzoyl)morpholine,
3-fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}-N-methylbenzenesulfonamide,
2-(5-{3-[4-(azetidin-1-ylsulfonyl)-2-fluorophenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole,
2-(3-fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}phenyl)-5-methyl-1,3,4-oxadiazole,
2-(3-fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}phenyl)-5-methyl-1,3,4-thiadiazole,
2-(5-{3-[4-(azetidin-1-ylcarbonyl)-2-methylphenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole,
2-(5-{3-[4-(azetidin-1-ylcarbonyl)-2-(trifluoromethyl)phenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole,
5-(azetidin-1-ylcarbonyl)-2-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}pyridine,
5-(azetidin-1-ylcarbonyl)-3-chloro-2-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}pyridine,

5-(azetidin-1-ylcarbonyl)-3-chloro-2-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}pyridine,

5-(azetidin-1-ylcarbonyl)-3-chloro-2-{3-[5-(4,5-dihydro-1,3-oxazol-2-yl)-1H-pyrrol-2-yl]-5-[(1S)-2-methoxy-1-methylethoxy]phenoxy}pyridine,

5-(azetidin-1-ylcarbonyl)-3-chloro-2-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)pyridine,

5-(azetidin-1-ylcarbonyl)-2-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}-3-methylpyridine,

5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}-2-(methylsulfonyl)pyridine,

5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-2-(methylsulfonyl)pyridine,

2-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}-5-[(4-methylpiperazin-1-yl)carbonyl]pyrazine,

5-(fluoromethyl)-2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-oxazole,

(5R)-2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5-(trifluoromethyl)-4,5-dihydro-1,3-oxazole,

[(5R)-2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-oxazol-5-yl]methanol,

2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-N,N-dimethyl-4,5-dihydro-1,3-oxazole-5-carboxamide,

N-(2-chloroethyl)-5-{3-[(1S)-2-hydroxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carboxamide,

(2S)-2-{3-[4-(methylsulfonyl}phenoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl)phenoxy]propan-1-ol,

(2S)-2-{3-[5-(4,5-dihydro-1,3-thiazol-2-yl)-1H-pyrrol-2-yl]-5-

[4-(methylsulfonyl)phenoxy]phenoxy}propan-1-ol,
(2S)-2-{3-[5-(4,5-dihydro-1,3-oxazol-2-yl)-1H-pyrrol-2-yl]-5-[4-(methylsulfonyl)phenoxy]phenoxy}propan-1-ol,
(2S)-2-(3-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-[4-(methylsulfonyl)phenoxy]phenoxy)propan-1-ol,
(2S)-2-{3-[4-(azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}propan-1-ol,
(2S)-2-(3-[4-(azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)propan-1-ol,
(2S)-2-(3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrrol-2-yl]phenoxy)propan-1-ol,
(2S)-2-(3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)propan-1-ol, or
(2S)-2-(3-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol.

(26) the compound or pharmacologically acceptable salt thereof described in (1) above, wherein the compound represented by the general formula (I) is:
1-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)ethanone,
2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole,
2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-1,3-thiazole,
2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-thiazole,
2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-oxazole,
(5S)-2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-

(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-4,5-dihydro-1,3-oxazole,
(5R)-2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-4,5-dihydro-1,3-oxazole,
[2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-oxazol-5-yl]methanol,
2-(5-{3-[4-(azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl-1,3-thiazole,
2-(5-{3-[4-(azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-oxazole,
(5S)-2-(5-{3-[4-(azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-4,5-dihydro-1,3-oxazole,
2-(5-{3-[2-fluoro-4-(pyrrolidin-1-ylcarbonyl)phenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole,
5-(azetidin-1-ylcarbonyl)-3-chloro-2-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}pyridine,
5-(azetidin-1-ylcarbonyl)-3-chloro-2-{3-[5-(4,5-dihydro-1,3-oxazol-2-yl)-1H-pyrrol-2-yl]-5-[(1S)-2-methoxy-1-methylethoxy]phenoxy}pyridine,
5-(azetidin-1-ylcarbonyl)-3-chloro-2-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)pyridine,
5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}-2-(methylsulfonyl)pyridine,
5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-2-(methylsulfonyl)pyridine,
2-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}-5-[(4-methylpiperazin-1-yl)carbonyl]pyrazine,
[(5R)-2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-

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(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-oxazol-5-yl]methanol,
(2S)-2-{3-[4-(methylsulfonyl)phenoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl)phenoxy]propan-1-ol,
(2S)-2-{3-[5-(4,5-dihydro-1,3-thiazol-2-yl)-1H-pyrrol-2-yl]-5-[4-(methylsulfonyl)phenoxy]phenoxy}propan-1-ol,
(2S)-2-{3-[5-(4,5-dihydro-1,3-oxazol-2-yl)-1H-pyrrol-2-yl]-5-[4-(methylsulfonyl)phenoxy]phenoxy}propan-1-ol,
(2S)-2-(3-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-[4-(methylsulfonyl)phenoxy]phenoxy)propan-1-ol,
(2S)-2-{3-[4-(azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}propan-1-ol,
(2S)-2-(3-[4-(azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)propan-1-ol,
(2S)-2-(3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)propan-1-ol, or
(2S)-2-(3-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol.

(27) the compound described in (1) above, wherein the compound represented by the general formula (I) is:
1-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)ethanone,
2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole,
2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-1,3-thiazole,
2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-thiazole,
2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-oxazole,

(5S)-2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-4,5-dihydro-1,3-oxazole,
(5R)-2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-4,5-dihydro-1,3-oxazole,
[2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-oxazol-5-yl]methanol,
2-(5-{3-[4-(azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl-1,3-thiazole,
2-(5-{3-[4-(azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-oxazole,
(5S)-2-(5-{3-[4-(azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-4,5-dihydro-1,3-oxazole,
2-(5-{3-[2-fluoro-4-(pyrrolidin-1-ylcarbonyl)phenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole,
5-(azetidin-1-ylcarbonyl)-3-chloro-2-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}pyridine,
5-(azetidin-1-ylcarbonyl)-3-chloro-2-{3-[5-(4,5-dihydro-1,3-oxazol-2-yl)-1H-pyrrol-2-yl]-5-[(1S)-2-methoxy-1-methylethoxy]phenoxy}pyridine,
5-(azetidin-1-ylcarbonyl)-3-chloro-2-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)pyridine,
5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}-2-(methylsulfonyl)pyridine,
5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-2-(methylsulfonyl)pyridine,
2-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}-5-[(4-methylpiperazin-1-yl)carbonyl]pyrazine,

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[(5R)-2-(5-{3-[(1S)-2-methoxy-1-methylethoxy}-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-oxazol-5-yl]methanol,
(2S)-2-{3-[4-(methylsulfonyl)phenoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl)phenoxy]propan-1-ol,
(2S)-2-{3-[5-(4,5-dihydro-1,3-thiazol-2-yl)-1H-pyrrol-2-yl]-5-[4-(methylsulfonyl)phenoxy]phenoxy}propan-1-ol,
(2S)-2-{3-[5-(4,5-dihydro-1,3-oxazol-2-yl)-1H-pyrrol-2-yl]-5-[4-(methylsulfonyl)phenoxy]phenoxy}propan-1-ol,
(2S)-2-(3-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-[4-(methylsulfonyl)phenoxy]phenoxy)propan-1-ol,
(2S)-2-{3-[4-(azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}propan-1-ol,
(2S)-2-(3-[4-(azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)propan-1-ol,
(2S)-2-(3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)propan-1-ol, or
(2S)-2-(3-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol.

(28) a compound or pharmacologically acceptable salt thereof described in (1) above, wherein the compound represented by the general formula (I) is:
(2S)-2-(3-[5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrrol-2-yl]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol,
{(5R)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-5-yl}methanol,
(2S)-2-(3-{5-[(4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol,
(2S)-2-(3-{5-[(4R)-4-ethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol,

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{(4R)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}methanol,
(2S)-2-(3-{5-[(4R,5S)-4,5-dimethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol,
{(4R,5R)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4-methyl-4,5-dihydro-1,3-oxazol-5-yl}methanol,
{(4R,5S)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazol-4-yl}methanol,
(1S)-1-{(4S)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol,
(1R)-1-{(4S)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol,
(2S)-2-(3-[5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrrol-2-yl]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol,
(2S)-2-(3-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol,
{(5R)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-5-yl}methanol,
(5S)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazol-4-ol,
(2S)-2-(3-{5-[(4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol,
(2S)-2-(3-{5-[(4R)-4-ethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol,
(2S)-2-(3-{5-[(4R,5S)-4,5-dimethyl-4,5-dihydro-1,3-oxazol-2-yl]-

1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol,
{(4R,5S)-2-[5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazol-4-yl}methanol,
(1S)-1-{(4S)-2-[5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol,
(1R)-1-{(4S)-2-[5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol,
5-(3-[(1S)-2-Hydroxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-N-methylpyridin-2-sulfonamide,
5-(3-[(1S)-2-hydroxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-N-methylpyridine-2-carboxamide,
5-(3-{5-[(5R)-5-(hydroxymethyl)-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-[(1S)-2-methoxy-1-methylethoxy]phenoxy)-N-methylpyridin-2-carboxamide, or
5-(3-{5-[(5R)-5-(hydroxymethyl)-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-[(1S)-2-methoxy-1-methylethoxy]phenoxy)-N-methylpyridin-2-sulfonamide.

(29) a compound or pharmacologically acceptable salt thereof described in (1) above, wherein the compound represented by the general formula (I) is:
{(5R)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-5-yl}methanol,
(2S)-2-(3-{5-[(4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol,
(2S)-2-(3-{5-[(4R)-4-ethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol,
{(4R)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-

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(methylsulfonyl)pyridin-3-yl]oxy}phenyl}-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}methanol,
(2S)-2-(3-{5-[(4R,5S)-4,5-dimethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol,
{(4R,5R)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4-methyl-4,5-dihydro-1,3-oxazol-5-yl}methanol,
{(4R,5S)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazol-4-yl}methanol,
(1S)-1-{(4S)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol,
(1R)-1-{(4S)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol,
(2S)-2-(3-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol,
{(5R)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-5-yl}methanol,
(2S)-2-(3-{5-[(4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol,
(2S)-2-(3-{5-[(4R)-4-ethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol,
(2S)-2-(3-{5-[(4R,5S)-4,5-dimethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol,
{(4R,5S)-2-[5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazol-4-yl}methanol,
(1S)-1-{(4S)-2-[5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-{[5-

(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol, or
(1R)-1-{(4S)-2-[5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol.

(30) a compound described in (1) above, wherein the compound represented by the general formula (I) is:
{(5R)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-5-yl}methanol,
(2S)-2-(3-{5-[(4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol,
(2S)-2-(3-{5-[(4R)-4-ethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol,
{(4R)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}methanol,
(2S)-2-(3-{5-[(4R,5S)-4,5-dimethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol,
{(4R,5R)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4-methyl-4,5-dihydro-1,3-oxazol-5-yl}methanol,
{(4R,5S)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazol-4-yl}methanol,
(1S)-1-{(4S)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol,
(1R)-1-{(4S)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol,
(2S)-2-(3-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-

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yl]oxy}phenoxy)propan-1-ol,
{(5R)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-5-yl}methanol,
(2S)-2-(3-{5-[(4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol,
(2S)-2-(3-{5-[(4R)-4-ethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol,
(2S)-2-(3-{5-[(4R,5S)-4,5-dimethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol,
{(4R,5S)-2-[5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazol-4-yl}methanol,
(1S)-1-{(4S)-2-[5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol, or
(1R)-1-{(4S)-2-[5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol.

(31) a glucokinase activator containing as an active ingredient thereof a compound or pharmacologically acceptable salt thereof described in any one selected from (1) to (30) above;

(32) a pharmaceutical composition containing as an active ingredient thereof a compound or pharmacologically acceptable salt thereof described in any one selected from (1) to (30) above;

(33) the pharmaceutical composition described in (32) above, wherein the pharmaceutical composition has glucokinase activating activity;

(34) the pharmaceutical composition described in (32) above, wherein the pharmaceutical composition is for treating and/or preventing a disease that is treatable and/or preventable by

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glucokinase activating activity;

(35) the pharmaceutical composition described in (32) above, wherein the pharmaceutical composition is for treating and/or preventing a disease for which the symptoms thereof are treated, improved, diminished and/or prevented by activation of glucokinase and maintenance of glucose homeostasis or regulation of blood glucose level;

(36) the pharmaceutical composition described in (32) above, wherein the pharmaceutical composition is for treating and/or preventing diabetes, impaired glucose tolerance, gestational diabetes, chronic complications of diabetes (including diabetic peripheral neuropathy, diabetic nephropathy, diabetic retinopathy and diabetic macroangiopathy) or metabolic syndrome;

(37) the pharmaceutical composition described in (32) above, wherein the pharmaceutical composition is for treating and/or preventing diabetes or impaired glucose tolerance;

(38) a use of a compound, or pharmacologically acceptable salt thereof, described in any one selected from (1) to (30) above, for producing a pharmaceutical composition;

(39) the use described in (38) above, wherein the pharmaceutical composition is a composition for activating glucokinase;

(40) the use described in (38) above, wherein the pharmaceutical composition is a composition for treating and/or preventing diabetes, impaired glucose tolerance, gestational diabetes, chronic complications of diabetes (including diabetic peripheral neuropathy, diabetic nephropathy, diabetic retinopathy and diabetic macroangiopathy) or metabolic syndrome;

(41) the use described in (38) above, wherein the pharmaceutical composition is a composition for treating and/or preventing diabetes or impaired glucose tolerance;

(42) a glucokinase activation method, comprising administering a pharmacologically effective amount of a compound or pharmacologically acceptable salt thereof described in any one selected from (1) to (30) above to a warm-blooded animal;

(43) a method for treating and/or preventing a disease,

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comprising administering a pharmacologically effective amount of a compound or pharmacologically acceptable salt thereof described in any one selected from (1) to (30) above to a warm-blooded animal;

(44) the method described in (43) above, wherein the disease is diabetes, impaired glucose tolerance, gestational diabetes, chronic complications of diabetes (including diabetic peripheral neuropathy, diabetic nephropathy, diabetic retinopathy and diabetic macroangiopathy) or metabolic syndrome;

(45) the method described in (43) above, wherein the disease is diabetes or impaired glucose tolerance; and,

(46) the method described in any one selected from (42) to (45) above, wherein the warm-blooded animal is a human.

In the present invention, a "halogen atom" refers to a fluorine atom, a chlorine atom, a bromine atom or an iodine atom. The halogen atom is preferably a fluorine atom or a chlorine atom, and more preferably a chlorine atom.

In the present invention, a "C_1-C_6 alkyl group" refers to a linear or branched alkyl group having 1 to 6 carbon atom(s). Examples of the C_1-C_6 alkyl group include a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an isobutyl group, an s-butyl group, a t-butyl group, a pentyl group, an isopentyl group, a 2-methylbutyl group, a neopentyl group, a 1-ethylpropyl group, a hexyl group, an isohexyl group, a 4-methylpentyl group, a 3-methylpentyl group, a 2-methylpentyl group, a 1-methylpentyl group, a 3,3-dimethylbutyl group, a 2,2-dimethylbutyl group, a 1,1-dimethylbutyl group and a 1,2-dimethylbutyl group, and the C_1-C_6 alkyl group is preferably a linear or branched alkyl group having 1 to 4 carbon atom(s) (C_1-C_4 alkyl group), more preferably a methyl group or an ethyl group (C_1-C_2 alkyl group), and even more preferably a methyl group.

In the present invention, a "C_1-C_6 halogenated alkyl group" refers to a group in which 1 to 5 of the same or different above-mentioned "halogen atom" are bonded to the above-mentioned "C_1-C_6 alkyl group". Examples of C_1-C_6

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halogenated alkyl groups include a trifluoromethyl group, a trichloromethyl group, a difluoromethyl group, a dichloromethyl group, a dibromomethyl group, a fluoromethyl group, a 2,2,2-trifluoroethyl group, a 2,2,2-trichloroethyl group, a 2-bromoethyl group, a 2-chloroethyl group and a 2-fluoroethyl group, and the C_1-C_6 halogenated alkyl group is preferably a group in which 1 to 5 of the same or different above-mentioned "halogen atom" are bonded to the above-mentioned "C_1-C_4 alkyl group" (C_1-C_4 halogenated alkyl group), more preferably a group in which 1 to 5 of the same or different above-mentioned "halogen atom" are bonded to the above-mentioned "C_1-C_2 alkyl group" (C_1-C_2 halogenated alkyl group), and even more preferably a trifluoromethyl group or a fluoromethyl group.

In the present invention, a "C_2-C_6 alkenyl group" refers to a group among above-mentioned "C_1-C_6 alkyl group" having one double bond and 2 to 6 carbon atoms. Examples of the C_2-C_6 alkenyl group include an ethenyl group, a 1-propenyl group, a 2-propenyl group, a 1-methyl-2-propenyl group, a 1-methyl-1-propenyl group, a 2-methyl-1-propenyl group, a 2-methyl-2-propenyl group, a 1-butenyl group, a 2-butenyl group, a 3-butenyl group, a 1-pentenyl group, a 4-pentenyl group, a 1-methyl-4-pentenyl group and a 5-hexenyl group, and the C_2-C_6 alkenyl group is preferably an alkenyl group having 2 to 4 carbon atoms (C_2-C_4 alkenyl group), and more preferably a 2-propenyl group.

In the present invention, a "C_2-C_6 alkynyl group" refers to a group among above-mentioned "C_1-C_6 alkyl group" having one triple bond and 2 to 6 carbon atoms. Examples of the C_2-C_6 alkynyl group include an ethynyl group, a 1-propynyl group, a 2-propynyl group, a 1-methyl-2-propynyl group, a 1-butynyl group, a 2-butynyl group, a 1-methyl-2-butynyl group, a 3-butynyl group, a 2-pentynyl group and a 5-hexynyl group, and the C_2-C_6 alkynyl group is preferably an alkynyl group having 2 to 4 carbon atoms (C_2-C_4 alkynyl group), and more preferably a 2-propynyl group or a 2-butynyl group.

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In the present invention, a "C_1-C_6 alkyl group substituted with 1 or 2 hydroxy group(s)" refers to a group in which 1 or 2 hydroxy group(s) are bonded to the above-mentioned "C_1-C_6 alkyl group". Examples of the C_1-C_6 alkyl group substituted with 1 or 2 hydroxy group(s) include a hydroxymethyl group, a 2-hydroxyethyl group, a 1-hydroxyethyl group, a 3-hydroxypropyl group, a 1,2-dihydroxyethyl group and a 2,3-dihydroxypropyl group, and the C_1-C_6 alkyl group substituted with 1 or 2 hydroxy group(s) is preferably a group in which 1 or 2 hydroxy group(s) are bonded to the above-mentioned "C_1-C_4 alkyl group", more preferably a group in which 1 or 2 hydroxy group(s) are bonded to the above-mentioned "C_1-C_2 alkyl group", and even more preferably a hydroxymethyl group or a hydroxyethyl group.

In the present invention, a "C_1-C_6 alkoxy group" refers to a group in which the above-mentioned "C_1-C_6 alkyl group" is bonded to an oxygen atom, and is a linear or branched alkoxy group having 1 to 6 carbon atom(s). Examples of the C_1-C_6 alkoxy group include a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, a butoxy group, an isobutoxy group, an s-butoxy group, a t-butoxy group, a pentoxy group, a 2-methylbutoxy group, a 3-ethylpropoxy group, a neopentoxy group, a hexyloxy group and a 2,3-dimethylbutoxy group, and the C_1-C_6 alkoxy group is preferably a linear or branched alkoxy group having 1 to 4 carbon atom(s) (C_1-C_4 alkoxy group), more preferably a methoxy group, an ethoxy group, a propoxy group or an isopropoxy group (C_1-C_3 alkoxy group), even more preferably a methoxy group or an ethoxy group (C_1-C_2 alkoxy group), and particularly preferably a methoxy group.

In the present invention, a "C_1-C_6 halogenated alkoxy group" refers to a group in which 1 to 5 of the same or different above-mentioned "halogen atom" are bonded to the above-mentioned "C_1-C_6 alkoxy group". Examples of the C_1-C_6 halogenated alkoxy group include a trifluoromethoxy group, a trichloromethoxy group, a difluoromethoxy group, a dichloromethoxy group, a dibromomethoxy group, a fluoromethoxy group, a 2,2,2-trifluoroethoxy group, a 2,2,2-trichloroethoxy

group, a 2-chloroethoxy group, a 2-fluoroethoxy group, and a pentafluoroethoxy group, and the C_1-C_6 halogenated alkoxy group is preferably a group in which 1 to 5 of the same or different above-mentioned "halogen atom" are bonded to the above-mentioned "C_1-C_4 alkoxy group" (C_1-C_4 halogenated alkoxy group), more preferably a group in which 1 to 5 of the same or different above-mentioned "halogen atom" are bonded to the above-mentioned "C_1-C_2 alkoxy group" (C_1-C_2 halogenated alkoxy group), and even more preferably a trifluoromethoxy group.

In the present invention, a "(C_1-C_6 alkoxy)-(C_1-C_6 alkyl) group" refers to a group in which one above-mentioned "C_1-C_6 alkoxy group" is bonded to the above-mentioned "C_1-C_6 alkyl group". Examples of the (C_1-C_6 alkoxy)-(C_1-C_6 alkyl) group include a methoxymethyl group, an ethoxymethyl group, a propoxymethyl group, an isopropoxymethyl group, a butoxymethyl group, an s-butoxymethyl group, a t-butoxymethyl group, a 2-methoxyethyl group and a 3-isopropoxypropyl group, and the (C_1-C_6 alkoxy)-(C_1-C_6 alkyl) group is preferably a group in which one above-mentioned "C_1-C_4 alkoxy group" is bonded to the above-mentioned "C_1-C_4 alkyl group" ((C_1-C_4 alkoxy)-(C_1-C_4 alkyl) group), more preferably a group in which one above-mentioned "C_1-C_2 alkoxy group" is bonded to the above-mentioned "C_1-C_2 alkyl group" ((C_1-C_2 alkoxy)-(C_1-C_2 alkyl) group), and even more preferably a methoxymethyl group.

In the present invention, a "(C_1-C_6 alkoxy)-(C_1-C_6 alkoxy) group" refers to a group in which one above-mentioned "C_1-C_6 alkoxy group" is bonded to the above-mentioned "C_1-C_6 alkoxy group". Examples of the (C_1-C_6 alkoxy)-(C_1-C_6 alkoxy) group include a methoxymethyloxy group, an ethoxymethyloxy group, a propoxymethyloxy group, a butoxymethyloxy group, a 2-methoxyethyloxy group and a 3-isopropoxypropyloxy group, and the (C_1-C_6 alkoxy)-(C_1-C_6 alkoxy) group is preferably a group in which one above-mentioned "C_1-C_4 alkoxy group" group is bonded to the above-mentioned "C_1-C_4 alkoxy group" ((C_1-C_4 alkoxy)-(C_1-C_4 alkoxy) group), more preferably a group in which one above-mentioned "C_1-C_2 alkoxy group" is bonded to the above-mentioned

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"C_1-C_2 alkoxy group" ((C_1-C_2 alkoxy)-(C_1-C_2 alkoxy) group), and even more preferably a methoxymethyloxy group.

In the present invention, a "C_2-C_7 alkylcarbonyl group" refers to a group in which one above-mentioned "C_1-C_6 alkyl group" is bonded to a carbonyl group. Examples of the C_2-C_7 alkylcarbonyl group include an acetyl group, a propionyl group, a butyryl group, an isobutyryl group, a pentanoyl group, a pivaloyl group and a valeryl group, and the C_2-C_7 alkylcarbonyl group is preferably a group in which one above-mentioned "C_1-C_4 alkyl group" is bonded to a carbonyl group (C_2-C_5 alkylcarbonyl group), more preferably an acetyl group or a propionyl group (C_2-C_3 alkylcarbonyl group), and even more preferably an acetyl group.

In the present invention, a "C_2-C_7 alkoxycarbonyl group" refers to a group in which one above-mentioned "C_1-C_6 alkoxy group" is bonded to a carbonyl group. Examples of the C_2-C_7 alkoxycarbonyl group include a methoxycarbonyl group, an ethoxycarbonyl group, a propoxycarbonyl group, an isopropoxycarbonyl group, a butoxycarbonyl group, an isobutoxycarbonyl group, an s-butoxycarbonyl group and a t-butoxycarbonyl group, and the C_2-C_7 alkoxycarbonyl group is preferably a group in which one above-mentioned "C_1-C_4 alkoxy group" is bonded to a carbonyl group (C_2-C_5 alkoxycarbonyl group), more preferably a methoxycarbonyl group or an ethoxycarbonyl group (C_2-C_3 alkoxycarbonyl group), and even more preferably a methoxycarbonyl group.

In the present invention, a "C_2-C_7 alkylcarbonyloxy group" refers to a group in which a carbonyl group to which is bonded one above-mentioned "C_1-C_6 alkyl group" is bonded to an oxygen atom. Examples of the C_2-C_7 alkylcarbonyloxy group include an acetoxy group, a propionyloxy group, a butyryloxy group, an isobutyryloxy group, a pentanoyloxy group, a pivaloyloxy group, a valeryloxy group and an isovaleryloxy group, and the C_2-C_7 alkylcarbonyloxy group is preferably a group in which a carbonyl group to which is bonded one above-mentioned "C_1-C_4 alkyl group" is bonded to an oxygen atom (C_2-C_5 alkylcarbonyloxy group), more

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preferably an acetoxy group or a propionyloxy group (C_2-C_3 alkylcarbonyloxy group), and even more preferably an acetoxy group.

In the present invention, a "C_2-C_7 alkoxycarbonyloxy group" refers to a group in which a carbonyl group to which is bonded one above-mentioned "C_1-C_6 alkoxy group" is bonded to an oxygen atom. Examples of the C_2-C_7 alkoxycarbonyloxy group include a methoxycarbonyloxy group, an ethoxycarbonyloxy group, a propoxycarbonyloxy group, an isopropoxycarbonyloxy group, a butoxycarbonyloxy group, an s-butoxycarbonyloxy group and a t-butoxycarbonyloxy group, and the C_2-C_7 alkoxycarbonyloxy group is preferably a group in which a carbonyl group to which is bonded one above-mentioned "C_1-C_4 alkoxy group" is bonded to an oxygen atom (C_2-C_5 alkoxycarbonyloxy group), more preferably a methoxycarbonyloxy group or an ethoxycarbonyloxy group (C_2-C_3 alkoxycarbonyloxy group), and even more preferably a methoxycarbonyloxy group.

In the present invention, a "mono-C_1-C_6 alkylamino group" refers to a group in which one above-mentioned "C_1-C_6 alkyl group" is bonded to an amino group. Examples of the mono-C_1-C_6 alkylamino group include a methylamino group, an ethylamino group, a propylamino group, an isopropylamino group, a butylamino group, an isobutylamino group, an s-butylamino group, a t-butylamino group, a pentylamino group, an isopentylamino group, a 2-methylbutylamino group, a neopentylamino group, a 1-ethylpropylamino group, a hexylamino group and an isohexylamino group, and the mono-C_1-C_6 alkylamino group is preferably a group in which one above-mentioned "C_1-C_4 alkyl group" is bonded to an amino group (mono-C_1-C_4 alkylamino group), more preferably a methylamino group or an ethylamino group (mono-C_1-C_2 alkylamino group), and even more preferably a methylamino group.

In the present invention, a "mono-C_1-C_6 halogenated alkylamino group" refers to a group in which one above-mentioned "C_1-C_6 halogenated alkyl group" is bonded to an amino group. Examples of the mono-C_1-C_6 halogenated alkylamino group include a trifluoromethylamino group, a trichloromethylamino group, a

difluoromethylamino group, a dichloromethylamino group, a dibromomethylamino group, a fluoromethylamino group, a 2,2,2-trifluoroethylamino group, a 2,2,2-trichloroethylamino group, a 2-bromoethylamino group, a 2-chloroethylamino group and a 2-fluoroethylamino group, and the mono-C_1-C_6 halogenated alkylamino group is preferably a group in which one above-mentioned "C_1-C_4 halogenated alkyl group" is bonded to an amino group (mono-C_1-C_4 halogenated alkylamino group), more preferably a group in which one above-mentioned "C_1-C_2 halogenated alkyl group" is bonded to an amino group (mono-C_1-C_2 halogenated alkylamino group), and even more preferably a 2-chloroethylamino group.

In the present invention, a "di-(C_1-C_6 alkyl)amino group" refers to a group in which two of the same or different above-mentioned "C_1-C_6 alkyl group" is bonded to an amino group. Examples of the di-(C_1-C_6 alkyl)amino group include a dimethylamino group, a diethylamino group, a dipropylamino group, a diisopropylamino group, a dibutylamino group, a diisobutylamino group, a dipentylamino group, a diisopentylamino group, a dineopentylamino group, a dihexylamino group, an N-ethyl-N-methylamino group, an N-methyl-N-propyl amino group, an N-isopropyl-N-methylamino group, an N-butyl-N-methylamino group, an N-isobutyl-N-methylamino group, an N-methyl-N-pentylamino group, an N-isopentyl-N-methylamino group, an N-ethyl-N-propylamino group, an N-ethyl-N-isopropylamino group, an N-butyl-N-ethylamino group and an N-ethyl-N-isopentylamino group, and the di-(C_1-C_6 alkyl)amino group is preferably a group in which two of the same or different above-mentioned "C_1-C_4 alkyl group" is bonded to an amino group (di-(C_1-C_4 alkyl)amino group), more preferably a dimethylamino group, a diethylamino group or an N-ethyl-N-methylamino group (di-(C_1-C_2 alkyl)amino group), and even more preferably a dimethylamino group.

In the present invention, a "di-(C_1-C_6 halogenated alkyl)amino group" refers to a group in which two of the same or different above-mentioned "C_1-C_6 halogenated alkyl group" is bonded to an amino group. Examples of the "di-(C_1-C_6 halogenated alkyl)amino group include a di-(trifluoromethyl)amino group, a

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di-(fluoromethyl)amino group, a di-(2,2,2-trichloroethyl)amino group, a di-(2-chloroethyl)amino group and an N-(2-chloroethyl)-N-(2-fluoroethyl)amino group, and the di-(C_1-C_6 halogenated alkyl)amino group is preferably a group in which two of the same or different above-mentioned "C_1-C_4 halogenated alkyl group" is bonded to an amino group (di-(C_1-C_4 halogenated alkyl)amino group), and more preferably a di-(2-chloroethyl)amino group.

In the present invention, a "C_1-C_6 alkylthio group" refers to a group in which one above-mentioned "C_1-C_6 alkyl group" is bonded to a sulfur atom, and is a linear or branched alkylthio group having 1 to 6 carbon atom(s). Examples of the C_1-C_6 alkylthio group include a methylthio group, an ethylthio group, a propylthio group, an isopropylthio group, a butylthio group, an isobutylthio group, an s-butylthio group, a pentylthio group, a 1-ethylpropylthio group and a hexylthio group, and the C_1-C_6 alkylthio group is preferably a linear or branched alkylthio group having 1 to 4 carbon atom(s) (C_1-C_4 alkylthio group), more preferably a methylthio group or an ethylthio group (C_1-C_2 alkylthio group), and even more preferably a methylthio group.

In the present invention, a "C_1-C_6 alkylsulfonyl group" refers to a group in which one above-mentioned "C_1-C_6 alkyl group" is bonded to a sulfonyl group, and is a linear or branched alkylsulfonyl group having 1 to 6 carbon atom(s). Examples of the C_1-C_6 alkylsulfonyl group include a methylsulfonyl group, an ethylsulfonyl group, a propylsulfonyl group, an isopropylsulfonyl group, a butylsulfonyl group, an isobutylsulfonyl group, an s-butylsulfonyl group and a pentylsulfonyl group, and the C_1-C_6 alkylsulfonyl group is preferably a linear or branched alkylsulfonyl group having 1 to 4 carbon atom(s) (C_1-C_4 alkylsulfonyl group), more preferably a methylsulfonyl group or an ethylsulfonyl group (C_1-C_2 alkylsulfonyl group), and even more preferably a methylsulfonyl group.

In the present invention, a "C_3-C_6 cycloalkylsulfonyl group" refers to a cyclopropylsulfonyl group, a cyclobutylsulfonyl group, a cyclopentylsulfonyl group or a

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cyclohexylsulfonyl group. The C_3-C_6 cycloalkylsulfonyl group is preferably a cyclopropylsulfonyl group.

In the present invention, a "C_1-C_6 hydroxyalkylsulfonyl group" refers to a group in which one above-mentioned "C_1-C_6 alkyl group" to which is bonded one hydroxy group is bonded to a sulfonyl group, and is a linear or branched hydroxyalkylsulfonyl group having 1 to 6 carbon atom(s). Examples of the C_1-C_6 hydroxyalkylsulfonyl group include a hydroxymethylsulfonyl group, a 2-hydroxyethylsulfonyl group, a 1-hydroxyethylsulfonyl group and a 3-hydroxypropylsulfonyl group, and the C_1-C_6 hydroxyalkylsulfonyl group is preferably a linear or branched hydroxyalkylsulfonyl group having 1 to 4 carbon atom(s) (C_1-C_4 hydroxyalkylsulfonyl group), more preferably a hydroxymethylsulfonyl group or a hydroxyethylsulfonyl group (C_1-C_2 hydroxyalkylsulfonyl group), and even more preferably a hydroxymethylsulfonyl group.

In the present invention, a "(C_1-C_6 alkoxy)-(C_1-C_6 alkylsulfonyl) group" refers to a group in which one above-mentioned "C_1-C_6 alkoxy group" is bonded to the above-mentioned "C_1-C_6 alkylsulfonyl group". Examples of the (C_1-C_6 alkoxy)-(C_1-C_6 alkylsulfonyl) group include a methoxymethylsulfonyl group, an ethoxymethylsulfonyl group, a propoxymethylsulfonyl group, an isopropoxymethylsulfonyl group, a butoxymethylsulfonyl group and an s-butoxymethylsulfonyl group, and the (C_1-C_6 alkoxy)-(C_1-C_6 alkylsulfonyl) group is preferably a group in which one above-mentioned "C_1-C_4 alkoxy group" is bonded to the above-mentioned "C_1-C_4 alkylsulfonyl group" ((C_1-C_4 alkoxy)-(C_1-C_4 alkylsulfonyl) group), more preferably a group in which one above-mentioned "C_1-C_2 alkoxy group" is bonded to the above-mentioned "C_1-C_2 alkylsulfonyl group" ((C_1-C_2 alkoxy)-(C_1-C_2 alkylsulfonyl) group), and even more preferably a methoxymethylsulfonyl group.

In the present invention, a "group represented by the formula -V-NR^5R^6 (wherein V represents a carbonyl group or a sulfonyl group, and R^5 and R^6 may be the same or different and respectively represent a hydrogen atom or a C_1-C_6 alkyl group, or R^5 and R^6 together with the nitrogen atom bonded thereto form a

4- to 6-membered saturated heterocycle that may be substituted with 1 or 2 group(s) independently selected from a C_1-C_6 alkyl group and a hydroxy group, and the 4- to 6-membered saturated heterocycle may further contain one oxygen atom or nitrogen atom)" refers to a "group represented by the formula -C(=O)-NR^5R^6" or a "group represented by the formula -SO_2-NR^5R^6", the "group represented by the formula -C(=O)-NR^5R^6" is a carbamoyl group, "mono-C_1-C_6 alkylaminocarbonyl group (group in which an amino group to which is bonded one above-mentioned "C_1-C_6 alkyl group" is bonded to a carbonyl group)", "di(C_1-C_6 alkyl)aminocarbonyl group (group in which an amino group to which are bonded two of the same or different above-mentioned "C_1-C_6 alkyl group" is bonded to a carbonyl group)" or "group in which a nitrogen atom of a 4- to 6-membered saturated heterocycle, which may be substituted with 1 or 2 group(s) independently selected from a C_1-C_6 alkyl group and a hydroxy group (4- to 6-membered completely reduced saturated heterocyclic group that contains one nitrogen atom and may further contain one oxygen atom or nitrogen atom), is bonded to a carbonyl group", and the "group represented by the formula -SO_2-NR^5R^6" is a sulfamoyl group, "mono-C_1-C_6 alkylaminosulfonyl group (group in which an amino group to which is bonded one above-mentioned "C_1-C_6 alkyl group" is bonded to a sulfonyl group", "di-(C_1-C_6 alkyl)aminosulfonyl group (group in which an amino group to which are bonded two of the same or different above-mentioned "C_1-C_6 alkyl group" is bonded to a sulfonyl group", or "group in which a nitrogen atom of a 4- to 6-membered saturated heterocycle, which may be substituted with 1 or 2 group(s) independently selected from a C_1-C_6 alkyl group and a hydroxy group (4- to 6-membered completely reduced saturated heterocyclic group that contains one nitrogen atom and may further contain one oxygen atom or nitrogen atom), is bonded to a sulfonyl group". Examples of the aforementioned group include a carbamoyl group, a methylaminocarbonyl group, an ethylaminocarbonyl group, a propylaminocarbonyl group, a dimethylaminocarbonyl group, a diethylaminocarbonyl group, a

dipropylaminocarbonyl group, an N-ethyl-N-methylaminocarbonyl group, an N-methyl-N-propylaminocarbonyl group, a (1-azetidinyl)carbonyl group, a (3-hydroxy-1-azetidinyl)carbonyl group, a (1-pyrrolidinyl)carbonyl group, a (4-morpholinyl)carbonyl group, a (4-methyl-1-piperazinyl)carbonyl group, a sulfamoyl group, a methylaminosulfonyl group, an ethylaminosulfonyl group, a propylaminosulfonyl group, a dimethylaminosulfonyl group, a diethylaminosulfonyl group, a dipropylaminosulfonyl group, an N-ethyl-N-methylaminosulfonyl group, an N-methyl-N-propylaminosulfonyl group and a (1-azetidinyl)sulfonyl group, and the aforementioned group is preferably a carbamoyl group, a methylaminocarbonyl group, a dimethylaminocarbonyl group, a (1-azetidinyl)carbonyl group, a (1-pyrrolidinyl)carbonyl group, a (4-morpholinyl)carbonyl group, a (4-methyl-1-piperazinyl)carbonyl group, a methylaminosulfonyl group or a (1-azetidinyl)sulfonyl group, more preferably a dimethylaminocarbonyl group, a (1-azetidinyl)carbonyl group, a (1-pyrrolidinyl)carbonyl group or a (4-methyl-1-piperazinyl)carbonyl group, and even more preferably a dimethylaminocarbonyl group or a (1-azetidinyl)carbonyl group.

In the present invention, a "mono-C_2-C_7 alkylcarbonylamino group" refers to a group in which a carbonyl group to which is bonded one above-mentioned "C_1-C_6 alkyl group" is bonded to an amino group. Examples of the mono-C_2-C_7 alkylcarbonylamino group include an acetamido group, an ethylcarbonylamino group, a propylcarbonylamino group, an isopropylcarbonylamino group, a butylcarbonylamino group and an isobutylcarbonylamino group, and the mono-C_2-C_7 alkylcarbonylamino group is preferably a group in which a carbonyl group to which is bonded one above-mentioned "C_1-C_4 alkyl group" is bonded to an amino group (mono-C_2-C_5 alkylcarbonylamino group), more preferably an acetamido group or an ethylcarbonylamino group (mono-C_2-C_3 alkylcarbonylamino group), and even more preferably an acetamido group.

In the present invention, a "mono-C_1-C_6 alkylaminocarbonyloxy group" refers to a group in which a carbonyl group, to which is bonded an amino group bonded to one

above-mentioned "C_1-C_6 alkyl group", is bonded to an oxygen atom. Examples of the mono-C_1-C_6 alkylaminocarbonyloxy group include a methylaminocarbonyloxy group, an ethylaminocarbonyloxy group, a propylaminocarbonyloxy group, an isopropylaminocarbonyloxy group and a butylaminocarbonyloxy group, and the mono-C_1-C_6 alkylaminocarbonyloxy group is preferably a methylaminocarbonyloxy group or an ethylaminocarbonyloxy group (mono-C_1-C_2 alkylaminocarbonyloxy group), and more preferably a methylaminocarbonyloxy group.

In the present invention, a "di-(C_1-C_6 alkyl)aminocarbonyloxy group" refers to a group in which a carbonyl group, to which is bonded an amino group bonded to two of the same or different above-mentioned "C_1-C_6 alkyl group", is bonded to an oxygen atom. Examples of the di-(C_1-C_6 alkyl)aminocarbonyloxy group include a dimethylaminocarbonyloxy group, a diethylaminocarbonyloxy group, a dipropylaminocarbonyloxy group, an N-ethyl-N-methylaminocarbonyloxy group and an N-methyl-N-propylaminocarbonyloxy group, and the di-(C_1-C_6 alkyl)aminocarbonyloxy group is preferably a dimethylaminocarbonyloxy group, a diethylaminocarbonyloxy group or an N-ethyl-N-methylaminocarbonyloxy group (di-(C_1-C_2 alkyl)aminocarbonyloxy group), and more preferably a dimethylaminocarbonyloxy group.

In the present invention, a "mono-C_2-C_7 alkoxycarbonylamino group" refers to a group in which a carbonyl group to which is bonded one above-mentioned "C_1-C_6 alkoxy group" is bonded to an amino group. Examples of the mono-C_2-C_7 alkoxycarbonylamino group include a methoxycarbonylamino group, an ethoxycarbonylamino group, a propoxycarbonylamino group, an isopropoxycarbonylamino group and a butoxycarbonylamino group, and the mono-C_2-C_7 alkoxycarbonylamino group is preferably a methoxycarbonylamino group or an ethoxycarbonylamino group (C_2-C_3 alkoxycarbonylamino group), and more preferably a methoxycarbonylamino group.

In the present invention, a "mono-C_1-C_6 alkylsulfonylamino

group" refers to a group in which a sulfonyl group to which is bonded one above-mentioned "C_1-C_6 alkyl group" is bonded to an amino group. Examples of the mono-C_1-C_6 alkylsulfonylamino group include a methylsulfonylamino group, an ethylsulfonylamino group, a propylsulfonylamino group, an isopropylsulfonylamino group, a butylsulfonylamino group, a t-butylsulfonylamino group and a 2-ethylbutylsulfonylamino group, and the mono-C_1-C_6 alkylsulfonylamino group is preferably a group in which a sulfonyl group to which is bonded one above-mentioned "C_1-C_4 alkyl group" is bonded to an amino group (mono-C_1-C_4 alkylsulfonylamino group), more preferably a methylsulfonylamino group or an ethylsulfonylamino group (mono-C_1-C_2 alkylsulfonylamino group), and even more preferably a methylsulfonylamino group.

In the present invention, a "1,3,4-oxadiazol-2-yl group optionally substituted with a C_1-C_6 alkyl group at the 5-position" refers to a group in which a C_1-C_6 alkyl group is substituted at the 5-position of a 1,3,4-oxadiazol-2-yl group. Examples of the aforementioned group include a 5-methyl-1,3,4-oxadiazol-2-yl group and a 5-ethyl-1,3,4-oxadiazol-2-yl group, and the aforementioned group is preferably a 5-methyl-1,3,4-oxadiazol-2-yl group.

In the present invention, a "1,3,4-thiadiazol-2-yl group optionally substituted with a C_1-C_6 alkyl group at the 5-position" refers to a group in which a C_1-C_6 alkyl group is substituted at the 5-position of a 1,3,4-thiadiazol-2-yl group. Examples of the aforementioned group include a 5-methyl-1,3,4-thiadiazol-2-yl group and a 5-ethyl-1,3,4-thiadiazol-2-yl group, and the aforementioned group is preferably a 5-methyl-1,3,4-thiadiazol-2-yl group.

In the present invention, a "heterocyclic group" refers to a 4- to 7-membered heterocyclic group that contains 1 to 3 sulfur atom(s), oxygen atom(s) and/or nitrogen atom(s), and may further contain 1 or 2 nitrogen atom(s), and in which the sulfur atom(s) may be bonded to 2 oxygen atoms. Examples of the heterocyclic group include an "aromatic heterocyclic group" such

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as a furyl group, a thienyl group, a pyrrolyl group, an azepinyl group, a pyrazolyl group, an imidazolyl group, an oxazolyl group, an isoxazolyl group, a thiazolyl group, an isothiazolyl group, a 1,3,4-oxadiazolyl group, a 1,3,4-thiadiazolyl group, a triazolyl group, a tetrazolyl group, a thiadiazolyl group, a pyranyl group, a pyridyl group, a pyridazinyl group, a pyrimidinyl group and a pyrazinyl group, and a "partially or completely reduced saturated heterocyclic group" such as a tetrahydropyranyl group, a tetrahydrothienyl group, a morpholinyl group, a thiomorpholinyl group, a pyrrolidinyl group, a pyrrolinyl group, an imidazolidinyl group, a pyrazolidinyl group, a piperidinyl group, a piperazinyl group, an oxazolinyl group, an oxazolidinyl group, an isoxazolidinyl group, a thiazolinyl group, a thiazolidinyl group, a pyrazolidinyl group, a dioxolanyl group, a dioxanyl group and a 5,6-dihydro-4H-1,3-oxazine group, and the above heterocyclic group may be fused with another cyclic group such as a benzene ring ("fused bicyclic heteroaryl group"), for example, a benzothienyl group, a benzothiazolyl group, a benzooxazolyl group, an isobenzofuranyl group, a 1,3-dihydroisobenzofuranyl group, a quinolyl group, a 1,3-benzodioxolanyl group, a 1,4-benzodioxanyl group, an indolyl group, an isoindolyl group and an indolinyl group. Heterocyclic groups formed by A and R^1 together with the carbon atom bonded thereto, that may be substituted with 1 to 3 group(s) independently selected from Substituent Group α, are preferably a 2-pyridyl group, a 5,6-dihydro-4H-1,3-oxazin-2-yl group, a 1,3-thiazol-2-yl group, a 1,3-oxazol-2-yl group, a 1,3,4-oxadiazol-2-yl group, a 1,3,4-thiadiazol-2-yl group, a 4,5-dihydro-1,3-thiazol-2-yl group, a 4,5-dihydro-1,3-oxazol-2-yl group or a 4,5-dihydro-1,3-benzothiazol-2-yl group, more preferably a 1,3-thiazol-2-yl group, a 1,3,4-oxadiazol-2-yl group, a 4,5-dihydro-1,3-thiazol-2-yl group, a 4,5-dihydro-1,3-oxazol-2-yl group, a 1,3,4-thiadiazol-2-yl group or a 5,6-dihydro-4H-1,3-oxazin-2-yl group, and even more preferably a 4,5-dihydro-1,3-oxazol-2-yl group. In R^2, the heterocyclic group is preferably a 6-membered heterocyclic group containing 1

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or 2 nitrogen atom(s), more preferably a pyridyl group or a pyrazinyl group, and even more preferably a 2-pyridyl group, a 3-pyridyl group or a 2-pyrazinyl group.

In the present invention, a "group represented by formula $=NOR^4$" refers to a group in which one hydroxy group or one above-mentioned "C_1-C_6 alkoxy group" is bonded to an imino group. The group represented by formula $=NOR^4$ is preferably a group represented by the formula =NOH.

In the present invention, a "heterocyclic group formed by A and R^1 together with the carbon atom bonded thereto and which may be substituted with 1 to 3 group(s) independently selected from Substituent Group α" refers to the above-mentioned "heterocyclic group" or the above-mentioned "heterocyclic group" that is substituted by 1 to 3 group(s) independently selected from Substituent Group α. The aforementioned group is preferably a 2-pyridyl group, 5,6-dihydro-4H-1,3-oxazin-2-yl group, 1,3-thiazol-2-yl group, 1,3-oxazol-2-yl group, 1,3,4-oxadiazol-2-yl group, 1,3,4-thiadiazol-2-yl group, 4,5-dihydro-1,3-thiazol-2-yl group, 4,5-dihydro-1,3-oxazol-2-yl group or 4,5-dihydro-1,3-benzothiazol-2-yl group that may be substituted with 1 to 3 group(s) independently selected from Substituent Group γ, more preferably a 1,3-thiazol-2-yl group, a 5-methyl-1,3-thiazol-2-yl group, a 5-methyl-1,3,4-oxadiazol-2-yl group, a 4,5-dihydro-1,3-thiazol-2-yl group, a 4,5-dihydro-1,3-oxazol-2-yl group, a (5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5R)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a 5-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5R)-5-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-ethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4S)-4-[(1R)-1-hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl group, a (4S)-4-[(1S)-1-hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5S)-4,5-dimethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5S)-4-hydroxy-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5S)-4-hydroxymethyl-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a

(4R,5R)-5-hydroxymethyl-4-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a 5-carboxyl-1,3-thiazol-2-yl group, a 5-dimethylaminocarbonyl-1,3-thiazol-2-yl group, a 5-methyl-1,3,4-thiadiazol-2-yl group or a 5,6-dihydro-4H-1,3-oxazin-2-yl group, even more preferably a 4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-ethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5R)-5-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4S)-4-[(1R)-1-hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl group, a (4S)-4-[(1S)-1-hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5S)-4,5-dimethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5S)-4-hydroxymethyl-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5R)-5-hydroxymethyl-4-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a 1,3-thiazol-2-yl group, a 5-carboxyl-1,3-thiazol-2-yl group, a 5-dimethylaminocarbonyl-1,3-thiazol-2-yl group, a 5-methyl-1,3,4-thiadiazol-2-yl group, a 5-methyl-1,3,4-oxadiazol-2-yl group, a 4,5-dihydro-1,3-thiazol-2-yl group or a 5,6-dihydro-4H-1,3-oxazin-2-yl group, and particularly preferably a 4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-ethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5R)-5-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4S)-4-[(1R)-1-hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl group, a (4S)-4-[(1S)-1-hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5S)-4,5-dimethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5S)-4-hydroxymethyl-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group or a (4R,5R)-5-hydroxymethyl-4-methyl-4,5-dihydro-1,3-oxazol-2-yl group.

In the present invention, a "phenyl group that may be substituted with 1 to 5 group(s) independently selected from Substituent Group α" refers to a phenyl group or a phenyl group substituted with 1 to 5 group(s) independently selected from Substituent Group α. The aforementioned group is preferably a

phenyl group that may be substituted with 1 to 5 group(s) independently selected from Substituent Group δ, more preferably a 4-acetylphenyl group, a 4-(1-hydroxyethyl)phenyl group, a 4-methylsulfonylphenyl group, a 4-(1-azetidinyl)sulfonylphenyl group, a 2-fluoro-4-methoxycarbonylphenyl group, a 4-carbamoyl-2-fluorophenyl group, a 2-fluoro-4-methylaminocarbonylphenyl group, a 4-dimethylaminocarbonyl-2-fluorophenyl group, a 4-(1-azetidinyl)carbonyl-2-fluorophenyl group, a 2-fluoro-4-(1-pyrroiidinyl)carbonylphenyl group, a 2-fluoro-4-(4-morpholinyl)carbonylphenyl group, a 2-fluoro-4-methylaminosulfonylphenyl group, a 4-(1-azetidinyl)sulfonyl-2-fluorophenyl group, a 2-fluoro-4-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl group, a 2-fluoro-4-(5-methyl-1,3,4-thiadiazol-2-yl)phenyl group, a 4-(1-azetidinyl)carbonyl-2-methylphenyl group or a 4-(1-azetidinyl)carbonyl-2-trifluoromethylphenyl group, even more preferably a 4-methylsulfonylphenyl group, a 4-(1-azetidinyl)carbonyl-2-fluorophenyl group or a 2-fluoro-4-(1-pyrrolidinyl)carbonylphenyl group, and particularly preferably a 4-methylsulfonylphenyl group.

In the present invention, a "heterocyclic group that may be substituted with 1 to 3 group(s) independently selected from Substituent Group α" in R^2 refers to the above-mentioned "heterocyclic group" or the above-mentioned "heterocyclic group" that is substituted with 1 to 3 group(s) independently selected from Substituent Group α. The aforementioned group is preferably a 2-pyridyl group, 3-pyridyl group or 2-pyrazinyl group that may be substituted with 1 to 3 group(s) independently selected from Substituent Group δ, more preferably a 5-(1-azetidinyl)carbonyl-3-chloro-2-pyridyl group, a 2-methylsulfonyl-5-pyridyl group, a 5-(4-methyl-1-piperazinyl)carbonyl-2-pyrazinyl group, a 2-methylaminocarbonyl-5-pyridyl group, a 2-methylaminosulfonyl-5-pyridyl group or a 5-methylsulfonyl-2-pyrazinyl group, and even more preferably a 2-methylsulfonyl-5-pyridyl group, a 5-methylsulfonyl-2-pyrazinyl group or a 5-(1-azetidinyl)carbonyl-3-chloro-2-pyridyl group.

In the present invention, the general formula (I) is

preferably the general formula (Ia).

In the present invention, A is preferably a group represented by the formula =NOH or an oxygen atom, and more preferably an oxygen atom.

In the present invention, R^1 is preferably a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group or a mono-C_1-C_6 halogenated alkylamino group, and more preferably a methyl group or a 2-chloroethylamino group.

In the present invention, the heterocyclic group formed by A and R^1 together with the carbon atom bonded thereto that may be substituted with 1 to 3 group(s) independently selected from Substituent Group α is preferably a 2-pyridyl group, 5,6-dihydro-4H-1,3-oxazin-2-yl group, 1,3-thiazol-2-yl group, 1,3-oxazol-2-yl group, 1,3,4-oxadiazol-2-yl group, 1,3,4-thiadiazol-2-yl group, 4,5-dihydro-1,3-thiazol-2-yl group, 4,5-dihydro-1,3-oxazol-2-yl group or 4,5-dihydro-1,3-benzothiazol-2-yl group that may be substituted with 1 to 3 group(s) independently selected from Substituent Group γ, more preferably a 1,3-thiazol-2-yl group, a 5-methyl-1,3-thiazol-2-yl group, a 5-methyl-1,3,4-oxadiazol-2-yl group, a 4,5-dihydro-1,3-thiazol-2-yl group, a 4,5-dihydro-1,3-oxazol-2-yl group, a (5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5R)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a 5-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5R)-5-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-ethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4S)-4-[(1R)-1-hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl group, a (4S)-4-[(1S)-1-hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5S)-4,5-dimethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5S)-4-hydroxy-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5S)-4-hydroxymethyl-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5R)-5-hydroxymethyl-4-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a 5-carboxyl-1,3-thiazol-2-yl group, a 5-dimethylaminocarbonyl-1,3-thiazol-2-yl group, a 5-methyl-1,3,4-thiadiazol-2-yl group or a 5,6-dihydro-4H-1,3-oxazin-2-yl group,

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even more preferably a 4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-ethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5R)-5-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4S)-4-[(1R)-1-hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl group, a (4S)-4-[(1S)-1-hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5S)-4,5-dimethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5S)-4-hydroxymethyl-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5R)-5-hydroxymethyl-4-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a 1,3-thiazol-2-yl group, a 5-carboxyl-1,3-thiazol-2-yl group, a 5-dimethylaminocarbonyl-1,3-thiazol-2-yl group, a 5-methyl-1,3,4-thiadiazol-2-yl group, a 5-methyl-1,3,4-oxadiazol-2-yl group, a 4,5-dihydro-1,3-thiazol-2-yl group or a 5,6-dihydro-4H-1,3-oxazin-2-yl group, and particularly preferably a 4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-ethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5R)-5-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4S)-4-[(1R)-1-hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl group, a (4S)-4-[(1S)-1-hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5S)-4,5-dimethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5S)-4-hydroxymethyl-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group or a (4R,5R)-5-hydroxymethyl-4-methyl-4,5-dihydro-1,3-oxazol-2-yl group.

In the present invention, R^2 is preferably a phenyl group that may be substituted with 1 to 5 group(s) independently selected from Substituent Group δ or a 2-pyridyl group, 3-pyridyl group or 2-pyrazinyl group that may be substituted with 1 to 3 group(s) independently selected from Substituent Group δ, more preferably a 4-methylsulfonylphenyl group, a 4-(1-azetidinyl)carbonyl-2-fluorophenyl group, a 2-fluoro-4-(1-pyrrolidinyl)carbonylphenyl group, a 5-(1-azetidinyl)carbonyl-3-chloro-2-pyridyl group, a 2-methylsulfonyl-5-pyridyl group, a 5-

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(4-methyl-1-piperazinyl)carbonyl-2-pyrazinyl group, a 2-methylaminocarbonyl-5-pyridyl group, a 2-methylaminosulfonyl-5-pyridyl group or a 5-methylsulfonyl-2-pyrazinyl group, and even more preferably a 4-methylsulfonylphenyl group, a 2-methylsulfonyl-5-pyridyl group, a 5-methylsulfonyl-2-pyrazinyl group or a 5-(1-azetidinyl)carbonyl-3-chloro-2-pyridyl group.

In the present invention, R^3 is preferably a hydroxy group or a methoxy group.

In the present invention, R^4 is preferably a hydrogen atom.

The compound or pharmacologically acceptable salt thereof represented by the general formula (I) of the present invention has all isomers (such as a keto-enol isomer, a diastereomer, an optical isomer, a rotamer, etc.).

The compound or pharmacologically acceptable salt thereof represented by the general formula (I) of the present invention has various isomers because asymmetric carbon atom(s) exist in the molecule. These isomers and mixtures of these isomers of the present invention are all represented by a single formula, specifically, the general formula (I). Accordingly, the present invention includes all of these isomers and mixtures of these isomers in arbitrary ratios.

The aforementioned stereoisomers can be obtained by synthesizing the compound of the present invention using a stereospecific raw material compound or using an asymmetric synthesis or asymmetric induction technique or by isolating the synthesized compound of the present invention by a common optical resolution or separation method if desired.

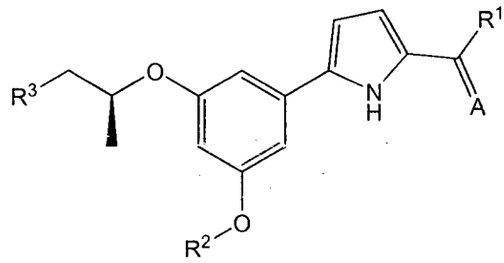
The compound or pharmacologically acceptable salt thereof represented by the general formula (Ia) of the present invention is more preferred than a compound or pharmacologically acceptable salt thereof represented by the general formula (Ib) of the present invention.

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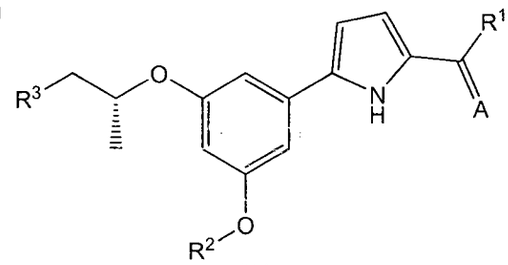
In the present invention, A is preferably a group represented by the formula =NOH or an oxygen atom, and more preferably an oxygen atom.

In the present invention, R^1 is preferably a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group or a mono-C_1-C_6 halogenated alkylamino group, and more preferably a methyl group or a 2-chloroethylamino group.

In the present invention, the heterocyclic group formed by A and R^1 together with the carbon atom bonded thereto that may be substituted with 1 to 3 group(s) independently selected from Substituent Group α is preferably a 2-pyridyl group, 5,6-dihydro-4H-1,3-oxazin-2-yl group, 1,3-thiazol-2-yl group, 1,3-oxazol-2-yl group, 1,3,4-oxadiazol-2-yl group, 1,3,4-thiadiazol-2-yl group, 4,5-dihydro-1,3-thiazol-2-yl group, 4,5-dihydro-1,3-oxazol-2-yl group or ~~4,5-dihydro-~~1,3-benzothiazol-2-yl group that may be substituted with 1 to 3 group(s) independently selected from Substituent Group γ, more preferably a 1,3-thiazol-2-yl group, a 5-methyl-1,3-thiazol-2-yl group, a 5-methyl-1,3,4-oxadiazol-2-yl group, a 4,5-dihydro-1,3-thiazol-2-yl group, a 4,5-dihydro-1,3-oxazol-2-yl group, a (5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5R)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a 5-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5R)-5-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-ethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4S)-4-[(1R)-1-hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl group, a (4S)-4-[(1S)-1-hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5S)-4,5-dimethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5S)-4-hydroxy-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5S)-4-hydroxymethyl-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5R)-5-hydroxymethyl-4-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a 5-carboxyl-1,3-thiazol-2-yl group, a 5-dimethylaminocarbonyl-1,3-thiazol-2-yl group, a 5-methyl-1,3,4-thiadiazol-2-yl group or a 5,6-dihydro-4H-1,3-oxazin-2-yl group, even more preferably a 4,5-dihydro-1,3-oxazol-2-yl group, a



(Ia)



(Ib)

A "pharmacologically acceptable salt thereof" refers to a salt that is free of prominent toxicity and which can be used as a pharmaceutical. The compound represented by the general formula (I) of the present invention can be converted to a salt by reacting with an acid in the case the compound has a basic group such as an amino group, or by reacting with a base in the case of having an acidic group such as a carboxyl group.

Examples of salts based on a basic group include salts of hydrohalic acids such as hydrofluorides, hydrochlorides, hydrobromides or hydroiodides, salts of inorganic acids such as nitrates, perchlorates, sulfates or phosphates; C_1-C_6 alkylsulfonates such as methanesulfonates, trifluoromethanesulfonates or ethanesulfonates, arylsulfonates such as benzenesulfonates or p-toluenesulfonates; salts of organic acids such as acetates, malates, fumarates, succinates, citrates, ascorbates, tartrates, oxalates or maleates; and, salts of amino acids such as salts of glycine, lysine, arginine, ornithine, glutamatic acid and aspartatic acid.

On the other hand, examples of salts based on acidic groups include metal salts such as alkali metal salts such as sodium salts, potassium salts or lithium salts, alkaline earth metal salts such as calcium salts or magnesium salts, metal salts such as aluminum salts or iron salts; amine salts such as inorganic salts such as ammonium salts, or organic salts such as salts of t-octylamine, dibenzylamine, morpholine, glucosamine, phenylglycine alkyl esters, ethylenediamine, N-methylglucamine, guanidine, diethylamine, triethylamine, dicyclohexylamine, N,N'-dibenzylethylenediamine, chloroprocaine, procaine, diethanolamine, N-benzylphenethylamine, piperazine, tetramethylammonium or tris(hydroxymethyl)aminomethane; and,

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salts of amino acids such as salts of glycine, lysine, arginine, ornithine, glutamatic acid and aspartatic acid.

The compound or pharmacologically acceptable salt thereof represented by the general formula (I) of the present invention may become a hydrate by incorporating water molecule(s) by being left in the atmosphere or by recrystallizing, and such hydrates are also included in the salts of the present invention.

The compound or pharmacologically acceptable salt thereof represented by the general formula (I) of the present invention may become a solvate by absorbing another type of solvent, and such solvates are also included in the salts of the present invention.

In the present invention, "metabolic syndrome" refers to a disease state that is based on insulin resistance for which there is considerably higher risk for coronary artery disease due to accumulation of multiple coronary vessel risk factors (including lifestyle diseases such as hyperlipemia, diabetes, obesity and hypertension) (Diabetes, Obesity and Metabolism, 9, 2007, 246-258; Journal of the American Medical Association, 285, 2486-2497 (2001); Diabet. Med., 15, 539-553 (1998)).

[Effect of the Invention]

The compound represented by the general formula (I) of the present invention, or a pharmacologically acceptable salt thereof, has superior GK activating activity, and is useful as a pharmaceutical for the prevention and/or treatment of a disease selected from the group consisting of diabetes, impaired glucose tolerance, gestational diabetes, chronic complications of diabetes (including diabetic peripheral neuropathy, diabetic nephropathy, diabetic retinopathy and diabetic macroangiopathy) and metabolic syndrome in warm-blooded animals (and preferably in mammals, including humans). In addition, the novel compound represented by the general formula (I) provided by the present invention, or a pharmacologically acceptable salt thereof, has superior GK activating activity and is useful as an active ingredient of a pharmaceutical for the prevention and/or

treatment of the aforementioned diseases in warm-blooded animals (and preferably in mammals, including humans). Preferred examples of diseases include diabetes and impaired glucose tolerance. The compound represented by the general formula (I) of the present invention, or a pharmacologically acceptable salt thereof, can preferably be used as a pharmaceutical for treatment of the aforementioned diseases.

BEST MODE FOR CARRYING OUT THE INVENTION

The compound represented by the general formula (I) of the present invention can be produced according to the Methods A to L described below.

There are no particular limitations on the solvent used in the reactions of each of the steps of the following Methods A to L provided it dissolves the starting raw material to a certain extent without impairing the reaction, and the solvent is, for example, selected from the solvent group indicated below. The solvent group is composed of hydrocarbons such as pentane, hexane, octane, petroleum ether, ligroin or cyclohexane; amides such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone, N-methyl-2-pyrrolidinone or hexamethylphosphate triamide; ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane or diethylene glycol dimethyl ether; alcohols such as methanol, ethanol, n-propanol, i-propanol, n-butanol, 2-butanol, 2-methyl-1-propanol, t-butanol, isoamyl alcohol, diethylene glycol, glycerin, octanol, cyclohexanol or methyl cellosolve; sulfoxides such as dimethyl sulfoxide; sulfones such as sulfolan; nitriles such as acetonitrile, propionitrile, butyronitrile or isobutyronitrile; esters such as ethyl formate, ethyl acetate, propyl acetate, butyl acetate or diethyl carbonate; ketones such as acetone, methyl ethyl ketone, 4-methyl-2-pentanone, methyl isobutyl ketone, isophorone or cyclohexanone; nitro compounds such as nitroethane or nitrobenzene; halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, chlorobenzene, dichlorobenzene, chloroform or carbon tetrachloride; aromatic

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hydrocarbons such as benzene, toluene or xylene; carboxylic acids such as acetic acid, formic acid, propionic acid, butyric acid or trifluoroacetic acid; amines such as N-methylmorpholine, triethylamine, tripropylamine, tributylamine, diisopropylethylamine, dicyclohexylamine, N-methylpiperidine, pyridine, 2,6-lutidine, 4-pyrrolidinopyridine, picoline, 4-dimethylaminopyridine, 2,6-di(t-butyl)-4-methylpyridine, quinoline, N,N-dimethylaniline, N,N-diethylaniline, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or piperidine; water; and, mixed solvents thereof.

Examples of bases used in the reactions of each of the steps of the following Methods A to L include inorganic bases such as alkali metal carbonates such as sodium carbonate, potassium carbonate, lithium carbonate or cesium carbonate; alkali metal hydrogencarbonates such as sodium hydrogencarbonate, potassium hydrogencarbonate or lithium hydrogencarbonate; alkali metal acetates such as sodium acetate, potassium acetate, lithium acetate or cesium acetate; alkali metal hydrides such as lithium hydride, sodium hydride or potassium hydride; alkali metal hydroxides such as sodium hydroxide, potassium hydroxide, barium hydroxide or lithium hydroxide; and, alkali metal fluorides such as sodium fluoride or potassium fluoride; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, sodium t-butoxide, potassium methoxide, potassium ethoxide, potassium t-butoxide or lithium methoxide; alkali metal trialkyl siloxides such as sodium trimethyl siloxide, potassium trimethyl siloxide or lithium trimethyl siloxide; alkali metal mercaptans such as sodium thiomethoxide or sodium thioethoxide; organic bases such as N-methylmorpholine, triethylamine, tripropylamine, tributylamine, N,N-diisopropylethylamine, dicyclohexylamine, N-methylpiperidine, pyridine, 2,6-lutidine, 4-pyrrolidinopyridine, picoline, 4-dimethylaminopyridine, 2,6-di(t-butyl)-4-methylpyridine, quinoline, N,N-dimethylaniline, N,N-diethylaniline, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,4-diazabicyclo[2.2.2]octane (DABCO) or 1,8-

diazabicyclo[5.4.0]undec-7-ene (DBU); organometallic bases such as n-butyl lithium, lithium diisopropylamide or lithium bis(trimethylsilyl)amide; and, amino acids such as proline.

Examples of condensation agents used in the reactions of each of the steps of the following Methods A to L include O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), 1-propanephosphonic acid cyclic anhydride (T3P), dicyclohexylcarbodiimide (DCCD), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (WSCI·HCl), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCl), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDAC), 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride n hydrate (DMT-MM), isobutyl chloroformate (IBCF), 1,1'-carbonylbis-1H-imidazole (CDI), diethyl cyanophosphonate (DEPC), diphenyl phosphorazidate (DPPA), N-hydroxysuccinimide, N-hydroxy-5-norbornene-2,3-dicarboxyimide and dipyridyl disulfide, and these can be used in the presence of 1-hydroxybenzotriazole (HOBt) or 1-hydroxybenzotriazole monohydrate as necessary.

Examples of demethylation agents used in the reactions of each of the steps of the following Methods A to L include sodium thiomethoxide, sodium thioethoxide, sodium thiophenoxide, iodotrimethylsilane, aluminum chloride, aluminum bromide, boron tribromide, boron triiodide, methylmagnesium iodide and hydrogen bromide.

Examples of palladium catalysts used in the reactions of each of the steps of the following Methods A to L include zero-valent palladium catalysts or divalent palladium catalysts such as tetrakis(triphenylphosphine) palladium (0), palladium-active carbon, palladium (II) acetate, palladium (II) trifluoroacetate, palladium black, palladium (II) bromide, palladium (II) chloride, palladium (II) iodide, palladium (II) cyanide, palladium (II) nitrate, palladium (II) oxide, palladium (II) sulfate, palladium (II) dichlorobis(acetonitrile), palladium (II) dichlorobis(benzonitrile), palladium (II) dichloro(1,5-cyclooctadiene), palladium (II) acetylacetone, palladium (II) sulfide, [1,1'-bis(diphenylphosphino)ferrocene] palladium (II)

dichloride, tris(dibenzylideneacetone) dipalladium (0), tetrakis(acetonitrile) palladium (II) tetrafluoroborate and aryl chloride-palladium dimers.

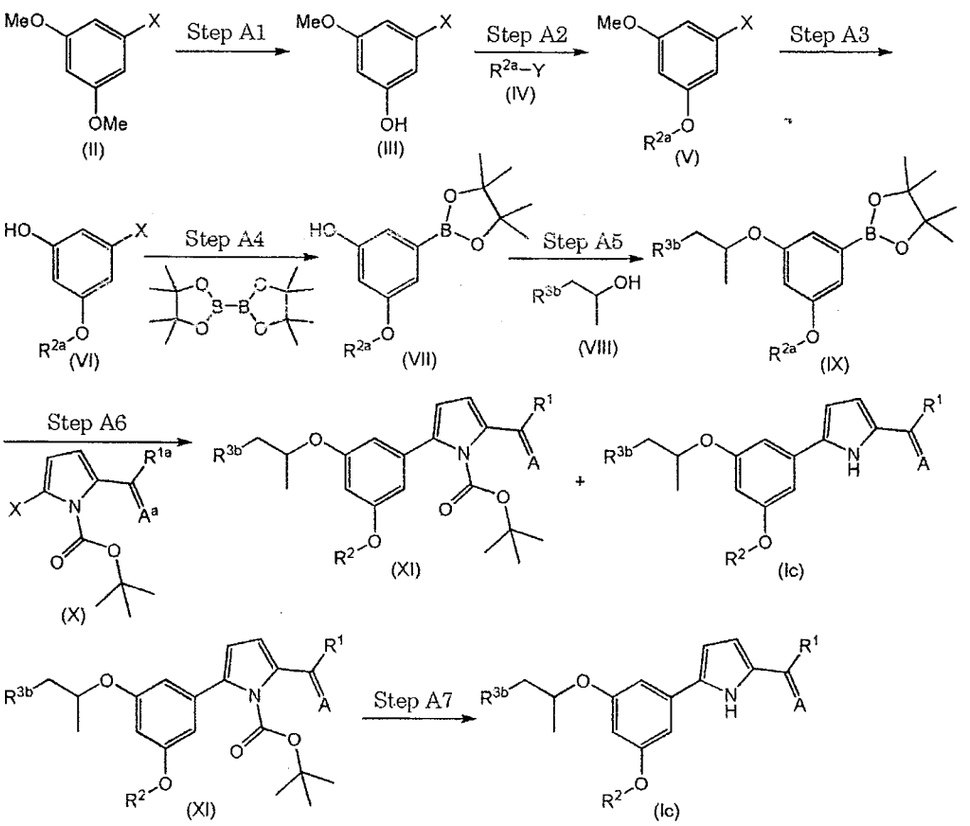
The reaction temperatures in the reactions of each of the steps of the following Methods A to L vary depending on the solvent, starting raw material, reagents and the like, while the reaction times vary depending on the solvent, starting raw material, reagents, reaction temperature and the like.

In the reactions of each of the steps of the following Methods A to L, each desired compound is collected from the reaction mixture according to conventional methods after completion of the reaction. The desired compound is obtained as follows, for example. The reaction mixture is appropriately neutralized and insoluble matter, if present, is removed by filtration. Then, water and an immiscible organic solvent such as ethyl acetate are added, and the organic layer containing the desired compound is separated. The organic layer is washed with water or the like and then dried over anhydrous magnesium sulfate, anhydrous sodium sulfate, anhydrous sodium bicarbonate or the like and filtered. Then, the solvent is evaporated. The resulting desired compound may be isolated and purified if necessary by appropriately combining usual methods, for example, methods suitably used for isolation and purification of organic compounds such as recrystallization and reprecipitation and eluting with an appropriate eluent by application of chromatography. The desired compound insoluble in a solvent may be purified by washing the resulting solid crude product with a solvent. The desired compound in each step may also be used as is for the next reaction without purification.

Method A is a method for producing a compound represented by general formula (Ic) in which R^3 is a C_1-C_6 alkoxy group among compounds represented by general formula (I).

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Method A



In the present invention, A, R^1 and R^2 are as defined above, R^{3b} represents a C_1-C_6 alkoxy group, X represents a halogen atom (preferably a chlorine atom, a bromine atom or an iodine atom, and more preferably a bromine atom), Y represents a halogen atom, a C_1-C_6 alkylsulfonyloxy group, a C_1-C_6 alkoxysulfonyloxy group or a C_6-C_{10} arylsulfonyloxy group (preferably a halogen atom, more preferably a fluorine atom or a chlorine atom, and even more preferably a fluorine atom), and A^a, R^{1a} and R^{2a} are groups in which an amino group, hydroxy group and/or carboxyl group contained as a substituent in groups A, R^1 and R^2 is an optionally protected amino group, hydroxy group and/or carboxyl group, or represent the same groups as defined for groups A, R^1 and R^2.

Step A1

This step is a step for producing a compound represented by general formula (III).

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This step is carried out by reacting a compound represented by general formula (II) with a demethylation agent in a solvent.

The compound represented by general formula (II) used in this step is either a known compound or is easily produced in accordance with a known method or method similar thereto by using a known compound for the starting raw material.

The solvent used in this step is preferably an amide and more preferably N-methyl-2-pyrrolidone.

The demethylation agent used in this step is preferably sodium thiomethoxide.

The reaction temperature in this step is normally 50 to 140°C and preferably 80 to 120°C.

The reaction time in this step is normally 0.5 to 12 hours and preferably 1 to 5 hours.

Step A2

This step is a step for producing a compound represented by general formula (V).

This step is carried out by reacting a compound represented by general formula (III) with a compound represented by general formula (IV) in a solvent and in the presence of a base.

The compound represented by general formula (IV) used in this step is either a known compound or is easily produced in accordance with a known method or method similar thereto by using a known compound for the starting raw material.

The solvent used in this step is preferably an amide, and more preferably N,N-dimethylformamide.

The base used in this step is preferably an alkali metal carbonate, and more preferably potassium carbonate.

The reaction temperature in this step is normally 50 to 140°C and preferably 80 to 120°C.

The reaction time in this step is normally 12 to 72 hours and preferably 24 to 48 hours.

Step A3

This step is a step for producing a compound represented by general formula (VI).

This step is carried out by reacting a compound represented by general formula (V) with a demethylation agent in a solvent.

The solvent used in this step is preferably a halogenated hydrocarbon, and more preferably dichloromethane.

The demethylation agent used in this step is preferably boron tribromide.

The reaction temperature in this step is normally -100 to 40°C and preferably -78 to 25°C.

The reaction time in this step is normally 1 to 72 hours and preferably 12 to 36 hours.

Step A4

This step is a step for producing a compound represented by general formula (VII).

This step is carried out by reacting a compound represented by general formula (VI) with bis(pinacolato)diborane in a solvent and in the presence of a palladium catalyst and inorganic base.

The solvent used in this step is preferably an amide, and more preferably N,N-dimethylformamide.

The palladium catalyst used in this step is preferably a divalent palladium catalyst, and more preferably [1,1'-bis(diphenylphosphino)ferrocene] palladium (II) dichloride dichloromethane complex.

The inorganic base used in this step is preferably an alkali metal acetate, and more preferably potassium acetate.

The reaction temperature in this step is normally 50 to 130°C and preferably 70 to 110°C.

The reaction time in this step is normally 1 to 24 hours and preferably 2 to 10 hours.

Step A5

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This step is a step for producing a compound represented by general formula (IX).

This step is carried out by reacting a compound represented by general formula (VII) with a compound represented by general formula (VIII) in a solvent and in the presence of triphenylphosphine and diethyl azodicarboxylate.

The compound represented by general formula (VIII) used in this step, and its optical isomers, are either known compounds or are easily produced in accordance with a known method or method similar thereto by using a known compound for the starting raw material.

The solvent used in this step is preferably an ether, and more preferably tetrahydrofuran.

The reaction temperature in this step is normally -20 to 40°C and preferably 0 to 25°C.

The reaction time in this step is normally 0.5 to 72 hours and preferably 1 to 36 hours.

Step A6

This step is a step for producing a compound represented by general formula (XI) and a compound represented by general formula (Ic).

This step is carried out by reacting a compound represented by general formula (IX) with a compound represented by general formula (X) in a solvent and in the presence of a palladium catalyst and inorganic base, followed by removing a protecting group of an amino group, a hydroxy group and/or a carboxyl group in A^a, R^{1a} and R^{2a} as desired.

The solvent used in this step is preferably an ether, an aromatic hydrocarbon, an alcohol, water or a mixed solvent thereof, more preferably dioxane, toluene, ethanol, water or a mixed solvent thereof, and even more preferably a mixed solvent of dioxane and water or a mixed solvent of toluene, ethanol and water.

The palladium catalyst used in this step is preferably a divalent palladium catalyst, and more preferably [1,1'-

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bis(diphenylphosphino)ferrocene] palladium (II) dichloride dichloromethane complex.

The inorganic base used in this step is preferably an alkaline metal carbonate, and more preferably potassium carbonate.

The reaction temperature in this step is normally 25 to 100°C and preferably 40 to 70°C.

The reaction time in this step is normally 0.5 to 12 hours and preferably 1 to 5 hours.

Step A7

This step is a step for producing a compound represented by general formula (Ic).

This step is carried out by reacting a compound represented by general formula (XI) with an acid in a solvent.

The solvent used in this step is preferably a halogenated hydrocarbon, and more preferably dichloromethane.

The acid used in this step is, for example, hydrogen halides such as hydrogen chloride gas or hydrogen bromide gas; mineral acids such as sulfuric acid, methyl sulfate, hydrobromic acid or hydrochloric acid; organic sulfonic acids such as methanesulfonic acid, p-toluenesulfonic acid, pyridinium p-toluenesulfonate (PPTS), camphorsulfonic acid or trifluoromethanesulfonic acid; carboxylic acids such as acetic acid, formic acid or trifluoroacetic acid; Lewis acids such as aluminum chloride, zinc chloride, zinc iodide, tin tetrachloride, titanium trichloride, boron trifluoride or boron tribromide; or an acidic ion exchange resin, preferably a carboxylic acid, and more preferably trifluoroacetic acid.

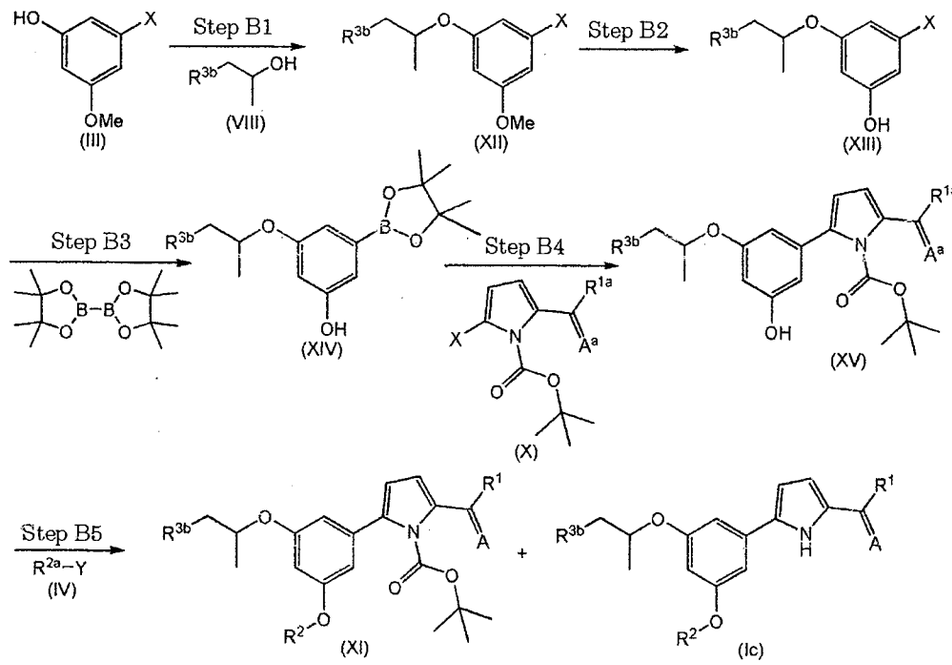
The reaction temperature in this step is normally -20 to 60°C and preferably 0 to 40°C.

The reaction time in this step is normally 0.1 to 5 hours and preferably 0.5 to 3 hours.

Method B is a method for producing a compound represented by general formula (Ic) in which R^3 is a C_1-C_6 alkoxy group among compounds represented by general formula (I).

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Method B



In the present invention, A, R^1, R^2, R^{3b}, A^a, R^{1a}, R^{2a}, X and Y are as defined above.

Step B1

This step is a step for producing a compound represented by general formula (XII).

This step is carried out by reacting a compound represented by general formula (III) obtained in above-mentioned Step A1 of Method A with a compound represented by general formula (VIII) in a solvent and in the presence of triphenylphosphine and diethyl azodicarboxylate.

The solvent used in this step is preferably an aromatic hydrocarbon, and more preferably toluene.

The reaction temperature in this step is normally -20 to 40°C and preferably 0 to 25°C.

The reaction time in this step is normally 0.1 to 72 hours and preferably 0.5 to 36 hours.

Step B2

This step is a step for producing a compound represented by general formula (XIII).

This step is carried out in the same manner as above-mentioned Step A1 of Method A by reacting a compound represented by general formula (XII) with a demethylation agent.

Step B3

This step is a step for producing a compound represented by general formula (XIV).

This step is carried out in the same manner as above-mentioned Step A4 of Method A by reacting a compound represented by general formula (XIII) with bis(pinacolato)diborane in a solvent and in the presence of a palladium catalyst and inorganic base.

Step B4

This step is a step for producing a compound represented by general formula (XV).

This is carried out in the same manner as above-mentioned Step A6 of Method A by reacting a compound represented by general formula (XIV) with a compound represented by general formula (X) in a solvent and in the presence of a palladium catalyst and inorganic base.

Step B5

This step is a step for producing a compound represented by general formula (XI) and a compound represented by general formula (Ic).

This step is carried out by reacting a compound represented by general formula (XV) with a compound represented by general formula (IV) in a solvent and in the presence of a base, followed by removing a protecting group of an amino group, hydroxy group and/or carboxyl group in A^a, R^{1a} and R^{2a} as desired.

The solvent used in this step is preferably a sulfoxide or an amide, and more preferably dimethyl sulfoxide or N,N-dimethylformamide.

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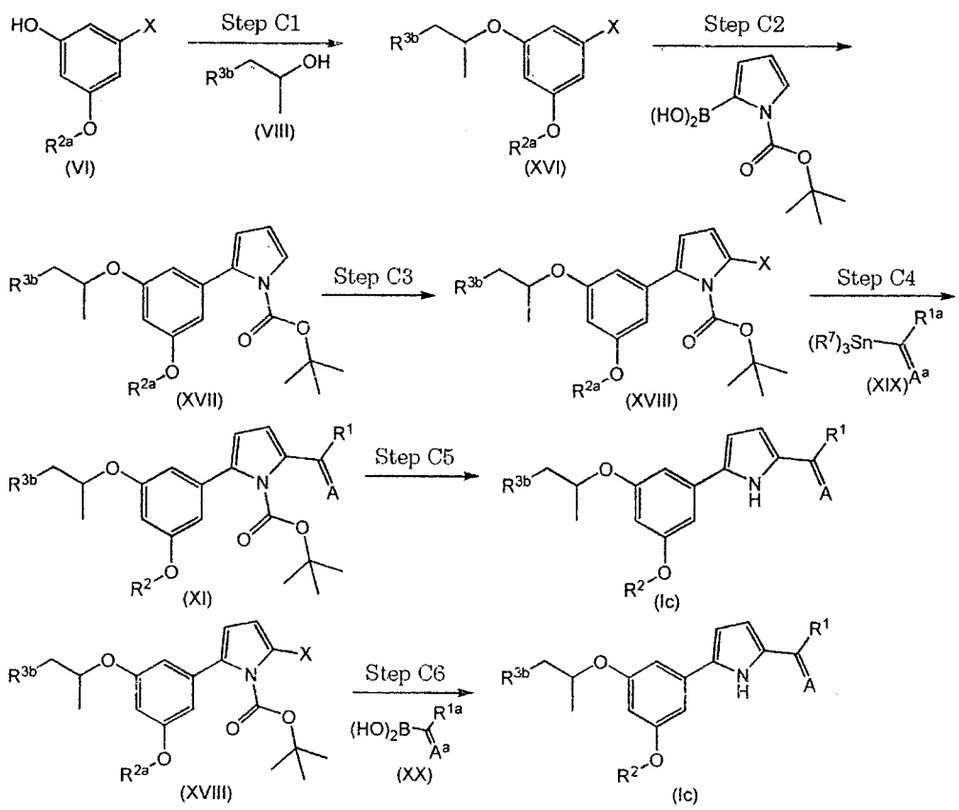
The base used in this step is preferably an alkali metal hydride or an alkali metal carbonate, and more preferably sodium hydride or potassium carbonate.

The reaction temperature in this step is normally 50 to 140°C and preferably 80 to 120°C.

The reaction time in this step is normally 1 to 72 hours and preferably 3 to 36 hours.

Method C is a method for producing a compound represented by general formula (Ic) in which R^3 is a C_1-C_6 alkoxy group among compounds represented by general formula (I).

Method C



In the present invention, A, R^1, R^2, R^{3b}, A^a, R^{1a}, R^{2a} and X are as defined above, and R^7 represents a C_1-C_6 alkyl group (and preferably an n-butyl group).

Step C1

This step is a step for producing a compound represented

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by general formula (XVI).

This step is carried out in the same manner as above-mentioned Step B1 of Method B by reacting a compound represented by general formula (VI) obtained in above-mentioned Step A3 of Method A with a compound represented by general formula (VIII) in a solvent and in the presence of triphenylphosphine and diethyl azodicarboxylate.

Step C2

This step is a step for producing a compound represented by general formula (XVII).

This step is carried out by reacting a compound represented by general formula (XVI) with 1-(t-butoxycarbonyl)pyrrole-2-boronic acid in a solvent and in the presence of a palladium catalyst, triphenylphosphine and an inorganic base.

The solvent used in this step is preferably an ether, water or a mixed solvent thereof, more preferably dimethoxyethane, water or a mixed solvent thereof, and even more preferably a mixed solvent of dimethoxyethane and water.

The palladium catalyst used in this step is preferably a divalent palladium catalyst, and more preferably palladium (II) acetate.

The base used in this step is preferably an alkali metal carbonate, and more preferably potassium carbonate.

The reaction temperature in this step is normally 40 to 100°C and preferably 60 to 90°C.

The reaction time in this step is normally 1 to 72 hours and preferably 3 to 24 hours.

Step C3

This step is a step for producing a compound represented by general formula (XVIII).

This step is carried out by reacting a compound represented by general formula (XVII) with a halogenating agent in a solvent.

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The solvent used in this step is preferably an ether or a mixed solvent of an ether and an alcohol, and more preferably tetrahydrofuran or a mixed solvent of tetrahydrofuran and methanol.

The halogenating agent used in this step is, for example, an inorganic acid such as hydrochloric acid, hydrogen bromide or hydrogen iodide; a halogen molecule such as chlorine, bromine or iodine; or a succinimide such as N-chlorosuccinimide, N-bromosuccinimide or N-iodosuccinimide, preferably a succinimide, and more preferably N-bromosuccinimide.

The reaction temperature in this step is normally -20 to 40°C and preferably 0 to 25°C.

The reaction time in this step is normally 0.5 to 24 hours and preferably 1 to 12 hours.

Step C4

This step is a step for producing a compound represented by general formula (XI).

This step is carried out by reacting a compound represented by general formula (XVIII) with a compound represented by general formula (XIX) in a solvent and in the presence of a palladium catalyst, followed by removing a protecting group of an amino group, hydroxy group and/or carboxyl group in A^a, R^{1a} and R^{2a} as desired.

The compound represented by general formula (XIX) used in this step is either a known compound or is easily produced in accordance with a known method or method similar thereto by using a known compound for the starting raw material.

The solvent used in this step is preferably an aromatic hydrocarbon, and more preferably toluene.

The palladium catalyst used in this step is preferably a zero-valent palladium catalyst, and more preferably tetrakis(triphenylphosphine) palladium (0).

The reaction temperature in this step is normally 90 to 130°C and preferably 100 to 120°C.

The reaction time in this step is normally 1 to 72 hours

and preferably 3 to 24 hours.

Step C5

This step is a step for producing a compound represented by general formula (Ic).

This step is carried out in the same manner as above-mentioned step A7 of Method A by reacting a compound represented by general formula (XI) with an acid.

Step C6

This step is a step for producing a compound represented by general formula (Ic).

This step is carried out by reacting a compound represented by general formula (XVIII) with a compound represented by general formula (XX) in a solvent and in the presence of a palladium catalyst and inorganic base, followed by removing a protecting group of an amino group, hydroxy group and/or carboxyl group in A^a, R^{1a} and R^{2a} as desired.

The compound represented by general formula (XX) used in this step is either a known compound or is easily produced in accordance with a known method or method similar thereto by using a known compound for the starting raw material.

The solvent used in this step is preferably an ether, water or a mixed solvent thereof, more preferably dimethoxyethane, water or a mixed solvent thereof, and even more preferably a mixed solvent of dimethoxyethane and water.

The palladium catalyst used in this step is preferably a divalent palladium catalyst, and more preferably [1,1'-bis(diphenylphosphino)ferrocene] palladium (II) dichloride dichloromethane complex.

The inorganic base used in this step is preferably an alkali metal carbonate, and more preferably potassium carbonate.

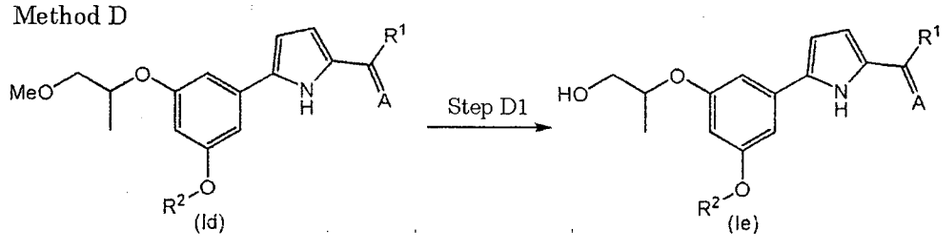
The reaction temperature in this step is normally 60 to 120°C and preferably 80 to 100°C.

The reaction time in this step is normally 1 to 480 hours and preferably 12 to 240 hours.

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Method D is a method for producing a compound represented by general formula (Ie) in which R^3 is a hydroxy group among compounds represented by general formula (I).

Method D



In the present invention, A, R^1 and R^2 are as defined above.

Step D1

This step is a step for producing a compound represented by general formula (Ie).

This step is carried out by reacting a compound represented by general formula (Id) in which R^{3b} is a methoxy group among compounds represented by general formula (Ic) obtained in above-mentioned Step A6 of Method A, above-mentioned Step A7 of Method A, above-mentioned Step B5 of Method B, above-mentioned Step C5 of Method C and above-mentioned Step C6 of Method C, with a demethylation agent in a solvent.

The solvent used in this step is preferably a halogenated hydrocarbon, and more preferably dichloromethane.

The demethylation agent used in this step is preferably iodotrimethylsilane or boron tribromide, and more preferably boron tribromide.

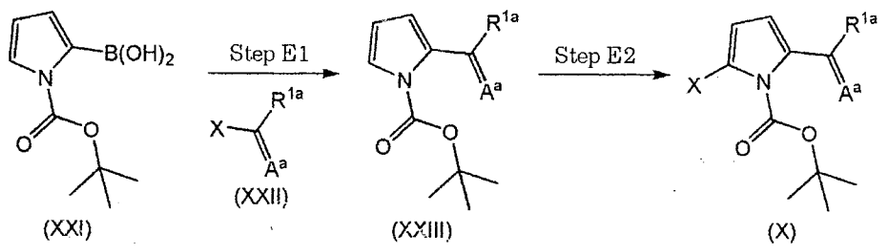
The reaction temperature in this step is normally -100 to 40°C and preferably -78 to 25°C.

The reaction time in this step is normally 0.05 to 12 hours and preferably 0.1 to 3 hours.

Method E is a method for producing a compound represented by general formula (X) used in above-mentioned Step A6 of Method A and in above-mentioned Step B4 of Step B.

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Method E



In the present invention, A^a, R^{1a} and X are as defined above.

Step E1

This step is a step for producing a compound represented by general formula (XXIII).

This step is carried out in the same manner as above-mentioned Step C2 of Method C by reacting 1-(t-butoxycarbonyl)pyrrole-2-boronic acid (XXI) with a compound represented by general formula (XXII) in a solvent and in the presence of a palladium catalyst, triphenylphosphine and an inorganic base.

The 1-(t-butoxycarbonyl)pyrrole-2-boronic acid (XXI) used in this step is easily produced in accordance with a known method or method similar thereto by using a known compound for the starting raw material.

The compound represented by general formula (XXII) used in this step is either a known compound or is easily produced in accordance with a known method or method similar thereto by using a known compound for the starting raw material.

Step E2

This step is a step for producing a compound represented by general formula (X).

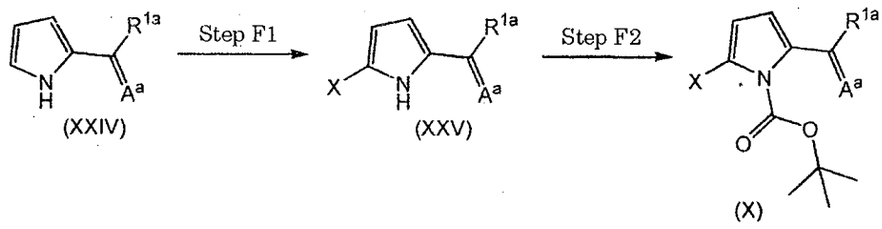
This step is carried out in the same manner as above-mentioned Step C3 of Method C by reacting a compound represented by general formula (XXIII) with a halogenating agent in a solvent.

Method F is a method for producing a compound represented by general formula (X) used in above-mentioned Step A6 of Method

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A and in Step B4 of Step B.

Method F



In the present invention, A^a, R^{1a} and X are as defined above.

Step F1

This step is a step for producing a compound represented by general formula (XXV).

This step is carried out in the same manner as above-mentioned Step C3 of Method C by reacting a compound represented by general formula (XXIV) with a halogenating agent in a solvent.

The compound represented by general formula (XXIV) used in this step is either a known compound or is easily produced in accordance with a known method or method similar thereto by using a known compound for the starting raw material.

Step F2

This step is a step for producing a compound represented by general formula (X).

This step is carried out by reacting a compound represented by general formula (XXV) with di-t-butyl dicarbonate in a solvent and in the presence of a base.

The solvent used in this step is preferably a halogenated hydrocarbon, and more preferably dichloromethane.

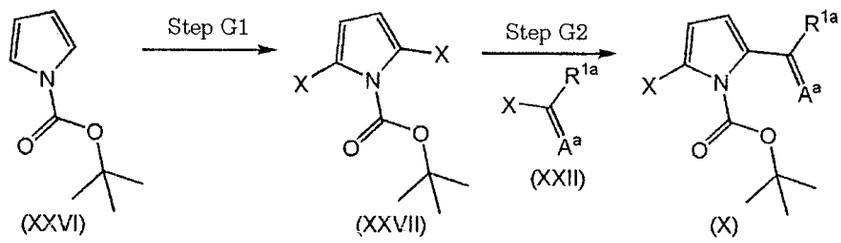
The base used in this step is preferably an organic base, more preferably triethylamine, 4-dimethylaminopyridine or a mixed base thereof, and even more preferably a mixed base of triethylamine and 4-dimethylaminopyridine.

The reaction temperature in this step is normally -20 to 40°C and preferably 0 to 25°C.

The reaction time in this step is normally 0.1 to 12 hours and preferably 0.5 to 3 hours.

Method G is a method for producing a compound represented by general formula (X) used in above-mentioned Step A6 of Method A and in above-mentioned Step B4 of Method B.

Method G



In the present invention, A^a, R^{1a} and X are as defined above.

Step G1

This step is a step for producing a compound represented by general formula (XXVII).

This step is carried out in the same manner as above-mentioned Step C3 of Method C by reacting t-butyl pyrrole-1-carbonate (XXVI) with a halogenating agent in a solvent.

The t-butyl pyrrole-1-carbonate (XXVI) used in this step is easily produced in accordance with a known method or method similar thereto by using a known compound for the starting raw material.

Step G2

This step is a step for producing a compound represented by general formula (X).

This step is carried out by reacting a compound represented by general formula (XXVII) with a compound represented by general formula (XXII) in a solvent and in the presence of a base.

The solvent used in this step is preferably an ether, and more preferably diethyl ether.

The base used in this step is preferably an organometallic base, and more preferably n-butyl lithium.

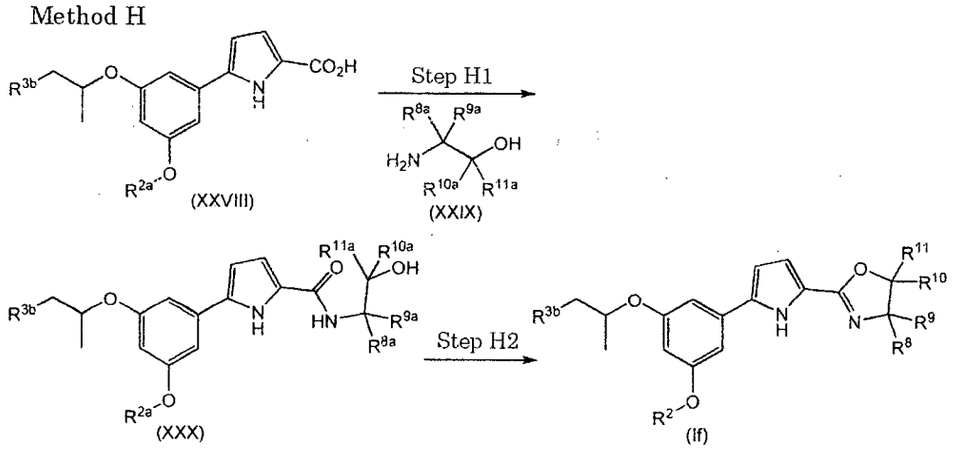
The reaction temperature in this step is normally -100 to 40°C and preferably -78 to 25°C.

The reaction time in this step is normally 0.5 to 24 hours and preferably 1 to 12 hours.

A compound represented by general formula (I) in which A and R^1 together with the carbon atom bonded thereto form a heterocyclic group that may be substituted with 1 to 3 group(s) independently selected from Substituent Group α may also be produced in accordance with a method that lastly constructs a heterocyclic ring. For example, Methods H and I indicate methods in the case the heterocyclic group is a 4,5-dihydro-1,3-oxazol-2-yl group or a 1,3,4-oxadiazol-2-yl group. Other heterocyclic groups are also easily produced according to similar methods.

Method H is a method for producing a compound represented by general formula (If), in which the heterocyclic group formed by A and R^1 together with the carbon atom bonded thereto that may be substituted with 1 to 3 group(s) independently selected from Substituent Group α is 4,5-dihydro-1,3-oxazol-2-yl group that may be substituted with 1 to 3 group(s) independently selected from Substituent Group α, and R^3 is a C_1-C_6 alkoxy group among compounds represented by general formula (I).

Method H



In the present invention, R^2, R^{3b} and R^{2a} are as defined above, R^8, R^9, R^{10} and R^{11} represent a hydrogen atom or a group belonging to Substituent Group α, and R^{8a}, R^{9a}, R^{10a} and R^{11a} are groups in which an amino group, hydroxy group and/or carboxyl group contained as a substituent in groups R^8, R^9, R^{10} and R^{11} is an optionally protected amino group, hydroxy group and/or carboxyl group, or represent the same groups as defined for groups R^8, R^9, R^{10} and R^{11}.

Step H1

This step is a step for producing a compound represented by general formula (XXX).

This step is carried out by reacting a compound represented by general formula (XXVIII) with a compound represented by general formula (XXIX) in a solvent and in the presence of a condensation agent and in the presence or absence of a base.

The compound represented by general formula (XXIX) used in this step is either a known compound or is easily produced in accordance with a known method or method similar thereto by using a known compound for the starting raw material.

The solvent used in this step is preferably an alcohol, a halogenated hydrocarbon or an amide, and more preferably methanol, dichloromethane or N,N-dimethylformamide.

The condensation agent used in this step is preferably DMT-MM, WSCI·HCl or HATU.

The base used in this step is preferably an organic base, and more preferably N-methylmorpholine, 4-dimethylaminopyridine or N,N-diisopropylethylamine.

The reaction temperature in this step is normally -20 to 60°C and preferably 0 to 30°C.

The reaction time in this step is normally 0.5 to 72 hours and preferably 1 to 24 hours.

Step H2

This step is a step for producing a compound represented

by general formula (If).

This step is carried out by reacting a compound represented by general formula (XXX) with a base and methanesulfonic acid anhydride or bis(2-methoxyethyl)aminosulfur trifluoride in a solvent, followed by removing a protecting group of an amino group, hydroxy group and/or carboxyl group in R^{2a}, R^{8a}, R^{9a}, R^{10a} and R^{11a}.

The solvent used in this step is preferably an ether, and more preferably tetrahydrofuran or dimethoxyethane.

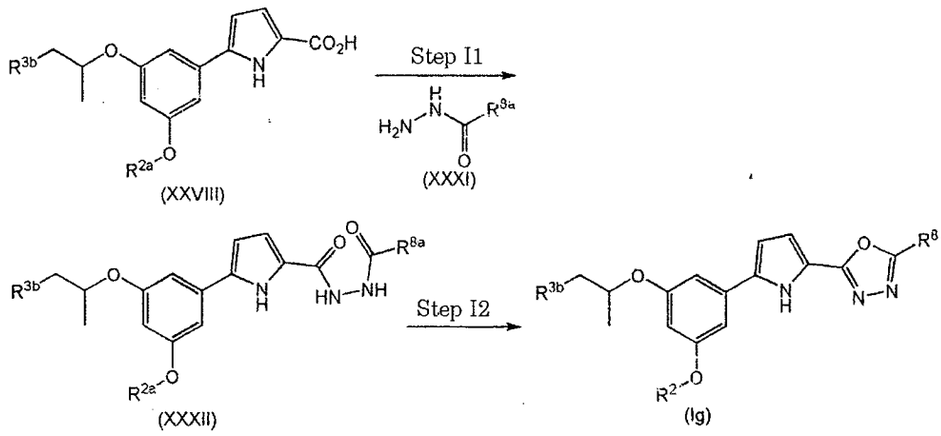
In the case of using methanesulfonic acid anhydride, the base used in this step is preferably an organic base, and more preferably triethylamine. In the case of using bis(2-methoxyethyl)aminosulfur trifluoride, the base is preferably an alkali metal carbonate, and more preferably potassium carbonate.

The reaction temperature in this step is normally -100 to 85°C, and in the case of using methanesulfonic acid anhydride, is preferably 10 to 60°C. In the case of using bis(2-methoxyethyl)aminosulfur trifluoride, the reaction temperature is preferably -78 to 30°C.

The reaction time in this step is normally 0.5 to 72 hours and preferably 1 to 24 hours.

Method I is a method for producing a compound represented by general formula (Ig), in which the heterocyclic group formed by A and R^1 together with the carbon atom bonded thereto that may be substituted with 1 to 3 group(s) independently selected from Substituent Group α is a 1,3,4-oxadiazol-2-yl group that may be substituted with 1 group selected from Substituent Group α, and R^3 is a C_1-C_6 alkoxy group among compounds represented by general formula (I).

Method I



In the present invention, R^2, R^{3b}, R^8, R^{2a} and R^{8a} are as defined above.

Step I1

This step is a step for producing a compound represented by general formula (XXXII).

This step is carried out in the same manner as above-mentioned Step H1 of Method H by reacting a compound represented by general formula (XXVIII) with a compound represented by general formula (XXXI) in a solvent, in the presence of a condensation agent and in the presence or absence of a base.

The compound represented by general formula (XXXI) used in this step is either a known compound or is easily produced in accordance with a known method or method similar thereto by using a known compound for the starting raw material.

Step I2

This step is a step for producing a compound represented by general formula (Ig).

This step is carried out by reacting a compound represented by general formula (XXXII) with p-toluenesulfonyl chloride and base in a solvent, followed by removing a protecting group of an amino group, hydroxy group and/or carboxyl group in R^{2a} and R^{8a} as desired.

The solvent used in this step is preferably a halogenated

hydrocarbon, and more preferably dichloromethane.

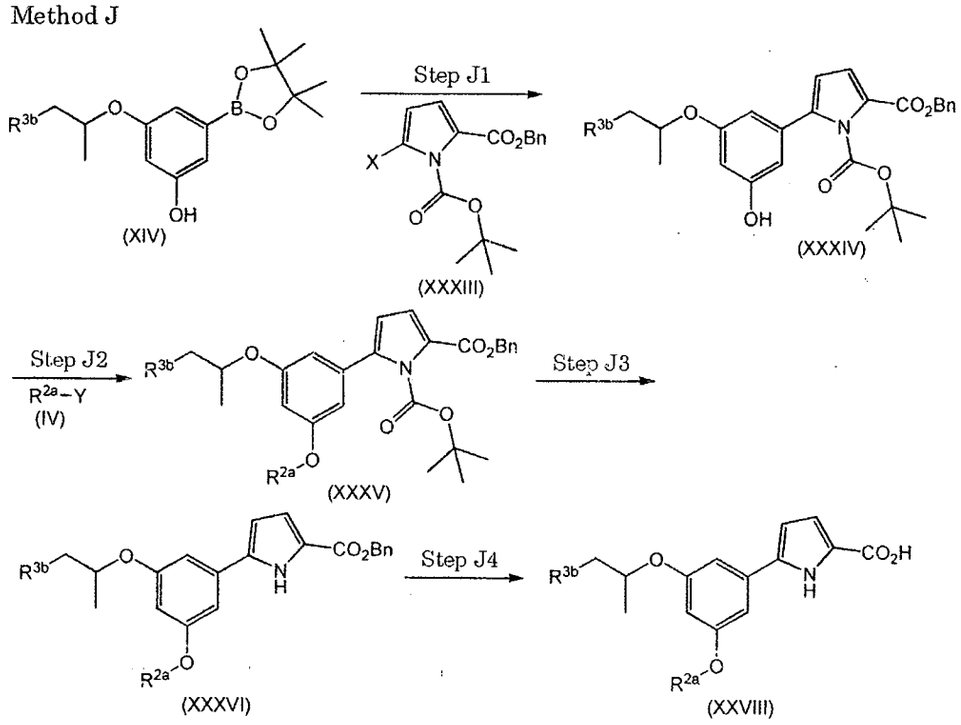
The base used in this step is preferably an organic base, and more preferably triethylamine.

The reaction temperature in this step is normally -20 to 40°C and preferably 0 to 30°C.

The reaction time in this step is normally 0.5 to 24 hours and preferably 1 to 12 hours.

Method J is a method for producing a compound represented by general formula (XXVIII) used in above-mentioned Step H1 of Method H, above-mentioned Step I1 of Method I and above-mentioned Step L1 of Method L.

Method J



In the present invention, R^{2a}, R^{3b}, X and Y are as defined above.

Step J1

This step is a step for producing a compound represented by general formula (XXXIV).

This step is carried out in the same manner as above-mentioned Step A6 of Method A by reacting a compound represented

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by general formula (XIV) obtained in above-mentioned Step B3 of Method B with a compound represented by general formula (XXXIII) in a solvent and in the presence of a palladium catalyst and inorganic base.

Step J2

This step is a step for producing a compound represented by general formula (XXXV).

This step is carried out by reacting a compound represented by general formula (XXXIV) with a compound represented by general formula (IV) in a solvent and in the presence of a base.

The solvent used in this step is preferably an amide or a nitrile, and more preferably N,N-dimethylformamide or acetonitrile.

The base used in this step is preferably an alkali metal carbonate, and more preferably potassium carbonate.

The reaction temperature in this step is normally 50 to 140°C and preferably 60 to 100°C.

The reaction time in this step is normally 1 to 72 hours and preferably 2 to 24 hours.

Step J3

This step is a step for producing a compound represented by general formula (XXXVI).

This step is carried out in the same manner as above-mentioned Step A7 of Method A by reacting a compound represented by general formula (XXXV) with an acid.

Step J4

This step is a step for producing a compound represented by general formula (XXVIII).

This step is carried out by reacting a compound represented by general formula (XXXVI) in a solvent and under hydrogen atmosphere in the presence of a palladium catalyst.

The solvent used in this step is preferably an ether, an

alcohol or an ester, and more preferably tetrahydrofuran, methanol, ethanol or ethyl acetate.

The palladium catalyst used in this step is preferably a zero-valent palladium catalyst, and more preferably palladium-active carbon.

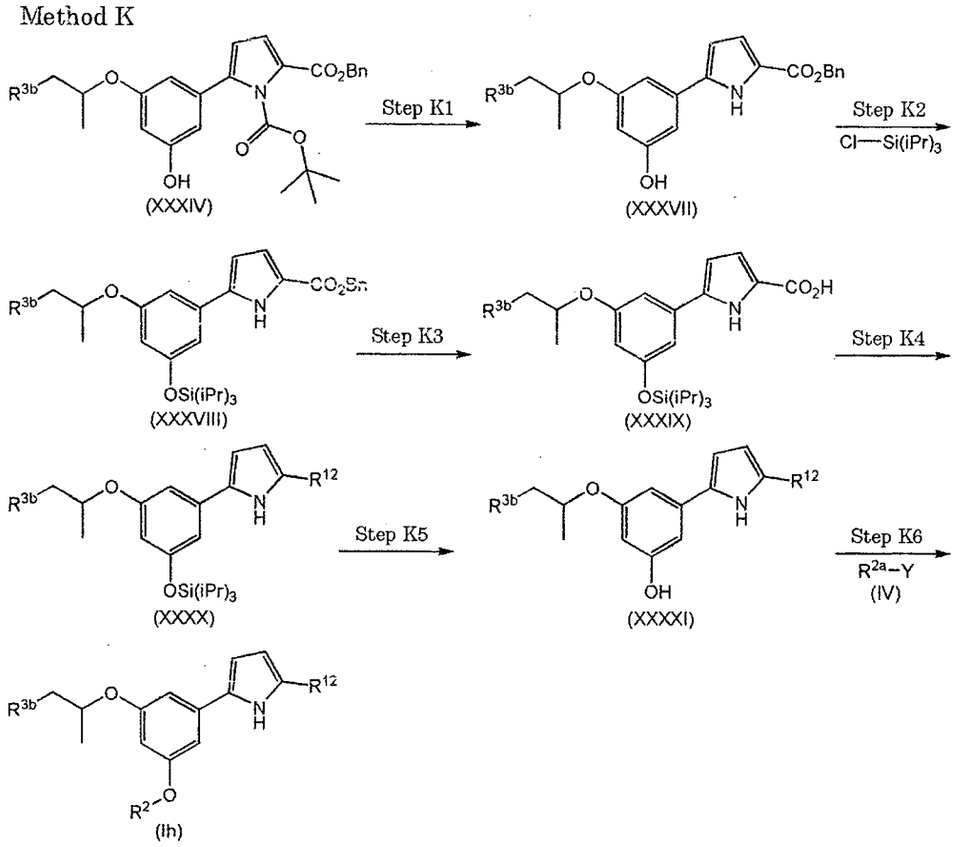
The reaction temperature in this step is normally -10 to 40°C and preferably 0 to 30°C.

The reaction time in this step is normally 0.1 to 72 hours and preferably 0.5 to 24 hours.

Method K is a method for producing a compound represented by general formula (Ih), in which the heterocyclic group formed by A and R^1 together with the carbon atom bonded thereto that may be substituted with 1 to 3 group(s) independently selected from Substituent Group α is a 4,5-dihydro-1,3-oxazol-2-yl group that may be substituted with 1 to 3 group(s) independently selected from Substituent Group α or a 1,3,4-oxadiazol-2-yl group that may be substituted with 1 group selected from Substituent Group α, and R^3 is a C_1-C_6 alkoxy group among compounds represented by general formula (I).

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Method K



In the present invention, R^2, R^{3b}, Y and R^{2a} are as defined above, and R^{12} represents a 4,5-dihydro-1,3-oxazol-2-yl group that may be substituted with 1 to 3 group(s) independently selected from Substituent Group α or a 1,3,4-oxadiazol-2-yl group that may be substituted with 1 group selected from Substituent Group α.

Step K1

This step is a step for producing a compound represented by general formula (XXXVII).

This step is carried out in the same manner as above-mentioned Step A7 of Method A by reacting a compound represented by general formula (XXXIV) obtained in above-mentioned Step J1 of Method J with an acid in a solvent.

Step K2

This step is a step for producing a compound represented

by general formula (XXXVIII).

This step is carried out by reacting a compound represented by general formula (XXXVII) with triisopropylsilyl chloride in a solvent and in the presence of a base.

The solvent used in this step is preferably a halogenated hydrocarbon, and more preferably dichloromethane.

The base used in this step is preferably an organic base, and more preferably triethylamine or a mixed base of triethylamine and 4-dimethylaminopyridine.

The reaction temperature in this step is normally -10 to 40°C and preferably 0 to 30°C.

The reaction time in this step is normally 0.1 to 72 hours and preferably 0.5 to 24 hours.

Step K3

This step is a step for producing a compound represented by general formula (XXXIX).

This step is carried out in the same manner as Step J4 of Method J by reacting a compound represented by general formula (XXXVIII) in a solvent and under hydrogen atmosphere in the presence of a palladium catalyst.

Step K4

This step is a step for producing a compound represented by general formula (XXXX).

This step is carried out in compliance with Method H (Step H1 and Step H2) or Method I (Step I1 and Step I2).

Step K5

This step is a step for producing a compound represented by general formula (XXXXI).

This step is carried out by reacting a compound represented by general formula (XXXX) with tetrabutylammonium fluoride in a solvent.

The solvent used in this step is preferably an ether, and more preferably tetrahydrofuran.

The reaction temperature in this step is normally -10 to 40°C and preferably 0 to 30°C.

The reaction time in this step is normally 0.1 to 12 hours and preferably 0.5 to 3 hours.

Step K6

This step is a step for producing a compound represented by general formula (Ih).

This step is carried out by reacting a compound represented by general formula (XXXXI) with a compound represented by general formula (IV) in a solvent and in the presence of a base, followed by removing a protecting group of an amino group, hydroxy group and/or carboxyl group in R^{2a} as desired.

The solvent used in this step is preferably an amide or a nitrile, and more preferably N,N-dimethylformamide or acetonitrile.

The base used in this step is preferably an alkali metal carbonate, and more preferably potassium carbonate or cesium carbonate.

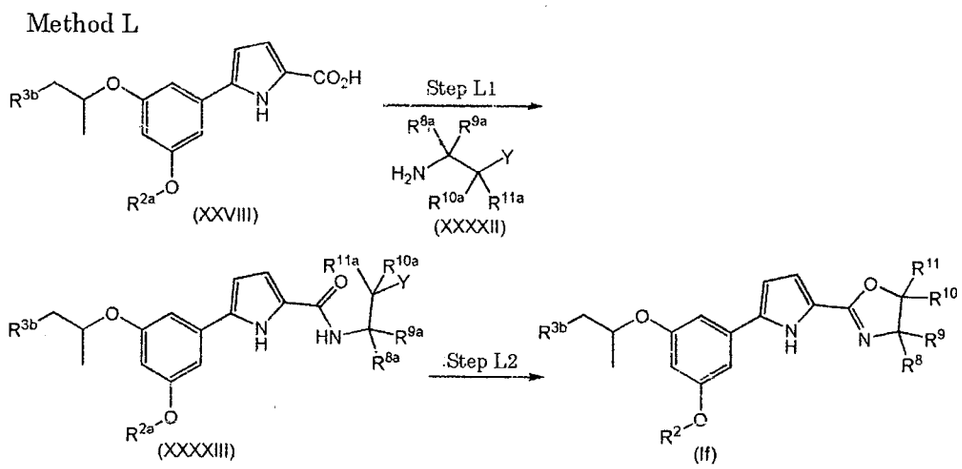
The reaction temperature in this step is normally 10 to 140°C and preferably 20 to 120°C.

The reaction time in this step is normally 1 to 72 hours and preferably 2 to 24 hours.

Method L is a method for producing a compound represented by general formula (If), in which the heterocyclic group formed by A and R^1 together with the carbon atom bonded thereto that may be substituted with 1 to 3 group(s) independently selected from Substituent Group α is a 4,5-dihydro-1,3-oxazol-2-yl group that may be substituted with 1 to 3 group(s) independently selected from Substituent Group α, and R^3 is a C_1-C_6 alkoxy group among compounds represented by general formula (I).

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Method L



(XXVIII) (XXXXII) (XXXXIII) (If)

In the present invention, R^2, R^8, R^9, R^{10}, R^{11}, R^{2a}, R^{3b}, R^{8a}, R^{9a}, R^{10a}, R^{11a} and Y are as defined above.

Step L1

This step is a step for producing a compound represented by general formula (XXXXIII).

This step is carried out in the same manner as above-mentioned Step H1 of Method H by reacting a compound represented by general formula (XXVIII) with a compound represented by general formula (XXXXII) in a solvent and in the presence of a condensation agent and base.

The compound represented by general formula (XXXXII) used in this step is either a known compound or is easily produced in accordance with a known method or method similar thereto by using a known compound for the starting raw material.

Step L2

This step is a step for producing a compound represented by general formula (If).

This step is carried out by reacting a compound represented by general formula (XXXXIII) with a base in a solvent, followed by removing a protecting group of an amino group, hydroxy group and/or carboxyl group in R^{2a}, R^{8a}, R^{9a}, R^{10a} and R^{11a} as desired.

The solvent used in this step is preferably an ether, and more preferably tetrahydrofuran.

The base used in this step is preferably an alkali metal hydride, and more preferably sodium hydride.

The reaction temperature in this step is normally -20 to 40°C and preferably 0 to 25°C.

The reaction time in this step is normally 0.5 to 48 hours and preferably 1 to 24 hours.

In the above descriptions, a protecting group of an "optionally protected amino group", "optionally protected hydroxy group" and "optionally protected carboxyl group" in the definitions of A^a, R^{1a}, R^{2a}, R^{8a}, R^{9a}, R^{10a} and R^{11a} refers to a protecting group able to be cleaved by a chemical method such as hydrogenolysis, hydrolysis, electrolysis or photolysis that is commonly used in organic synthetic chemistry (refer to, for example, T.W. Greene, et al., Protective Groups in Organic Synthesis, 3rd Edition, John Wiley & Sons, Inc. (1999)).

In the above descriptions, there are no particular limitations on the "protecting group" of an "optionally protected hydroxy group" in the definitions of A^a, R^{1a}, R^{2a}, R^{8a}, R^{9a}, R^{10a} and R^{11a} provided it is a hydroxy group protecting group used in the field of organic synthetic chemistry, and examples include "alkylcarbonyl groups" such as a formyl group, the above-mentioned "C_2-C_7 alkylcarbonyl group", halogenated alkylcarbonyl groups such as chloroacetyl, dichloroacetyl, trichloroacetyl and trifluoroacetyl, alkoxyalkylcarbonyl groups such as methoxyacetyl, and unsaturated alkylcarbonyl groups such as acryloyl, propioloyl, methacryloyl, crotonoyl, isocrotonoyl and (E)-2-methyl-2-butenoyl; "arylcarbonyl groups" such as an arylcarbonyl groups such as benzoyl, α-naphthoyl and β-naphthoyl, halogenated arylcarbonyl groups such as 2-bromobenzoyl and 4-chlorobenzoyl, C_1-C_6 alkylated arylcarbonyl groups such as 2,4,6-trimethylbenzoyl and 4-toluoyl, C_1-C_6 alkoxylated arylcarbonyl groups such as 4-anisoyl, nitroarylcarbonyl groups such as 4-nitrobenzoyl and 2-nitrobenzoyl, C_2-C_7 alkoxycarbonylated arylcarbonyl groups such as 2-(methoxycarbonyl)benzoyl, and arylated arylcarbonyl groups such as 4-phenylbenzoyl; "alkoxycarbonyl groups" such as the above-mentioned "C_2-C_7

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alkoxycarbonyl group", and C_2-C_7 alkoxycarbonyl groups substituted with a halogen or tri(C_1-C_5 alkyl)silyl such as 2,2,2-trichloroethoxycarbonyl and 2-trimethylsilylethoxycarbonyl group; "tetrahydropyranyl or tetrahydrothiopyranyl groups" such as tetrahydropyran-2-yl, 3-bromotetrahydropyran-2-yl, 4-methoxytetrahydropyran-4-yl, tetrahydrothiopyran-2-yl and 4-methoxytetrahydrothiopyran-4-yl; "tetrahydrofuranyl or tetrahydrothiofuranyl groups" such as tetrahydrofuran-2-yl and tetrahydrothiofuran-2-yl; "silyl groups" such as tri(C_1-C_6 alkyl)silyl groups such as trimethylsilyl, triethylsilyl, isopropyldimethylsilyl, t-butyldimethylsilyl, methyldiisopropylsilyl, methyl-di-t-butylsilyl and triisopropylsilyl, and (C_1-C_6 alkyl)diarylsilyl and di-(C_1-C_6 alkyl)arylsilyl groups such as diphenylmethylsilyl, diphenylbutylsilyl, diphenylisopropylsilyl and phenyldiisopropylsilyl; "alkoxymethyl groups" such as a (C_1-C_6 alkoxy)methyl groups such as methoxymethyl, 1,1-dimethyl-1-methoxymethyl, ethoxymethyl, propoxymethyl, isopropoxymethyl, butoxymethyl and t-butoxymethyl, (C_1-C_6 alkoxy)-(C_1-C_6 alkoxy)methyl groups such as 2-methoxyethoxymethyl, and (C_1-C_6 halogenated alkoxy)methyl groups such as 2,2,2-trichloroethoxymethyl and bis(2-chloroethoxy)methyl; "substituted ethyl groups" such as a (C_1-C_6 alkoxy)ethyl groups such as 1-ethoxyethyl and 1-(isopropoxy)ethyl, and halogenated ethyl groups such as 2,2,2-trichloroethyl; "aralkyl groups" such as a C_1-C_6 alkyl groups substituted with 1 to 3 aryl group(s) such as benzyl, α-naphthylmethyl, β-naphthylmethyl, diphenylmethyl, triphenylmethyl, α-naphthyldiphenylmethyl and 9-anthrylmethyl, and a C_1-C_6 alkyl groups substituted with 1 to 3 aryl group(s) in which an aryl ring is substituted with a C_1-C_6 alkyl, C_1-C_6 alkoxy, nitro, halogen or cyano group such as 4-methylbenzyl, 2,4,6-trimethylbenzyl, 3,4,5-trimethylbenzyl, 4-methoxybenzyl, 4-methoxyphenyldiphenylmethyl, 2-nitrobenzyl, 4-nitrobenzyl, 4-chlorobenzyl, 4-bromobenzyl and 4-cyanobenzyl; "alkenyloxycarbonyl groups" such as a vinyloxycarbonyl and allyloxycarbonyl; and, "aralkyloxycarbonyl groups" in which an

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aryl ring is optionally substituted with 1 or 2 C_1-C_6 alkoxy or nitro group(s) such as a benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl, and preferably alkylcarbonyl groups, silyl groups or aralkyl groups.

In the above descriptions, there are no particular limitations on the "protecting group" of an "optionally protected carboxyl group" in the definitions of A^a, R^{1a}, R^{2a}, R^{8a}, R^{9a}, R^{10a} and R^{11a} provided it is a carboxyl group protecting group used in the field of organic synthetic chemistry, and examples include the above-mentioned "C_1-C_6 alkyl group"; the above-mentioned "C_2-C_6 alkenyl group"; the above-mentioned "C_2-C_6 alkynyl group"; the above-mentioned "C_1-C_6 halogenated alkyl group"; C_1-C_6 hydroxyalkyl groups such as hydroxymethyl and 2-hydroxyethyl; (C_2-C_7 alkylcarbonyl)-(C_1-C_6 alkyl) groups such as acetylmethyl; the above-mentioned "aralkyl groups", and the above-mentioned "silyl groups", and preferably C_1-C_6 alkyl groups or aralkyl groups.

In the above descriptions, there are no particular limitations on the "protecting group" of an "optionally protected amino group" in the definitions of A^a, R^{1a}, R^{2a}, R^{8a}, R^{9a}, R^{10a} and R^{11a} provided it is an amino group protecting group used in the field of organic synthetic chemistry, and examples include groups similar to the "alkylcarbonyl groups", "arylcarbonyl groups", "alkoxycarbonyl groups", "silyl groups", "aralkyl groups", "alkenyloxycarbonyl groups" and "aralkyloxycarbonyl groups" in the previously listed "hydroxy group protecting groups", and "substituted methylene groups that form a Schiff's base" such as N,N-dimethylaminomethylene, benzylidene, 4-methoxybenzylidene, 4-nitrobenzylidene, salicylidene, 5-chlorosalicylidene, diphenylmethylene and (5-chloro-2-hydroxyphenyl)phenylmethylene, preferably alkylcarbonyl groups, arylcarbonyl groups or alkoxycarbonyl groups, and more preferably alkoxycarbonyl groups.

The steps requiring protection/deprotection are performed according to known methods (for example, the methods described

in Theodora W. Greene, Peter G. M. Wuts, "Protective Groups in Organic Synthesis," 1999, A Wiley-Interscience Publication, etc.).

The compound or pharmacologically acceptable salt thereof of the present invention can be administered in various forms. Examples of the route of administration include oral administration using tablets, capsules, granules, emulsions, pills, powders, syrups (solutions), and the like and parenteral administration using injections (intravenous, intramuscular, subcutaneous, or intraperitoneal administration), drip infusions, suppositories (rectal administration), and the like. These various formulations can be prepared as drug products according to usual methods using aids usually used in the field of drug formulation such as excipients, binders, disintegrants, lubricants, flavoring agents, dissolving aids, suspending agents, and coating agents in addition to an active ingredient.

In the use as a tablet, examples of carriers that can be used include excipients such as lactose, sucrose, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose, and silicic acid; binders such as water, ethanol, propanol, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethylcellulose, shellac, methylcellulose, potassium phosphate, and polyvinylpyrrolidone; disintegrants such as dry starch, sodium alginate, agar powder, laminaran powder, sodium hydrogencarbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulfate, stearic monoglyceride, starch, and lactose; disintegration inhibitors such as sucrose, stearin, cocoa butter, and hydrogenated oil; absorption enhancers such as quaternary ammonium salts and sodium lauryl sulfate; humectants such as glycerine and starch; adsorbents such as starch, lactose, kaolin, bentonite, and colloidal silicic acid; lubricants such as purified talc, stearate, fluoboric acid powder, and polyethylene glycol, and so forth. Furthermore, tablets coated in usual ways such as, for example, sugar-coated tablets, gelatin-coated tablets, enteric-coated tablets, film-coated tablets, double-

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layer tablets, and multilayered tablets can be prepared as required.

In the use as a pill, examples of carriers that can be used include excipients such as glucose, lactose, cocoa butter, starch, hydrogenated vegetable oil, kaolin, and talc; binders such as powdered gum arabic, powdered tragacanth, gelatin, and ethanol; disintegrants such as laminaran agar, and so forth.

In the use as a suppository, a wide range of carriers known in this field can be used, and examples thereof include polyethylene glycol, cocoa butter, higher alcohols, higher alcohol esters, gelatin, semisynthetic glycerides, and so forth.

In the use as an injection, the formulations can be prepared as solutions, emulsions, or suspensions. Preferably, these solutions, emulsions, and suspensions are sterilized and are isotonic with blood. Solutions for producing these solutions, emulsions, and suspensions are not particularly limited so long as they can be used as diluents for medical use, and examples thereof include water, ethanol, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol, polyoxy ethylene sorbitan fatty acid esters, and so forth. In this case, a sufficient amount of sodium chloride, glucose, or glycerine may be added to the formulation to prepare an isotonic solution, and usual dissolving aids, buffers, soothing agents, and the like may also be added.

Furthermore, coloring agents, preservatives, perfumes, flavoring agents, sweeteners, and the like can be added to the above-mentioned formulation, if necessary. Furthermore, other drugs can also be added.

The amount of active ingredient compound contained in the above-mentioned formulations is not particularly limited, but is usually 0.5 to 70% by weight of the total composition, preferably 1 to 30% by weight.

The dose varies depending on symptoms, age, and the like of the patient (a warm-blooded animal, in particular, a human). In the case of oral administration, the recommended adult daily dosage is from 0.1 mg as the lower limit (preferably 1 mg, more

preferably 10 mg) to 2000 mg as the upper limit (preferably 100 mg), which is divided into 1 to 6 doses depending on the symptoms.

[Examples]

Although the following provides a more detailed explanation of the present invention through examples and test examples thereof, the scope of the present invention is not limited thereby.

Elution in column chromatography indicated in the examples was carried out under observation by thin layer chromatography (TLC). During TLC observations, Silica Gel $60F_{254}$ manufactured by Merck was used for the TLC plate, the solvent used for the elution solvent in column chromatography was used for the developing solvent, and a UV detector was used for the detection method. Silica Gel SK-85 (230 to 400 mesh) manufactured by Merck or Silica Gel FL100B manufactured by Fuji Silysia Chemical was used for the column silica gel. An automated chromatography system (Purif-α2) and a disposable column (Purif-pack) manufactured by Moritex were also suitably used in addition to ordinary column chromatography. A Silica Gel $60F_{254}$ plate having a thickness of 0.5 mm and measuring 20 x 20 cm manufactured by Merck was used for purification by preparative TLC. Furthermore, the abbreviations used in the examples have the meanings indicated below:
mg: milligrams, g: grams, mL: milliliters, MHz: megahertz, HATU: O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, WSCI·HCl: 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride, HOBT·H_2O: 1-hydroxybenzotriazole monohydrate.

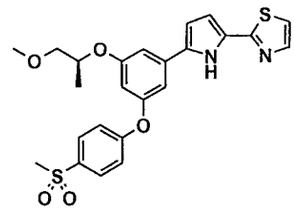
In the following examples, nuclear magnetic resonance (referred to as ^{1}H-NMR) spectra were obtained using tetramethylsilane for the standard substance, and chemical shift values are indicated with δ values (ppm). In the splitting patterns, a singlet is indicated with an "s", a doublet with a "d", a triplet with a "t", a quartet with a "q", a broad pattern

with "br", and a multiplet with an "m".

Mass spectrometry referred to as (MS) was carried out with the Fast Atom Bombardment (FAB) method, Electron Ionization (EI) method or Electron Spray Ionization (ESI) method.

(Example 1)

2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole



(1a) 3-Bromo-5-methoxyphenol

Commercially available 1-bromo-3,5-dimethoxybenzene (18.74 g, 86.3 mmol) was dissolved in 1-methyl-2-pyrrolidone (100 mL), and sodium thiomethoxide (6.74 g, 96.2 mmol) was added, followed by stirring at 100°C for 3 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, 1N hydrochloric acid (200 mL) was added, and extraction was carried out with diethyl ether (500 mL). The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=20%-25%) to afford the desired compound (15.03 g, yield 86%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.77 (3H, s), 4.82 (1H, s), 6.33 (1H, t, J=2.4 Hz), 6.61 (1H, t, J=2.0 Hz), 6.66 (1H, t, J=2.0 Hz).

(1b) 1-Bromo-3-methoxy-5-[4-(methylsulfonyl)phenoxy]benzene

3-Bromo-5-methoxyphenol (13.10 g, 64.5 mmol) synthesized in Example (1a) and commercially available 4-fluorophenylmethylsulfone (10.45 g, 60.0 mmol) were dissolved in N,N-dimethylformamide (100 mL), and potassium carbonate (25.00 g, 181 mmol) was added, followed by stirring at 100°C for 36 hours

under nitrogen atmosphere. The reaction solution was cooled to room temperature, with potassium carbonate being removed by Celite filtration, and subsequently 0.1N hydrochloric acid (500 mL) was added and extraction was carried out twice with diethyl ether (400 mL) and ethyl acetate (100 mL). The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting solid was washed with diethyl ether to afford the desired compound (18.30 g, yield 79%) as a pale brown solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.07 (3H, s), 3.80 (3H, s), 6.56 (1H, t, J=2.4 Hz), 6.81 (1H, t, J=2.0 Hz), 6.92 (1H, t, J=2.0 Hz), 7.12 (2H, d, J=9.0 Hz), 7.92 (2H, d, J=9.0 Hz).

(1c) 3-Bromo-5-[4-(methylsulfonyl)phenoxy]phenol

1-Bromo-3-methoxy-5-[4-(methylsulfonyl)phenoxy]benzene (18.29 g, 51.2 mmol) synthesized in Example (1b) was dissolved in dichloromethane (400 mL) and cooled to -78°C, and boron tribromide (1.0M dichloromethane solution, 100 mL, 100 mmol) was added using a dropping funnel over 30 minutes under nitrogen atmosphere. The mixture was stirred at -78°C for 2 hours, followed by raising the temperature naturally, and stirring at room temperature overnight. A saturated aqueous sodium hydrogencarbonate solution was added under cooling with an ice bath to neutralize the reaction solution, and extraction was carried out twice with dichloromethane (500 mL) and methanol (50 mL). The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure to afford the desired compound (16.89 g, yield 96%) as a pale yellow solid.

^{1}H-NMR (DMSO-D_6, 400 MHz): δ 3.19 (3H, s), 6.49 (1H, t, J=2.1 Hz), 6.77 (1H, t, J=2.0 Hz), 6.84 (1H, t, J=2.0 Hz), 7.23 (2H, d, J=8.6 Hz), 7.94 (2H, d, 9.0 Hz), 10.27 (1H, s).

(1d) 3-[4-(Methylsulfonyl)phenoxy]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol

3-Bromo-5-[4-(methylsulfonyl)phenoxy]phenol (10.10 g, 29.4 mmol) synthesized in Example (1c) was dissolved in N,N-dimethylformamide (100 mL), and bis(pinacolato) diboron (11.09 g, 43.7 mmol), [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloride dichloromethane complex (722 mg, 0.884 mmol) and potassium acetate (14.92 g, 152 mmol) were added, followed by stirring at 90°C for 5 hours under nitrogen atmosphere. After the reaction solution was cooled to room temperature, it was diluted with ethyl acetate (400 mL), and the insolubles were removed by Celite filtration. Water (400 mL) was added to the filtrate to separate it, and the organic layer was washed with saturated brine, followed by drying over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=30%-50%) to afford the desired compound (11.88 g, yield ~100%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (12H, s), 3.06 (3H, s), 5.16 (1H, s), 6.69 (1H, t, J=2.4 Hz), 7.06-7.12 (4H, m), 7.87 (2H, t, J=9.0 Hz).

(1e) 2-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

3-[4-(Methylsulfonyl)phenoxy]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (13.20 g, 33.8 mmol) synthesized in Example (1d) was dissolved in tetrahydrofuran (300 mL), and (R)-(-)-1-methoxy-2-propanol (3.70 mL, 37.8 mmol) and triphenylphosphine (9.78 g, 37.3 mmol) were added, and subsequently cooled to 0°C. Diethyl azodicarboxylate (40% toluene solution, 16.2 mL, 37.2 mmol) was added dropwise over 10 minutes under nitrogen atmosphere and stirring was carried out at 0°C for 30 minutes, followed by raising the temperature naturally and stirring at room temperature overnight. Water (300 mL) and ethyl acetate (300 mL) were added, and the solution was separated. The organic layer was washed with saturated

brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=20%-40%) to afford the desired compound (11.94 g, yield 76%) as a colorless oil.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J=6.7 Hz), 1.33 (12H, s), 3.05 (3H, s), 3.40 (3H, s), 3.48 (1H, dd, J=4.3, 10.2 Hz), 3.57 (1H, dd, J=5.9, 10.2 Hz), 4.58-4.62 (1H, m), 6.76 (1H, t, J=2.4 Hz), 7.05-7.09 (3H, m), 7.24 (1H, d, J=2.4 Hz), 7.87 (2H, d, J=9.0 Hz).

(1f) t-Butyl 2-(1,3-thiazol-2-yl)-1H-pyrrole-1-carboxylate

Commercially available 1-(t-butoxycarbonyl)pyrrole-2-boronic acid (10.06 g, 47.7 mmol) was dissolved in a mixed solvent of 1,2-dimethoxyethane (150 mL) and water (25 mL), and 2-bromothiazole (4.40 mL, 48.8 mmol), palladium (II) acetate (535 mg, 2.38 mmol), triphenylphosphine (2.50 g, 9.53 mmol) and potassium carbonate (19.50 g, 141 mmol) were added, followed by stirring at 90°C for 16 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, water (300 mL) and ethyl acetate (400 mL) were added, and the solution was separated. The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-20%) to afford the desired compound (6.71 g, yield 56%) as a pale yellow oil.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.42 (9H, s), 6.26 (1H, t, J=3.4 Hz), 6.58 (1H, dd, J=1.6, 3.5 Hz), 7.37 (1H, d, J=3.1 Hz), 7.41 (1H, dd, J=1.6, 3.1 Hz), 7.85 (1H, d, J=3.1 Hz).

(1g) t-Butyl 2-bromo-5-(1,3-thiazol-2-yl)-1H-pyrrole-1-carboxylate

t-Butyl 2-(1, 3-thiazol-2-yl)-1H-pyrrole-1-carboxylate (6.70 g, 26.8 mmol) synthesized in Example (1f) was dissolved in tetrahydrofuran (100 mL) and cooled to 0°C. With stirring under

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nitrogen atmosphere, N-bromosuccinimide (4.79 g, 26.9 mmol) was divided into 5 parts to be added every 10 minutes, followed by futher stirring at 0°C for 2 hours. A saturated aqueous sodium hydrogencarbonate solution (200 mL) was added, and extraction was carried out with ethyl acetate (300 mL). The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-16%) to afford the desired compound (7.55 g, yield 86%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.47 (9H, s), 6.30 (1H, d, J=3.9 Hz), 6.52 (1H, d, J=3.9 Hz), 7.29 (1H, d, J=3.1 Hz), 7.79 (1H, d, J=3.1 Hz).

(1h) t-Butyl 2-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-5-(1,3-thiazol-2-yl)-1H-pyrrole-1-carboxylate

2-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6.44 g, 13.9 mmol) synthesized in Example (1e) and t-butyl 2-bromo-5-(1,3-thiazol-2-yl)-1H-pyrrole-1-carboxylate (5.21 g, 15.8 mmol) synthesized in Example (1g) were dissolved in a mixed solvent of 1,4-dioxane (200 mL) and water (50 mL), and [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloride dichloromethane complex (564 mg, 0.691 mmol) and potassium carbonate (9.67 g, 70.0 mmol) were added, followed by stirring at 50°C for 3 hours under nitrogen atmosphere. After the reaction solution was cooled to room temperature, water (200 mL) was added, and extraction was carried out with ethyl acetate (400 mL). The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=30%-50%) to afford the desired compound (7.12 g, yield 88%) as a pale yellow oil.

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^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.31 (9H, s), 1.32 (3H, d, J=6.4 Hz), 3.05 (3H, s), 3.40 (3H, s), 3.49 (1H, dd, J= 3.9, 10.3 Hz), 3.58 (1H, dd, J=5.9, 10.3 Hz), 4.53-4.57 (1H, m), 6.27 (1H, d, J=3.9 Hz), 6.58 (1H, d, J=3.9 Hz), 6.65 (1H, s), 6.72 (1H, s), 6.89 (1H, s), 7.15 (2H, d, J=8.8 Hz), 7.31 (1H, d, J=3.4 Hz), 7.81 (1H, d, J=3.4 Hz), 7.89 (2H, d, J=8.8 Hz).

(1i) 2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole

t-Butyl 2-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-5-(1,3-thiazol-2-yl)-1H-pyrrole-1-carboxylate (7.16 g, 12.2 mmol) synthesized in Example (1h) was dissolved in dichloromethane (15 mL), and cooled to 0°C. Trifluoroacetic acid (30 mL) was added dropwise with stirring under nitrogen atmosphere. Stirring was carried out at room temperature for 30 minutes, followed by further stirring at 40°C for 30 minutes. The solvent was distilled off under reduced pressure followed by dilution with ethyl acetate (300 mL), a saturated aqueous sodium hydrogencarbonate solution (200 mL) was added, and the solution was separated. The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=30%-50%) to afford the desired compound (5.21 g, yield 88%) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J=6.3 Hz), 3.07 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J= 3.9, 10.2 Hz), 3.59 (1H, dd, J=5.9, 10.2 Hz), 4.55-4.60 (1H, m), 6.53-6.56 (2H, m), 6.73 (1H, dd, J=2.4, 3.5 Hz), 6.85 (1H, t, J=2.0 Hz), 7.02 (1H, t, J=2.0 Hz), 7.14 (2H, d, J=8.6 Hz), 7.17 (1H, d, J=3.5 Hz), 7.67 (1H, d, J=3.5 Hz), 7.91 (2H, d, J=8.6 Hz), 9.60 (1H, brs).

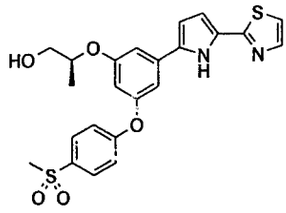
MS (ESI) m/z: 485.12291 $(M+H)^+$.

(Example 2)

(2S)-2-{3-[4-(Methylsulfonyl)phenoxy]-5-[5-(1,3-thiazol-2-yl)-

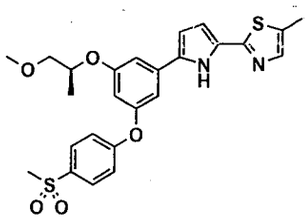
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1H-pyrrol-2-yl)phenoxy]propan-1-ol



Under nitrogen atmosphere, 2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole (88.8 mg, 0.183 mmol) synthesized in Example (1i) was dissolved in dichloromethane (5 mL), and a boron tribromide/dichloromethane solution (1.0M, 220 µL, 0.22 mmol) was added at -78°C. Subsequently, the temperature was brought back to room temperature, followed by stirring for 30 minutes. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and extraction was carried out with ethyl acetate. The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-50%) to afford the desired compound (52.2 mg, yield 61%) as a pale yellow solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.76-3.79 (2H, m), 4.56 (1H, dd, J = 10.6, 6.3 Hz), 6.52-6.55 (2H, m), 6.74 (1H, dd, J=3.7, 2.5 Hz), 6.87 (1H, t, J=1.8 Hz), 7.01 (1H, t, J=1.8 Hz), 7.14 (2H, d, J=9.0 Hz), 7.68 (1H, d, J=3.5 Hz), 7.91 (2H, dt, J=9.5, 2.3 Hz), 9.73 (1H, s).
MS (FAB) m/z: 471 $(M+H)^+$.

(Example 3)
2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-1,3-thiazole



(3a) 2-[1-(Triisopropylsilyl)-1H-pyrrol-2-yl]-1,3-thiazole

2-(1H-Pyrrol-2-yl)-1,3-thiazole (1.42 g, 9.45 mmol) known in the literature {Eur. J. Org. Chem (European Journal of Organic Chemistry) vol. 2000, no. 13, 2449-2458 (2000)} was dissolved in N,N-dimethylformamide (100 mL), and cooled to 0°C. Sodium hydride (60% oil, 570 mg, 14.3 mmol) and triisopropylsilyl chloride (4.0 mL, 18.7 mmol) were added, and stirring was carried out at room temperature for 30 minutes under nitrogen atmosphere. Water (100 mL) and diethyl ether (100 mL) were added, and the solution was separated. The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: hexane) to afford the desired compound (2.33 g, yield 80%) as a pale yellow oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.09 (18H, d, J=7.4 Hz), 1.74 (3H, m), 6.30 (1H, t, J=3.1 Hz), 6.78 (1H, dd, J=1.5, 3.1 Hz), 7.04 (1H, m), 7.13 (1H, d, J=3.1 Hz), 7.64 (1H, d, J=3.1 Hz).

(3b) 5-Methyl-2-[1-(triisopropylsilyl)-1H-pyrrol-2-yl]-1,3-thiazole

2-[1-(Triisopropylsilyl)-1H-pyrrol-2-yl]-1,3-thiazole (317 mg, 1.03 mmol) synthesized in Example (3a) was dissolved in tetrahydrofuran (10 mL), and cooled to -78°C. n-Butyl lithium (2.64M hexane solution, 0.51 mL, 1.35 mmol) was added dropwise, followed by stirring for 40 minutes, and subsequently iodomethane (0.13 mL, 2.09 mmol) was added and stirring was carried out for 3 hours with the temperature being gradually raised from -78°C to room temperature. Water (10 mL) was added, and extraction was carried out with diethyl ether (20 mL). The

organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: hexane) to afford the desired compound (215 mg, yield 65%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.09 (18H, d, J=7.8 Hz), 1.73 (3H, m), 2.44 (3H, s), 6.28 (1H, m), 6.68 (1H, m), 7.04 (1H, m), 7.01 (1H, m), 7.27 (1H, brs).

(3c) 5-Methyl-2-(1H-pyrrol-2-yl)-1,3-thiazole

5-Methyl-2-[1-(triisopropylsilyl)-1H-pyrrol-2-yl]-1,3-thiazole (215 mg, 0.67 mmol) synthesized in Example (3b) was dissolved in tetrahydrofuran (8 mL), and tetrabutylammonium fluoride (1M tetrahydrofuran solution, 0.87 mL, 0.87 mmol) was added, followed by stirring at room temperature for 30 minutes under nitrogen atmosphere. Water (10 mL) was added, and extraction was carried out with diethyl ether (20 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=5%-30%) to afford the desired compound (100 mg, yield 91%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.46 (3H, s), 6.25 (1H, m), 6.61 (1H, m), 6.87 (1H, m), 7.30 (1H, brs), 9.68 (1H, brs).

(3d) 2-(5-Bromo-1H-pyrrol-2-yl)-5-methyl-1,3-thiazole

5-Methyl-2-(1H-pyrrol-2-yl)-1,3-thiazole (100 mg, 0.61 mmol) synthesized in Example (3c) was dissolved in tetrahydrofuran (7 mL), and cooled to 0°C. N-Bromosuccinimide (108 g, 0.61 mmol) was added, and stirring was carried out at room temperature for 18 hours under nitrogen atmosphere. Water (10 mL) was added, and the solution was separated with diethyl ether (20 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate.

The solvent was distilled off under reduced pressure, and the resulting residue was used as it is in the next reaction.

(3e) t-Butyl 2-bromo-5-(5-methyl-1,3-thiazol-2-yl)-1H-pyrrole-1-carboxylate

A crude purified product of 2-(5-bromo-1H-pyrrol-2-yl)-5-methyl-1,3-thiazole synthesized in Example (3d) was dissolved in dichloromethane (8 mL), and di-t-butyl dicarbonate (165 mg, 1.35 mmol), triethylamine (0.18 mL, 1.29 mmol) and 4-dimethylaminopyridine (8.0 mg, 0.065 mmol) were added, followed by stirring at room temperature for 1.5 hours under nitrogen atmosphere. Water (10 mL) was added, and extraction was carried out with dichloromethane (10 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-20%) to afford the desired compound (172 mg, yield 84%, 2 steps) as a colorless oil.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.48 (9H, s), 2.47 (3H, s), 6.28 (1H, d, J=3.5 Hz), 6.45 (1H, d, J=3.5 Hz), 7.42 (1H, m).

(3f) 2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-1,3-thiazole

2-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (220 mg, 0.492 mmol) synthesized in Example (1e) and t-butyl 2-bromo-5-(5-methyl-1,3-thiazol-2-yl)-1H-pyrrole-1-carboxylate (598 mg, 1.49 mmol) synthesized in Example (3e) were dissolved in 1,4-dioxane (10 mL), and [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloride dichloromethane complex (20.0 mg, 0.024 mmol) and an aqueous sodium carbonate solution (3M, 0.33 mL, 0.990 mmol) were added, followed by stirring at 50°C for 20 hours under nitrogen atmosphere. After the reaction solution was cooled to room

temperature, water (10 mL) was added, and extraction was carried out with ethyl acetate (20 mL). The organic layer was washed with saturated brine, subsequently dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure.

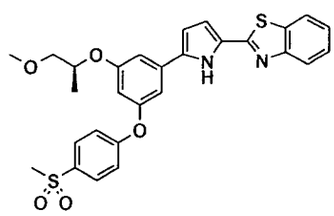
The resulting residue was dissolved in dichloromethane (10 mL), and cooled to 0°C. Trifluoroacetic acid (10 mL) was added dropwise with stirring under nitrogen atmosphere. After stirring at room temperature for 30 minutes, the solvent was distilled off under reduced pressure followed by dilution with ethyl acetate (30 mL), a saturated aqueous sodium hydrogencarbonate solution (20 mL) was added, and the solution was separated. The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=10%-40%) to afford the desired compound (49.6 mg, yield 20%) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J=6.3 Hz), 2.46 (3H, brs), 3.07 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J= 3.9, 10.2 Hz), 3.61 (1H, dd, J=5.9, 10.2 Hz), 4.56 (1H, m), 6.50-6.54 (2H, m), 6.63 (1H, dd, J=2.4, 3.9 Hz), 6.85 (1H, t, J=2.0 Hz), 7.02 (1H, t, J=2.0 Hz), 7.13 (1H, d, J=8.6 Hz), 7.29 (1H, t, J=2.0 Hz), 7.90 (2H, d, J=8.6 Hz), 9.89 (1H, brs).

MS (ESI) m/z: 521.11551 $(M+Na)^+$.

(Example 4)

2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-1,3-benzothiazole



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(4a) t-Butyl 2-(1,3-benzothiazol-2-yl)-1H-pyrrole-1-carboxylate

Commercially available 1-(t-butoxycarbonyl)pyrrole-2-boronic acid (417 mg, 1.98 mmol) was dissolved in 1,2-dimethoxyethane (20 mL), and 2-chloro-1,3-benzothiazole (0.25 mL, 2.02 mmol), palladium (II) acetate (23.0 mg, 0.102 mmol), triphenylphosphine (105 mg, 0.400 mmol) and an aqueous potassium carbonate solution (3M, 1.3 mL, 0.433 mmol) were added, followed by stirring at 100°C for 22 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, water (20 mL) and ethyl acetate (20 mL) were added, and the solution was separated. The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-20%) to afford the desired compound (490 mg, yield 82%) as a pale yellow oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.38 (9H, s), 6.30 (1H, t, J=3.1 Hz), 6.72 (1H, dd, J=2.0, 3.1 Hz), 7.39 (1H, ddd, J=1.2, 7.0, 8.0 Hz), 7.46 (1H, dd, J=2.0, 3.1 Hz), 7.49 (1H, ddd, J=1.2, 7.0, 8.0 Hz), 7.89 (1H, brd, J=8.0 Hz), 8.05 (1H, dt, J=1.2, 8.0 Hz).

(4b) t-Butyl 2-bromo-5-(1,3-benzothiazol-2-yl)-1H-pyrrole-1-carboxylate

t-Butyl 2-(1,3-benzothiazol-2-yl)-1H-pyrrole-1-carboxylate (490 mg, 1.63 mmol) synthesized in Example (4a) was dissolved in tetrahydrofuran (20 mL), and cooled to 0°C. N-Bromosuccinimide (290 mg, 1.63 mmol) was added, and stirring was carried out at room temperature for 14 hours under nitrogen atmosphere. Water (20 mL) was added, and extraction was carried out with diethyl ether (20 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-16%) to afford the desired compound (548 mg, yield 89%) as a pale yellow

solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.52 (9H, s), 6.34 (1H, d, J=3.9 Hz), 6.69 (1H, d, J=3.9 Hz), 7.37 (1H, dt, J=1.2, 8.0 Hz), 7.46 (1H, dt, J=1.2, 8.0 Hz), 7.86 (1H, brd, J=8.0 Hz), 7.93 (1H, brd, J=8.0 Hz).

(4c) 2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-1,3-benzothiazole

2-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (305 mg, 0.682 mmol) synthesized in Example (1e) and t-butyl 2-bromo-5-(1,3-benzothiazol-2-yl)-1H-pyrrole-1-carboxylate (260 mg, 0.686 mmol) synthesized in Example (4b) were dissolved in 1,2-dimethoxyethane (20 mL), and [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloride dichloromethane complex (28 mg, 0.034 mmol) and an aqueous potassium carbonate solution (3M, 0.44 mL, 1.32 mmol) were added, followed by stirring at 50°C for 17 hours under nitrogen atmosphere. After the reaction solution was cooled to room temperature, water (20 mL) was added, and extraction was carried out with ethyl acetate (20 mL). The organic layer was washed with saturated brine, subsequently dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure.

The resulting residue was dissolved in dichloromethane (10 mL), and cooled to 0°C. Trifluoroacetic acid (10 mL) was added dropwise with stirring under nitrogen atmosphere. After stirring at room temperature for 30 minutes, the solvent was distilled off under reduced pressure followed by dilution with ethyl acetate (30 mL), a saturated aqueous sodium hydrogencarbonate solution (20 mL) was added, and the solution was separated. The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column

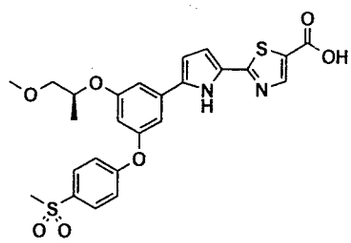
chromatography (elution solvent: ethyl acetate/hexane=10%-40%) to afford the desired compound (174 mg, yield 48%) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J=6.3 Hz), 3.07 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J= 3.9, 10.2 Hz), 3.61 (1H, dd, J=6.3, 10.2 Hz), 4.58 (1H, m), 6.57 (1H, t, J=2.0 Hz), 6.60 (1H, dd, J=2.7, 3.9 Hz), 6.88 (1H, dd, J=2.4, 3.9 Hz), 6.92 (1H, t, J=2.0 Hz), 7.08 (1H, t, J=2.0 Hz), 7.13 (2H, d, J=8.6 Hz), 7.32 (1H, dt, J=1.2, 7.4 Hz), 7.44 (1H, brt, J=7.4 Hz), 7.83 (1H, brd, J=7.4 Hz), 7.91 (2H, d, J=8.6 Hz), 10.10 (1H, brs).

MS (ESI) m/z: 535.13653 $(M+H)^+$.

(Example 5)

2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole-5-carboxylic acid



(5a) Ethyl 2-[1-(t-butoxycarbonyl)-1H-pyrrol-2-yl]-1,3-thiazole-5-carboxylate

Commercially available 1-(t-butoxycarbonyl)pyrrole-2-boronic acid (850 mg, 4.3 mmol) was dissolved in 1,2-dimethoxyethane (30 mL), and commercially available ethyl 2-bromo-1,3-thiazole-5-carboxylate (0.50 mL, 3.35 mmol), palladium (II) acetate (38.0 mg, 0.169 mmol), triphenylphosphine (176 mg, 0.671 mmol) and an aqueous potassium carbonate solution (3M, 2.20 mL, 6.60 mmol) were added, followed by stirring at 100°C for 14 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, water (30 mL) and ethyl acetate (40 mL) were added, and the solution was separated. The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off

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under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-30%) to afford the desired compound (800 mg, yield 74%) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.39 (3H, t, J=7.0 Hz), 1.50 (9H, s), 4.38 (2H, q, J=7.0 Hz), 6.28 (1H, dd, J=3.1,3.5 Hz), 6.79 (1H, dd, J=2.0, 3.5 Hz), 7.43 (1H, dd, J=2.0, 3.1 Hz), 8.39 (1H, s).

(5b) Ethyl 2-[5-bromo-1-(t-butoxycarbonyl)-1H-pyrrol-2-yl]-1,3-thiazole-5-carboxylate

Ethyl 2-[1-(t-butoxycarbonyl)-1H-pyrrol-2-yl]-1,3-thiazole-5-carboxylate (800 mg, 2.48 mmol) synthesized in Example (5a) was dissolved in tetrahydrofuran (30 mL), and cooled to 0°C. N-Bromosuccinimide (442 mg, 2.48 mmol) was added with stirring under nitrogen atmosphere, and subsequently stirring was carried out at room temperature for 19 hours. A saturated aqueous sodium hydrogencarbonate solution (30 mL) was added, and extraction was carried out with ethyl acetate (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-30%) to afford the desired compound (598 mg, yield 60%) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.39 (3H, t, J=7.0 Hz), 1.50 (9H, s), 4.38 (2H, q, J=7.0 Hz), 6.32 (1H, d, J=3.8 Hz), 6.64 (1H, d, J=3.8 Hz), 8.31 (1H, s).

(5c) Ethyl 2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole-5-carboxylate

2-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (666 mg, 1.49 mmol) synthesized in Example (1e) and ethyl 2-[5-bromo-1-(t-butoxycarbonyl)-1H-pyrrol-2-yl]-1,3-

thiazole-5-carboxylate (598 mg, 1.49 mmol) synthesized in Example (5b) were dissolved in a mixed solvent of toluene (14 mL) and ethanol (6 mL), and [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloride dichloromethane complex (61.0 mg, 0.075 mmol) and an aqueous sodium carbonate solution (2M, 1.50 mL, 3.00 mmol) were added, followed by stirring at 100°C for 19 hours under nitrogen atmosphere. After the reaction solution was cooled to room temperature, water (10 mL) was added, and extraction was carried out with ethyl acetate (20 mL). The organic layer was washed with saturated brine, subsequently dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure.

The resulting residue was dissolved in dichloromethane (10 mL), and cooled to 0°C. Trifluoroacetic acid (10 mL) was added dropwise with stirring under nitrogen atmosphere. After stirring at room temperature for 30 minutes, the solvent was distilled off under reduced pressure followed by dilution with ethyl acetate (30 mL), a saturated aqueous sodium hydrogencarbonate solution (20 mL) was added, and the solution was separated. The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=30%-50%) to afford the desired compound (505 mg, yield 61%) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J=6.3 Hz), 1.39 (3H, t, J=7.0 Hz), 3.07 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J= 4.3, 10.2 Hz), 3.61 (1H, dd, J=6.3, 10.2 Hz), 4.37 (2H, q, J=7.0 Hz), 4.59 (1H, m), 6.56 (1H, dd, J=2.7, 3.9 Hz), 6.58 (1H, t, J=2.0 Hz), 6.83 (1H, dd, J=2.7, 3.9 Hz), 6.87 (1H, t, J=2.0 Hz), 7.03 (1H, t, J=2.0 Hz), 7.14 (2H, d, J=9.0 Hz), 7.91 (2H, d, J=9.0 Hz), 8.25 (1H, s), 9.64 (1H, brs).

MS (ESI) m/z: 557.14052 $(M+H)^+$.

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(5d) 2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole-5-carboxylic acid

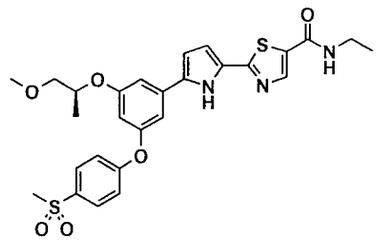
Ethyl 2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole-5-carboxylate (53.5 mg, 0.096 mmol) synthesized in Example (5c) was dissolved in ethanol (4 mL). An aqueous sodium hydroxide solution (5M, 2 mL) was added, and stirring was carried out at 70°C for 30 minutes. After cooling to room temperature, hydrochloric acid (2M, 5 mL) and ethyl acetate (10 mL) were added, and the solution was separated. The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, to afford the desired compound (52.5 mg, yield ~100%) as a pale yellow solid.

^{1}H-NMR (DMSO, 400 MHz): δ 1.25 (3H, d, J=6.3 Hz), 3.19 (3H, s), 3.30 (3H, s), 3.44-3.52 (2H, m), 4.78 (1H, m), 6.56 (1H, brt, J=2.0 Hz), 6.73 (1H, brd, J=10.2 Hz), 7.21 (2H, d, J=8.6 Hz), 7.27 (1H, brt, J=2.0 Hz), 7.41 (1H, brt, J=2.0 Hz), 7.93 (2H, d, J=8.6 Hz), 12.0 (1H, brs).

MS (ESI) m/z: 529.11053 $(M+H)^+$.

(Example 6)

N-Ethyl-2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole-5-carboxamide

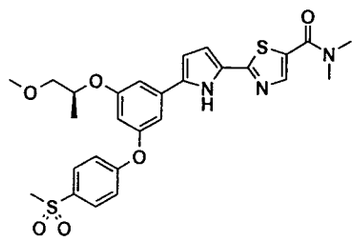


2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole-5-carboxylic acid (62.8 mg, 0.119 mmol) synthesized in Example (5d) was dissolved in N,N-dimethylformamide (5 mL), and

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ethylamine hydrochloride (23.3 mg, 0.286 mmol), HATU (63.8 mg, 0.168 mmol) and N,N-diisopropylethylamine (80 μL, 0.46 mmol) were added, followed by stirring at room temperature for 20 hours under nitrogen atmosphere. Water (20 mL) was added to the reaction solution, and extraction was carried out with ethyl acetate (20 mL). The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=50%-80%) to afford the desired compound (57.7 mg, yield 87%) as a yellow solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.27 (3H, t, J=7.4 Hz), 1.34 (3H, d, J=6.3 Hz), 3.08 (3H, s), 3.43 (3H, s), 3.47-3.53 (3H, m), 3.60 (1H, dd, J=6.3, 10.2 Hz), 4.56-4.60 (1H, m), 5.88 (1H, brs), 6.55-6.59 (2H, m), 6.80 (1H, dd, J=2.3, 3.9 Hz), 6.86 (1H, t, J=1.6 Hz), 7.02 (1H, t, J=1.8 Hz), 7.14 (2H, d, J=6.6 Hz), 7.92 (2H, d, J=6.6 Hz), 7.98 (1H, s), 9.56 (1H, brs).
MS (ESI) m/z: 556.15812 $(M+H)^+$.

(Example 7)
2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-N,N-dimethyl-1,3-thiazole-5-carboxamide

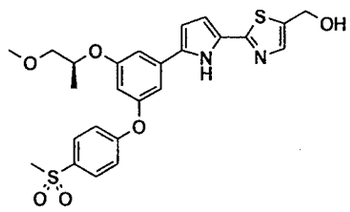


2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole-5-carboxylic acid (62.8 mg, 0.119 mmol) synthesized in Example (5d) was dissolved in N,N-dimethylformamide (5 mL), and dimethylamine hydrochloride (27.0 mg, 0.331 mmol), HATU (68.2 mg, 0.179 mmol) and N,N-diisopropylethylamine (80 μL, 0.46 mmol) were added, followed by stirring at room temperature for 20

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hours under nitrogen atmosphere. Water (20 mL) was added to the reaction solution, and extraction was carried out with ethyl acetate (20 mL). The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=60%-90%) to afford the desired compound (59.8 mg, yield 90%) as a yellow solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J=6.3 Hz), 3.07 (3H, s), 3.32 (6H, brs), 3.42 (3H, s), 3.51 (1H, dd, J=4.3, 10.2 Hz), 3.59 (1H, dd, J=6.3, 10.2 Hz), 4.55-4.60 (1H, m), 6.55-6.58 (2H, m), 6.79 (1H, dd, J=2.4, 3.9 Hz), 6.86 (1H, t, J=1.8 Hz), 7.02 (1H, t, J=1.8 Hz), 7.14 (2H, d, J=9.0 Hz), 7.89 (1H, s), 7.91 (2H, d, J=9.0 Hz), 9.52 (1H, brs).
MS (ESI) m/z: 556.15717 $(M+H)^+$.

(Example 8)
[2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazol-5-yl]methanol



Lithium aluminum hydride (22 mg, 0.580 mmol) was suspended in tetrahydrofuran (2 mL). Ethyl 2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole-5-carboxylate (106 mg, 0.190 mmol) synthesized in Example (5c) was dissolved in tetrahydrofuran (2 mL), followed by dropwise addition at 0°C under nitrogen atmosphere. After stirring at 0°C for 30 minutes, water (22 μL) and an aqueous sodium hydroxide solution (5M, 88 μL) were added dropwise sequentially and slowly. After filtration through Celite, the solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column

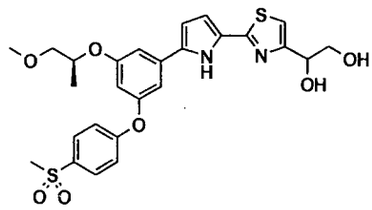
chromatography (elution solvent: ethyl acetate/hexane=50%-100%) to afford the desired compound (48 mg, yield 49%) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.30 (3H, d, J=6.3 Hz), 3.06 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J= 3.9, 10.5 Hz), 3.58 (1H, dd, J=6.3, 10.5 Hz), 4.48 (1H, m), 4.82 (2H, brs), 6.51-6.54 (2H, m), 6.70 (1H, dd, J=2.4, 3.9 Hz), 6.86 (1H, brt, J=2.0 Hz), 7.00 (1H, brt, J=2.0 Hz), 7.12 (2H, d, J=9.0 Hz), 7.47 (1H, brs), 7.89 (2H, d, J=9.0 Hz), 10.20 (1H, brs).

MS (ESI) m/z: 515.12920 $(M+H)^+$.

(Example 9)

1-[2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazol-4-yl]ethane-1,2-diol



(9a) Ethyl (2-bromo-1,3-thiazol-4-yl)(oxo)acetate

Commercially available ethyl (2-formamido-1,3-thiazol-4-yl)(oxo)acetate (5.09 g, 22.3 mmol) was dissolved in a mixed solvent of ethanol (50 mL) and 1,4-dioxane, and 30% sulfuric acid (12 mL) was added, followed by stirring at 60°C for 1 hour. The reaction solution was cooled to room temperature, water (20 mL) and ethyl acetate (20 mL) were added, and the solution was separated. The solvent was distilled off under reduced pressure, and 30% sulfuric acid (40 mL) and potassium bromide (9.3 g, 78.2 mmol) were added, followed by cooling to 0°C. Sodium nitrite (20.0 g, 290 mmol) was dissolved in water (40 mL), followed by dropwise addition over 1 hour, and stirring was further carried out at 0°C for 1 hour. The solution was separated with ethyl acetate (200 mL), the organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the

resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-20%) to afford the desired compound (3.07 g, yield 52%) as a yellow oil.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.43 (3H, t, J=7.0 Hz), 4.45 (2H, q, J=7.0 Hz) 8.55 (1H, s).

(9b) 1-(2-Bromo-1,3-thiazol-4-yl)ethane-1,2-diol

Ethyl (2-bromo-1,3-thiazol-4-yl)(oxo)acetate (3.07 g, 11.6 mmol) synthesized in Example (9a) was dissolved in methanol (100 mL), and cooled to 0°C. Sodium borohydride (1.32 g, 34.9 mmol) was added in small portions, and stirring was carried out at 0°C for 1.5 hours, followed by stirring at room temperature for further 2 hours. Dilute hydrochloric acid (1M, 100 mL) was added, and the solution was separated with ethyl acetate (200 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=20%-80%) to afford the desired compound (1.10 g, yield 42%) as a yellow oil.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.87 (1H, dd, J=5.9, 11.3 Hz), 3.97 (1H, dd, J=3.5, 11.3 Hz), 4.89 (1H, dd, J=3.5,5.3 Hz) 7.27 (1H, s).

(9c) t-Butyl 2-[4-(1,2-dihydroxyethyl)-1,3-thiazol-2-yl]-1H-pyrrole-1-carboxylate

1-(2-Bromo-1,3-thiazol-4-yl)ethane-1,2-diol (1.10 g, 4.91 mmol) synthesized in Example (9b) and commercially available 1-(t-butoxycarbonyl)pyrrole-2-boronic acid (1.55 g, 7.35 mmol) were dissolved in 1,2-dimethoxyethane (40 mL), and palladium (II) acetate (55.0 mg, 0.245 mmol), triphenylphosphine (260 mg, 0.991 mmol) and an aqueous potassium carbonate solution (3M, 4.9 mL, 14.7 mmol) were added, followed by stirring at 100°C for 14 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, water (30 mL) and ethyl acetate (40

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mL) were added, and the solution was separated. The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=50%-100%) to afford the desired compound (868 mg, yield 59%) as a brown oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.46 (9H, s), 3.95 (2H, m), 4.89 (1H, m), 6.25 (1H, t, J=3.5 Hz), 6.60 (1H, dd, J=2.0, 3.5 Hz), 7.31 (1H, brs), 7.40 (1H, dd, J=2.0, 3.5 Hz).

(9d) t-Butyl 2-bromo-5-[4-(1,2-dihydroxyethyl)-1,3-thiazol-2-yl]-1H-pyrrole-1-carboxylate

t-Butyl 2-[4-(1,2-dihydroxyethyl)-1,3-thiazol-2-yl]-1H-pyrrole-1-carboxylate (868 mg, 2.80 mmol) synthesized in Example (9c) was dissolved in tetrahydrofuran (30 mL), and cooled to 0°C. N-Bromosuccinimide (498 mg, 2.80 mmol) was added, and stirring was carried out at room temperature for 14 hours under nitrogen atmosphere. Water (20 mL) was added, and extraction was carried out with diethyl ether (20 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-30%) to afford the desired compound (527 mg, yield 48%) as a pale yellow oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.53 (9H, s), 3.92 (2H, m), 4.87 (1H, m), 6.31 (1H, d, J=3.5 Hz), 6.54 (1H, d, J=3.5 Hz), 7.23 (1H, brs).

(9e) 1-[2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazol-4-yl]ethane-1,2-diol

2-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (600 mg, 1.35 mmol) synthesized in Example (1e)

and t-butyl 2-bromo-5-[4-(1,2-dihydroxyethyl)-1,3-thiazol-2-yl]-1H-pyrrole-1-carboxylate (525 mg, 1.35 mmol) synthesized in Example (9d) were dissolved in a mixed solvent of toluene (30 mL) and ethanol (10 mL), and [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloride dichloromethane complex (55 mg, 0.067 mmol) and an aqueous potassium carbonate solution (3M, 0.90 mL, 2.70 mmol) were added, followed by stirring at 100°C for 16 hours under nitrogen atmosphere. After the reaction solution was cooled to room temperature, water (20 mL) was added, and extraction was carried out with ethyl acetate (40 mL). The organic layer was washed with saturated brine, subsequently dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure.

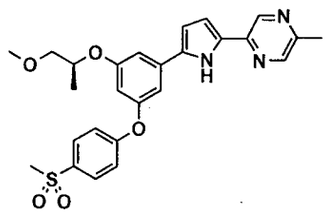
The resulting residue was dissolved in dichloromethane (10 mL), and cooled to 0°C. Trifluoroacetic acid (10 mL) was added dropwise with stirring under nitrogen atmosphere. After stirring at room temperature for 30 minutes, the solvent was distilled off under reduced pressure followed by dilution with ethyl acetate (30 mL), a saturated aqueous sodium hydrogencarbonate solution (20 mL) was added, and the solution was separated. The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=50%-100%) to afford the desired compound (331 mg, yield 45%) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J=6.3 Hz), 3.05 (3H, s), 3.40 (3H, s), 3.50 (1H, dd, J= 3.9, 10.2 Hz), 3.59 (1H, dd, J=6.3, 10.2 Hz), 3.85-3.98 (2H, m), 4.58 (1H, m), 4.90 (1H, brs), 6.48-6.54 (2H, m), 6.67 (1H, brs), 6.89 (1H, brs), 7.07 (1H, brs), 7.12 (2H, d, J=8.6 Hz), 7.88 (2H, d, J=8.6 Hz), 10.39 (1H, brs).

MS (ESI) m/z: 545.14151 $(M+H)^+$.

(Example 10)

2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5-methylpyrazine



(10a) t-Butyl 2-(5-methylpyrazin-2-yl]-1H-pyrrole-1-carboxylate

Commercially available 2-bromo-5-methylpyrazine (260 mg, 1.50 mmol) and commercially available 1-(t-butoxycarbonyl)pyrrole-2-boronic acid (380 mg, 1.80 mmol) were dissolved in 1,2-dimethoxyethane (20 mL), and palladium (II) acetate (17.0 mg, 0.076 mmol), triphenylphosphine (79.0 mg, 0.301 mmol) and an aqueous potassium carbonate solution (1.5M, 2.0 mL, 3.00 mmol) were added, followed by stirring at 100°C for 19 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, water (20 mL) and ethyl acetate (20 mL) were added, and the solution was separated. The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=5%-30%) to afford the desired compound (373 mg, yield 96%) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.41 (9H, s), 2.59 (3H, s), 6.28 (1H, m), 6.48 (1H, m), 7.41 (1H, m), 8.45 (1H, brs), 8.56 (1H, brs).

(10b) t-Butyl 2-bromo-5-(5-methylpyrazin-2-yl)-1H-pyrrole-1-carboxylate

t-Butyl 2-(5-methylpyrazin-2-yl]-1H-pyrrole-1-carboxylate (373 mg, 1.44 mmol) synthesized in Example (10a) was dissolved in tetrahydrofuran (20 mL), and cooled to 0°C. N-Bromosuccinimide (256 mg, 1.44 mmol) was added, and stirring was carried out at room temperature for 14 hours under nitrogen atmosphere. Water (20 mL) was added, and extraction was carried

out with diethyl ether (20 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-30%) to afford the desired compound (425 mg, yield 87%) as a pale yellow oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.50 (9H, s), 2.57 (3H, s), 6.33 (1H, d, J=3.5 Hz), 6.54 (1H, d, J=3.5 Hz), 8.35 (1H, brs), 8.62 (1H, brd, J=1.6 Hz).

(10c) 2-{5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5-methylpyrazine

2-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (250 mg, 0.559 mmol) synthesized in Example (1e) and t-butyl 2-bromo-5-(5-methylpyrazin-2-yl)-1H-pyrrole-1-carboxylate (200 mg, 0.591 mmol) synthesized in Example (10b) were dissolved in a mixed solvent of toluene (20 mL) and ethanol (8 mL), and [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloride dichloromethane complex (23 mg, 0.028 mmol) and an aqueous potassium carbonate solution (3M, 0.40 mL, 1.20 mmol) were added, followed by stirring at 100°C for 7 hours under nitrogen atmosphere. After the reaction solution was cooled to room temperature, water (20 mL) was added, and extraction was carried out with ethyl acetate (20 mL). The organic layer was washed with saturated brine, subsequently dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure.

The resulting residue was dissolved in dichloromethane (10 mL), and cooled to 0°C. Trifluoroacetic acid (10 mL) was added dropwise with stirring under nitrogen atmosphere. After stirring at room temperature for 30 minutes, the solvent was distilled off under reduced pressure followed by dilution with ethyl acetate (30 mL), a saturated aqueous sodium hydrogencarbonate solution (20 mL) was added, and the solution

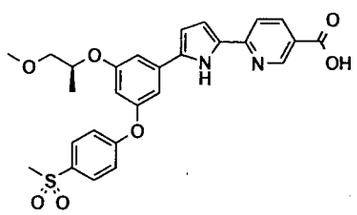
was separated. The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=10%-60%) to afford the desired compound (124 mg, yield 45%) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J=6.3 Hz), 2.55 (3H, s), 3.07 (3H, s), 3.42 (3H, s), 3.52 (1H, dd, J= 3.9, 10.2 Hz), 3.61 (1H, dd, J=5.9, 10.2 Hz), 4.58 (1H, m), 6.55 (1H, t, J=2.0 Hz), 6.59 (1H, dd, J=2.8, 3.9 Hz), 6.81 (1H, dd, J=2.4, 3.9 Hz), 6.88 (1H, t, J=2.0 Hz), 7.04 (1H, t, J=2.0 Hz), 7.14 (2H, d, J=9.0 Hz), 7.91 (2H, d, J=9.0 Hz), 8.28 (1H, brs), 8.76 (1H, d, J=1.6 Hz), 9.62 (1H, brs).

MS (ESI) m/z: 494.17511 $(M+H)^+$.

(Example 11)

6-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl) nicotinic acid



(11a) Methyl 6-[1-(t-butoxycarbonyl)-1H-pyrrol-2-yl]nicotinate

Commercially available methyl 6-bromonicotinate (650 mg, 3.01 mmol) and commercially available 1-(t-butoxycarbonyl)pyrrole-2-boronic acid (960 mg, 4.34 mmol) were dissolved in 1,2-dimethoxyethane (30 mL), and palladium (II) acetate (34.0 mg, 0.151 mmol), triphenylphosphine (158 mg, 0.602 mol) and an aqueous potassium carbonate solution (2M, 4.5 mL, 9.00 mmol) were added, followed by stirring at 100°C for 15 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, water (20 mL) and ethyl acetate (30 mL) were added, and the solution was separated. The organic layer was washed with saturated brine, and subsequently dried

over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-20%) to afford the desired compound (835 mg, yield 92%) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.39 (9H, s), 3.95 (3H, s), 6.26 (1H, t, J=3.5 Hz), 6.53 (1H, m), 7.39 (1H, m), 7.47 (1H, dd, J=0.8, 8.2 Hz), 8.27 (1H, dd, J=2.4, 8.2 Hz), 9.19 (1H, dd, J=0.8, 2.4 Hz).

(11b) Methyl 6-[5-bromo-1-(t-butytoxycarbonyl)-1H-pyrrol-2-yl]nicotinate

Methyl 6-[1-(t-butytoxycarbonyl)-1H-pyrrol-2-yl]nicotinate (835 mg, 2.76 mmol) synthesized in Example (11a) was dissolved in tetrahydrofuran (30 mL), and cooled to 0°C. N-Bromosuccinimide (492 mg, 2.76 mmol) was added, and stirring was carried out at room temperature for 19 hours under nitrogen atmosphere. Water (30 mL) was added, and extraction was carried out with diethyl ether (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-30%) to afford the desired compound (712 mg, yield 68%) as a pale yellow oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.54 (9H, s), 3.94 (3H, s), 6.30 (1H, d, J=3.5 Hz), 6.62 (1H, d, J=3.5 Hz), 7.51 (1H, brd, J=8.6 Hz), 8.23 (1H, dd, J=2.0, 8.6 Hz), 9.07 (1H, m).

(11c) Ethyl 6-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)nicotinate

2-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (398 mg, 0.890 mmol) synthesized in Example (1e) and methyl 6-[5-bromo-1-(t-butytoxycarbonyl)-1H-pyrrol-2-yl]nicotinate (403 mg, 0.493 mmol) synthesized in Example (11b)

were dissolved in a mixed solvent of toluene (20 mL) and ethanol (8 mL), and [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloride dichloromethane complex (40 mg, 0.049 mmol) and an aqueous potassium carbonate solution (3M, 0.60 mL, 1.80 mmol) were added, followed by stirring at 100°C for 20 hours under nitrogen atmosphere. After the reaction solution was cooled to room temperature, water (20 mL) was added, and extraction was carried out with ethyl acetate (20 mL). The organic layer was washed with saturated brine, subsequently dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure.

The resulting residue was dissolved in dichloromethane (10 mL), and cooled to 0°C. Trifluoroacetic acid (10 mL) was added dropwise with stirring under nitrogen atmosphere. After stirring at room temperature for 30 minutes, the solvent was distilled off under reduced pressure followed by dilution with ethyl acetate (30 mL), a saturated aqueous sodium hydrogencarbonate solution (20 mL) was added, and the solution was separated. The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=10%-60%) to afford the desired compound (173 mg, yield 35%) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J=6.3 Hz), 1.42 (3H, t, J=7.0 Hz), 3.07 (3H, s), 3.42 (3H, s), 3.52 (1H, dd, J= 3.9, 10.2 Hz), 3.61 (1H, dd, J=6.3, 10.2 Hz), 4.41 (2H, q, J=7.0 Hz), 4.58 (1H, m), 6.55 (1H, t, J=2.0 Hz), 6.60 (1H, dd, J=2.0, 3.9 Hz), 6.85 (1H, dd, J=2.0, 3.9 Hz), 7.06 (1H, t, J=2.0 Hz), 7.14 (2H, d, J=9.0 Hz), 7.57 (1H, dd, J=0.8, 8.6 Hz), 7.90 (2H, d, J=9.0 Hz), 8.21 (1H, dd, J=2.0, 8.6 Hz), 9.06 (1H, dd, J=0.8, 2.0 Hz), 9.94 (1H, brs), m).

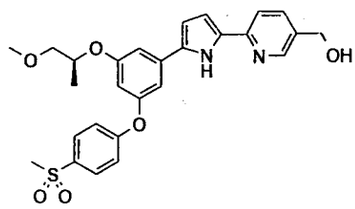
MS (ESI) m/z: 551.18403 $(M+H)^+$.

(11d) 6-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-

(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)nicotinic acid

Ethyl 6-{5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)nicotinate (42.0 mg, 0.076 mmol) synthesized in Example (11c) was dissolved in ethanol (4 mL). An aqueous sodium hydroxide solution (5M, 2 mL) was added, and stirring was carried out at 70°C for 2 hours. After cooling to room temperature, hydrochloric acid (2M, 5 mL) and ethyl acetate (10 mL) were added, and the solution was separated. The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, to afford the desired compound (39.6 mg, yield 99%) as a pale yellow solid.
^{1}H-NMR (DMSO, 400 MHz): δ 1.26 (3H, d, J=6.3 Hz), 3.20 (3H, s), 3.31 (3H, s), 3.45-3.55 (2H, m), 4.83 (1H, m), 6.58 (1H, brs), 6.80 (1H, brs), 7.01 (1H, brs), 7.22 (2H, d, J=9.0 Hz), 7.31 (1H, brs), 7.45 (1H, brs), 7.88 (1H, d, J=8.6 Hz), 7.93 (2H, d, J=9.0 Hz), 8.18 (1H, J=8.6 Hz), 9.00 (1H, s), 11.92 (1H, brs).
MS (ESI) m/z: 523.15247 $(M+H)^+$.

(Example 12)
[6-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)pyridin-3-yl]methanol



Lithium aluminum hydride (12 mg, 0.316 mmol) was suspended in tetrahydrofuran (2 mL). Ethyl 6-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)nicotinate (56.0 mg, 0.102 mmol) synthesized in Example (11c) was dissolved in tetrahydrofuran (2 mL), followed by dropwise addition at 0°C under nitrogen atmosphere. After stirring at 0°C for 30 minutes, water (12 μL) and an aqueous sodium hydroxide solution (5M, 48 μL) were added dropwise slowly and sequentially.

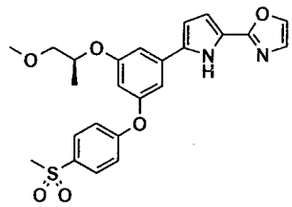
After filtration through Celite, the solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=50%-100%) to afford the desired compound (33 mg, yield 64%) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J=6.3 Hz), 3.06 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J= 3.9, 10.2 Hz), 3.60 (1H, dd, J=5.9, 10.2 Hz), 4.57 (1H, m), 4.69 (2H, brs), 6.52 (1H, brt, J=2.0 Hz), 6.57 (1H, m), 6.74 (1H, m), 6.90 (1H, brt, J=2.0 Hz), 7.06 (1H, brt, J=2.0 Hz), 7.13 (2H, d, J=8.6 Hz), 7.55 (1H, brd, J=8.2 Hz), 7.69 (1H, brd, J=8.2 Hz), 7.89 (2H, d, J=8.6 Hz), 8.41 (1H, brs), 10.00 (1H, brs).

MS (ESI) m/z: 509.17476 $(M+H)^+$.

(Example 13)

2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-1,3-oxazole



(13a) 1-Bromo-3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]benzene

3-Bromo-5-[4-(methylsulfonyl)phenoxy]phenol (4.86 g, 14.2 mmol) synthesized in Example (1c) was dissolved in toluene (100 mL), and (R)-(-)-1-methoxy-2-propanol (1.77 mL, 18.1 mmol) and triphenylphosphine (4.10 g, 15.6 mmol) were added, followed by cooling to 0°C. Under nitrogen atmosphere, diethyl azodicarboxylate (40% toluene solution, 7.75 mL, 17.1 mmol) was added dropwise over 10 minutes and stirring was carried out at 0°C for 30 minutes, followed by raising the temperature naturally and stirring at room temperature overnight. Water (100 mL) and ethyl acetate (100 mL) were added, and the solution was separated. The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate.

The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=20%-40%) to afford the desired compound (5.06 g, yield 86%) as a pale yellow oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.28 (3H, d, J=6.3 Hz), 3.05 (3H, s), 3.37 (3H, s), 3.46 (1H, dd, J= 3.9, 10.2 Hz), 3.54 (1H, dd, J=6.3, 10.2 Hz), 4.49 (1H, m), 6.56 (1H, d, J=2.0 Hz), 6.77 (1H, d, J=2.0 Hz), 6.93 (1H, d, J=2.0 Hz), 7.10 (2H, d, J=9.0 Hz), 7.89 (2H, d, J=9.0 Hz).

(13b) t-Butyl 2-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-1-carboxylate

1-Bromo-3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]benzene (2.38 g, 5.73 mmol) synthesized in Example (13a) and 1-(t-butoxycarbonyl)pyrrole-2-boronic acid (1.45 g, 6.87 mmol) were dissolved in a mixed solvent of 1,2-dimethoxyethane (50 mL) and water (6 mL), and palladium (II) acetate (40 mg, 0.178 mmol), triphenylphosphine (180 mg, 0.686 mmol) and potassium carbonate (2.38 g, 17.2 mmol) was added, followed by stirring at 90°C for 18 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, water (30 mL) and ethyl acetate (50 mL) were added, and the solution was separated. The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=20%-40%) to afford the desired compound (2.71 g, yield 94%) as a brown oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J=6.3 Hz), 1.44 (9H, s), 3.05 (3H, s), 3.41 (3H, s), 3.49 (1H, dd, J= 4.3, 10.2 Hz), 3.58 (1H, dd, J=6.3, 10.2 Hz), 4.53 (1H, m), 6.19-6.23 (2H, m), 6.61 (1H, t, J=2.4 Hz), 6.63 (1H, dd, J=1.6, 2.0 Hz), 6.79 (1H, dd, J=1.6, 2.4 Hz), 7.15 (2H, d, J=9.0 Hz), 7.31 (1H, dd, J=2.0, 3.2 Hz), 7.88 (2H, d, J=9.0 Hz).

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(13c) t-Butyl 2-bromo-5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-1-carboxylate

t-Butyl 2-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-1-carboxylate (2.70 g, 5.38 mmol) synthesized in Example (13b) was dissolved in tetrahydrofuran (50 mL), and cooled to 0°C. After addition of N-bromosuccinimide (960 mg, 5.38 mmol) with stirring under nitrogen atmosphere, stirring was carried out at room temperature for 4 hours. Water (50 mL) was added, and extraction was carried out with ethyl acetate (50 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=20%-40%) to afford the desired compound (2.93 g, yield 94%) as a brown oil.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J=6.3 Hz), 1.42 (9H, s), 3.05 (3H, s), 3.39 (3H, s), 3.48 (1H, dd, J= 4.3, 10.2 Hz), 3.57 (1H, dd, J=6.3, 10.2 Hz), 4.53 (1H, m), 6.21 (1H, d, J=3.5 Hz), 6.30 (1H, d, J=3.5 Hz), 6.57 (1H, t, J=2.4 Hz), 6.61 (1H, d, J=2.4 Hz), 6.75 (1H, d, J=2.4 Hz), 7.12 (2H, d, J=9.0 Hz), 7.89 (2H, d, J=9. Hz).

(13d) 2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-1,3-oxazole

t-Butyl 2-bromo-5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-1-carboxylate (102.9 mg, 0.177 mmol) synthesized in Example (13c) was dissolved in toluene (5 mL), and 2-(tri-n-butylstannyl)oxazole (133.7 mg, 0.373 mmol) and tetrakis(triphenylphosphine) palladium (20.5 mg, 0.0177 mmol) was added, followed by heating to reflux for 18 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, water (20 mL) was added thereto, and extraction was carried out with ethyl acetate (20 mL). The organic layer was washed with saturated brine, and subsequently

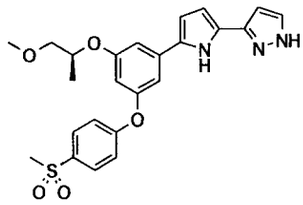
dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=35%-55%) to afford t-butyl 2-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-5-(1,3-oxazol-2-yl)-1H-pyrrole-1-carboxylate.

This was dissolved in dichloromethane (1 mL), and trifluoroacetic acid (2 mL) was added thereto, followed by stirring at room temperature for 2 hours, and subsequently the solvent was distilled off under reduced pressure. The residue was diluted with ethyl acetate (20 mL), washed with a saturated aqueous sodium hydrogencarbonate solution, followed by further washing with saturated brine and drying over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=65%) to afford the desired compound (15.6 mg, yield 19%) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ ppm 1.34 (3H, d, J=6.3 Hz), 3.07 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J=4.3, 10.2 Hz), 3.60 (1H, dd, J=6.3, 10.2 Hz), 4.56-4.60 (1H, m), 6.55-6.57 (2H, m), 6.84-6.86 (2H, m), 7.02 (1H, t, J=1.7 Hz), 7.13 (1H, s), 7.15 (2H, d, J=8.6 Hz), 7.61 (1H, s), 7.91 (2H, d, J=9.0 Hz), 9.52 (1H, brs).
MS (ESI) m/z: 469.14163 $(M+H)^+$.

(Example 14)

3-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-1H-pyrazole



t-Butyl 2-bromo-5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-1-carboxylate (375 mg, 0.446 mmol) synthesized in Example (13c) and commercially

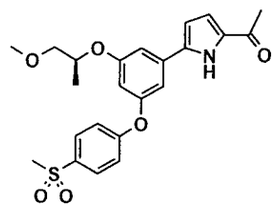
available 1H-pyrazol-3-ylboronic acid (120 mg, 1.00 mmol) were dissolved in a mixed solvent of 1,2-dimethoxyethane (20 mL) and water (5 mL), [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloride dichloromethane complex (28 mg, 0.034 mmol) and an aqueous potassium carbonate solution (3M, 0.65 mL, 1.95 mmol) were added, and stirring was carried out at 100°C for 7 days under nitrogen atmosphere. After the reaction solution was cooled to room temperature, water (10 mL) was added, and extraction was carried out with ethyl acetate (20 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=20%-80%) to afford the desired compound (106 mg, yield 35%) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J=6.3 Hz), 3.07 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J= 3.9, 10.2 Hz), 3.60 (1H, dd, J=6.3, 10.2 Hz), 4.57 (1H, m), 6.549-6.55 (4H, m), 6.83 (1H, brs), 7.00 (1H, brs), 7.14 (2H, d, J=9.0 Hz), 7.57 (1H, d, J=2.4 Hz), 7.90 (2H, d, J=9.0 Hz), 9.30 (1H, brs).

MS (ESI) m/z: 468.15954 $(M+H)^+$.

(Example 15)

1-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)ethanone



(15a) 1-(5-Bromo-1H-pyrrol-2-yl)ethanone

2-Acetylpyrrole (2.00 g, 18.3 mmol) was dissolved in a mixed solvent of tetrahydrofuran (100 mL) and methanol (50 mL), and N-bromosuccinimide (3.26 g, 18.3 mmol) was added with stirring at room temperature under nitrogen atmosphere. After stirring for 1 hour, the solvent was distilled off under reduced

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pressure. A saturated aqueous sodium hydrogencarbonate solution (200 mL) was added, and extraction was carried out with ethyl acetate (300 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=10%-20%) to afford the desired compound (770 mg, yield 22%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): 2.40 (3H, s), 6.24 (1H, dd, J=2.4, 4.0 Hz), 6.80 (1H, dd, J=2.9, 4.0 Hz), 9.37 (1H, brs).

(15b) t-Butyl 2-acetyl-5-bromo-1H-pyrrole-1-carboxylate

1-(5-Bromo-1H-pyrrol-2-yl)ethanone (770 mg, 4.1 mmol) synthesized in Example (15a) was dissolved in dichloromethane (30 mL), and triethylamine (0.57 mL, 4.1 mmol) and 4-dimethylaminopyridine (500 mg, 4.1 mmol) were added. Di-t-butyl dicarbonate (930 mg, 4.3 mmol) was dissolved in dichloromethane (10 mL), and the solution was added, followed by stirring at room temperature for 3 hours under nitrogen atmosphere. The reaction solution was diluted with dichloromethane (200 mL), washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-20%) to afford the desired product (538 mg, yield 46%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.64 (9H, s), 2.40 (3H, s), 6.24 (1H, d, J=3.9 Hz), 6.82 (1H, d, J=3.9 Hz).

(15c) 1-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)ethanone

2-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (146 mg, 0.33 mmol) synthesized in Example (1e)

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and t-butyl 2-acetyl-5-bromo-1H-pyrrole-1-carboxylate (141 mg, 0.49 mmol) synthesized in Example (15b) were dissolved in a mixed solvent of toluene (3 mL) and ethanol (1.3 mL), [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloride dichloromethane complex (13 mg, 0.016 mmol) and an aqueous potassium carbonate solution (2M, 0.41 mL, 0.83 mmol) were added, and stirring was carried out at 100°C for 1.5 hours under nitrogen atmosphere. After the reaction solution was cooled to room temperature, water (20 mL) was added, and extraction was carried out with ethyl acetate (60 mL). The organic layer was washed with saturated brine, subsequently dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure.

The resulting residue was dissolved in dichloromethane (2 mL), and trifluoroacetic acid (1 mL, 13.0 mmol) was added, followed by stirring at room temperature for 1 hour under nitrogen atmosphere. The solvent was distilled off under reduced pressure, a saturated aqueous sodium hydrogencarbonate solution (30 mL) was added, and extraction was carried out with ethyl acetate (70 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=10%-50%) to afford the desired compound (95 mg, yield 66%) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J=6.3 Hz,), 2.44 (3H, s), 3.07 (3H, s), 3.41 (3H, s), 3.51 (1H, dd, J=4.0, 10.2 Hz), 3.59 (1H, dd, J=6.2, 10.2 Hz), 4.56-4.59 (1H, m), 6.53 (1H, dd, J=2.9, 3.5 Hz), 6.62 (1H, t, J=2.0 Hz), 6.86 (1H, t, J=1.6 Hz), 6.93 (1H, dd, J=2.5, 3.9 Hz), 7.02 (1H, s), 7.14 (2H, d, J=8.9 Hz), 7.91 (2H, d, J=8.8 Hz), 9.64 (1H, brs).

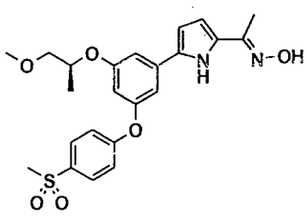
MS (ESI) m/z: 444.14808 $(M+H)^+$.

(Example 16)

(1E)-1-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-

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(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)ethanone oxime



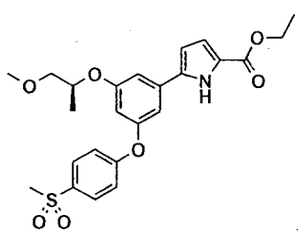
1-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)ethanone (117 mg, 0.26 mmol) synthesized in Example (15c) was dissolved in methanol (6 mL), and hydroxylamine hydrochloride (37 mg, 0.53 mmol) and sodium acetate (26 mg, 0.32 mmol) were added, followed by heating to reflux for 6 hours under nitrogen atmosphere. The reaction solution was diluted with dichloromethane (60 mL), washed with water and saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=30%-50%) to afford the desired product (50 mg, yield 41%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J=6.2 Hz), 2.19 (3H, s), 3.06 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J=4.1,10.2 Hz), 3.58 (1H, dd, J=6.1, 10.2 Hz), 4.52-4.57 (1H, m), 6.47 (2H, d, J=2.7 Hz), 6.53 (1H, t, J=2.0 Hz), 6.79 (1H, t, J=1.5 Hz), 6.89 (1H, brs), 6.95 (1H, t, J=1.8 Hz), 7.13 (2H, d, J=8.8 Hz), 7.90 (2H, d, J=8.8 Hz), 9.03 (1H, brs)

MS (ESI) m/z: 459.15898 $(M+H)^+$.

(Example 17)

Ethyl 5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carboxylate



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(17a) Ethyl 5-bromo-1H-pyrrole-2-carboxylate

Commercially available ethyl 1H-pyrrole-2-carboxylate (5.10 g, 30.7 mmol) was dissolved in a mixed solvent of tetrahydrofuran (120 mL) and methanol (60 mL), and cooled to 0°C. N-Bromosuccinimide (6.52 g, 30.7 mmol) was added, and stirring was carried out at room temperature for 18 hours under nitrogen atmosphere. Water (150 mL) and ethyl acetate (200 mL) were added, and the solution was separated. The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=5%-30%) to afford the desired compound (3.20 g, yield 40%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.36 (3H, t, J=7.1 Hz), 4.32 (2H, q, J=7.1 Hz), 6.21 (1H, dd, J=2.7, 3.9 Hz), 6.82 (1H, dd, J=2.7, 3.9 Hz), 9.21 (1H, brs).

(17b) 1-t-Butyl 2-ethyl 5-bromo-1H-pyrrole-1,2-dicarboxylate

Ethyl 5-bromo-1H-pyrrole-2-carboxylate (3.20 g, 14.7 mmol) synthesized in Example (17a) was dissolved in dichloromethane (100 mL), di-t-butyl dicarbonate (3.85 g, 17.6 mmol), triethylamine (4.10 mL, 19.4 mmol) and 4-dimethylaminopyridine (180 mg, 1.47 mmol) were added, and stirring was carried out at room temperature for 1 hour under nitrogen atmosphere. Water (100 mL) was added, and extraction was carried out with dichloromethane (100 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-20%) to afford the desired compound as a colorless oil (4.37 g, yield 94%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, t, J=7.0 Hz), 1.63 (9H, s), 4.30 (2H, q, J=7.0 Hz), 6.23 (1H, d, J=3.9 Hz), 6.83 (1H, d, J=3.9 Hz).

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(17c) 1-t-Butyl 2-ethyl 5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-1,2-dicarboxylate

2-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (8.73 g, 18.9 mmol) synthesized in Example (1e) and 1-t-butyl 2-ethyl 5-bromo-1H-pyrrole-1,2-dicarboxylate (8.37 g, 26.3 mmol) synthesized in Example (17b) were dissolved in a mixed solvent of toluene (180 mL) and ethanol (77 mL), [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloride dichloromethane complex (770 mg, 0.94 mmol) and an aqueous potassium carbonate solution (2M, 23.7 mL, 47.2 mmol) were added, and stirring was carried out at 100°C for 1 hour under nitrogen atmosphere. After the reaction solution was cooled to room temperature, water (200 mL) was added, and extraction was carried out with ethyl acetate (400 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=10%-50%) to afford the desired compound (9.44 g, yield 84%) as a pale yellow oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J=6.3 Hz), 1.35 (3H, t, J=7.0 Hz), 1.46 (9H, s), 3.05 (3H, s), 3.39 (3H, s), 3.48 (1H, dd, J= 4.3, 10.2 Hz), 3.57 (1H, dd, J=5.9, 10.2 Hz), 4.32 (2H, q, J=7.0 Hz), 4.53 (1H, m), 6.22 (1H, d, J=3.9 Hz), 6.65 (1H, m), 6.73 (1H, m), 6.88 (1H, m), 6.89 (1H, d, J=3.9 Hz), 7.12 (1H, d, J= 9.0 Hz), 7.89 (2H, d, J=9.0 Hz).

(17d) Ethyl 5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carboxylate

1-t-Butyl 2-ethyl 5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-1,2-dicarboxylate (9.44 g, 16.5 mmol) synthesized in Example (17c) was dissolved in dichloromethane (90 mL), and cooled to 0°C. Trifluoroacetic acid (45 mL) was added dropwise with stirring under nitrogen

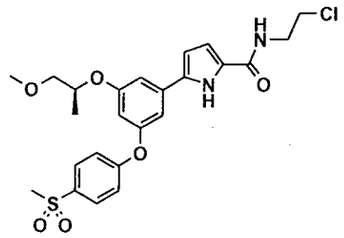
atmosphere, and stirring was carried out at room temperature for 1 hour. The solvent was distilled off under reduced pressure, followed by dilution with ethyl acetate (300 mL), a saturated aqueous sodium hydrogencarbonate solution (200 mL) was added, and the solution was separated. The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=10%-50%) to afford the desired compound (6.34 g, yield 81%) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J=6.3 Hz), 1.37 (2H, t, J=7.0 Hz), 3.07 (3H, s), 3.41 (3H, s), 3.51 (1H, dd, J= 3.9, 10.2 Hz), 3.60 (1H, dd, J=6.3, 10.2 Hz), 4.34 (2H, q, J=7.0 Hz), 4.58 (1H, m), 6.51 (1H, dd, J=2.5, 4.0 Hz), 6.58 (1H, m), 6.86 (1H, m), 6.93 (1H, dd, J=2.5, 4.0 Hz), 7.01 (1H, m), 7.13 (2H, d, J=8.8 Hz), 7.91 (2H, d, J=8.8 Hz), 9.41 (1H, brs).

MS (ESI) m/z: 474.16048 $(M+H)^+$.

(Example 18)

N-(2-Chloroethyl)-5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carboxamide



(18a) 5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carboxylic acid

Ethyl 5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carboxylate (4.36 g, 9.2 mmol) synthesized in Example (17d) was dissolved in ethanol (100 mL), and a 4N aqueous sodium hydroxide solution (23 mL, 92 mmol) was added, followed by heating to reflux for 1 hour under nitrogen atmosphere. To the reaction solution, 2N hydrochloric

acid (45 mL) was added to neutralize it, and the solvent was distilled off under reduced pressure. 1N hydrochloric acid was used to make the solution acidic, and extraction was carried out with ethyl acetate (300 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, to afford the desired product (4.06 g, yield 99%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J=6.3 Hz,), 3.07 (3H, s), 3.46 (3H, s), 3.55 (1H, dd, J=4.2, 10.4 Hz), 3.66 (1H, dd, J=6.3, 10.5 Hz), 4.70-4.75 (1H, m), 6.53 (1H, dd, J=2.6, 3.9 Hz), 6.59 (1H, t, J=2.0 Hz), 6.91 (1H, t, J=1.6 Hz,), 7.04 (1H, dd, J=2.3, 3.9 Hz), 7.25 (1H, m), 7.14 (2H, d, J=8.9 Hz), 7.91 (2H, d, J=8.8 Hz), 10.13 (1H, brs).

(18b) N-(2-Chloroethyl)-5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carboxamide

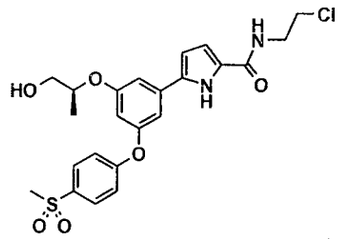
5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carboxylic acid (150 mg, 0.34 mmol) synthesized in Example (18a), 2-chloroethylamine hydrochloride (78 mg, 0.68 mmol) and 4-dimethylaminopyridine (41 mg, 0.34 mmol) were dissolved in dichloromethane (15 mL), WSCI·HCl (71 mg, 0.37 mmol) was added at room temperature, and stirring was carried out for 2 hours under nitrogen atmosphere. The reaction solution was diluted with dichloromethane (150 mL), washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=30%-60%) to afford the desired product (105 mg, yield 62%) as a white solid.

^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.33 (3H, d, J=6.3 Hz), 3.07 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J=4.0, 10.3 Hz), 3.59 (1H, dd, J=6.1,10.4 Hz), 3.70 (2H, t, J=5.4 Hz), 3.77 (2H, t, J=5.4 Hz),

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4.55-4.59 (1H, m), 6.26-6.29 (1H, brm), 6.50 (1H, dd, J=2.9, 3.9 Hz), 6.58 (1H, t, J=2.2 Hz), 6.63 (1H, dd, J=2.5, 3.8 Hz), 6.83 (1H, t, J=1.7 Hz), 6.99 (1H, t, J=2.0 Hz), 7.14 (2H, d, J=8.8 Hz), 7.91 (2H, d, J=8.8 Hz), 9.52 (1H, brs).
MS (ESI) m/z: 507.13566 $(M+H)^+$.

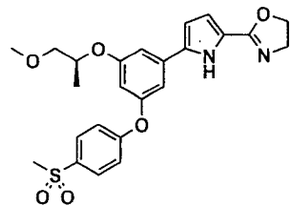
(Example 19)
N-(2-Chloroethyl)-5-{3-[(1S)-2-hydroxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carboxamide



N-(2-Chloroethyl)-5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carboxamide (88 mg, 0.17 mmol) synthesized in Example (18b) was dissolved in dichloromethane (5 mL), and cooled to -78°C, and a 1.0 mol/L boron tribromide dichloromethane solution (0.19 mL, 0.19 mmol) was added under nitrogen atmosphere. The temperature was raised naturally, the solution was stirred at room temperature for 30 minutes, subsequently a saturated aqueous sodium hydrogencarbonate solution was added to neutralize the reaction solution, and extraction was carried out with dichloromethane (60 mL). The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=50%-80%) to afford the desired product (55 mg, yield 64%) as a white solid.
^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.31 (3H, d, J=6.3 Hz), 2.1 (1H, brm), 3.08 (3H, s), 3.70 (2H, t, J=5.2 Hz), 3.76-3.80 (4H, m), 4.52-4.56 (1H, m), 6.27-6.30 (1H, brm), 6.50 (1H, dd, J=2.9, 3.8 Hz), 6.57 (1H, t, J=2.1 Hz), 6.64 (1H, dd, J=2.3, 3.9 Hz), 6.85 (1H, t, J=1.7 Hz), 6.98 (1H, t, J=1.8 Hz), 7.14 (2H, d, J=8.8 Hz),

7.91 (2H, d, J=8.8 Hz), 9.56 (1H, brs)
MS (FAB) m/z: 493 $(M+H)^+$.

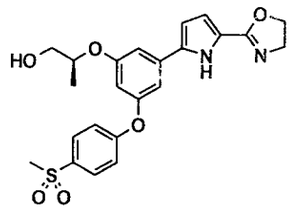
(Example 20)
2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-oxazole



N-(2-Chloroethyl)-5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carboxamide (177 mg, 0.349 mmol) synthesized in Example (18b) was dissolved in tetrahydrofuran (5 mL), and cooled to 0°C. Sodium hydride (40 mg, 0.917 mmol) was added, and the temperature was raised to room temperature, followed by stirring for 19 hours. After the reaction solution was cooled to 0°C, water (5 mL) was added, and extraction was carried out with ethyl acetate (10 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=50%-100%) to afford the desired compound (118 mg, yield 72%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J=6.3 Hz), 3.07 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J= 3.9, 10.2 Hz), 3.59 (1H, dd, J=6.3, 10.2 Hz), 3.98 (2H, t, J=9.4 Hz), 4.40 (2H, t, J=9.4 Hz), 4.56 (1H, m), 6.50 (1H, d, J=3.9 Hz), 6.56 (1H, brt, J=2.0 Hz), 6.75 (1H, d, J=3.9 Hz), 6.83 (1H, brt, J=2.0 Hz), 7.00 (1H, brt, J=2.0 Hz), 7.13 (2H, d, J=9.0 Hz), 7.90 (2H, d, J=9.0 Hz).
MS (ESI) m/z: 471.16050 $(M+H)^+$.

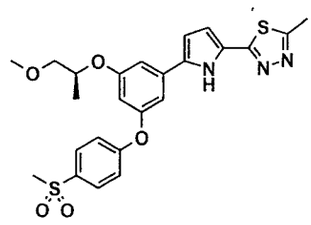
(Example 21)
(2S)-2-{3-[5-(4,5-Dihydro-1,3-oxazol-2-yl)-1H-pyrrol-2-yl]-5-[4-

(methylsulfonyl)phenoxy]phenoxy}propan-1-ol



2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-oxazole (3.17 g, 6.74 mmol) synthesized in Example 20 was dissolved in dichloromethane (100 mL), and cooled to -78°C, and a 1.0 mol/l boron tribromide dichloromethane solution (7.07 mL, 7.07 mmol) was added under nitrogen atmosphere. The temperature was raised naturally, followed by stirring at room temperature for 30 minutes, subsequently a saturated aqueous sodium hydrogencarbonate solution was added to neutralize the reaction solution, and extraction was carried out with dichloromethane (200 mL). The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was washed with ethyl acetate (100 mL) and ethanol (50 mL) to afford the desired product (1.96 g, yield 64%) as a white solid.
^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.29 (3H, d, J=6.3 Hz), 3.06 (3H, s), 3.79 (2H, d, J=5.9 Hz), 4.00 (2H, t, J=9.3 Hz), 4.42 (2H, t, J=9.4 Hz), 4.58-4.63 (1H, m), 6.40 (1H, t, J=2.2 Hz), 6.47 (1H, d, J=3.9 Hz), 6.75 (1H, d, J=3.8 Hz), 6.79 (1H, t, J=1.7 Hz), 6.94 (1H, t, J=1.8 Hz), 7.09 (2H, d, J=8.8 Hz), 7.88 (2H, d, J=8.8 Hz).
MS (ESI) m/z: 457.14357 $(M+H)^+$.

(Example 22)
2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-1,3,4-thiadiazole



(22a) N'-Acetyl-5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carbohydrazide

5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carboxylic acid (114.5 mg, 0.257 mmol) synthesized in Example (18a) was dissolved in N,N-dimethylformamide (4 mL), acetohydrazide (39.4 mg, 0.531 mmol), HATU (150.1 mg, 0.395 mol) and N,N-diisopropylethylamine (70 μL, 0.40 mmol) were added, and stirring was carried out at room temperature for 20 hours under nitrogen atmosphere. Water (20 mL) was added to the reaction solution, and extraction was carried out with ethyl acetate (20 mL). The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=10%-100%) to afford the desired compound (73.0 mg, yield 57%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.29 (3H, d, J=6.3 Hz), 1.99 (3H, s), 3.06 (3H, s), 3.40 (3H, s), 3.49 (1H, dd, J= 3.9, 10.2 Hz), 3.57 (1H, dd, J=6.3, 10.2 Hz), 4.58-4.63 (1H, m), 6.46 (1H, dd, J=2.7, 3.9 Hz), 6.53 (1H, s), 6.78 (1H, dd, J=2.4, 3.9 Hz), 6.86 (1H, s), 7.10 (2H, d, J=9.0 Hz), 7.13 (1H, s), 7.88 (2H, d, J=8.6 Hz), 8.63 (1H, brs), 9.08 (1H, brs), 10.20 (1H, brs).

MS (ESI) m/z: 524.14725 $(M+Na)^+$.

(22b) 2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-1,3,4-thiadiazole

N'-Acetyl-5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carbohydrazide (58.1 mg, 0.116 mmol) synthesized in Example (22a) was dissolved

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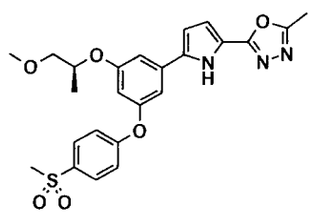
in toluene (4 mL), 2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (63.5 mg, 0.157 mmol) and pyridine (20 μL, 0.25 mmol) were added, and stirring was carried out at 90°C for 5 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, water (20 mL) was added to the reaction solution, and extraction was carried out with ethyl acetate (20 mL). The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=40%-80%) to afford the desired compound (50.6 mg, yield 87%) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.34 (3H, d, J=6.4 Hz), 2.77 (3H, s), 3.07 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J=4.4, 10.3 Hz), 3.60 (1H, dd, J=6.4, 10.3 Hz), 4.57-4.61 (1H, m), 6.55 (1H, t, J=3.4 Hz), 6.58 (1H, t, J=1.9 Hz), 6.67 (1H, dd, J=2.4, 3.9 Hz), 6.87 (1H, t, J=1.7 Hz), 7.03 (1H, s), 7.14 (2H, d, J=8.8 Hz), 7.91 (2H, d, J=8.8 Hz), 9.74 (1H, brs).

MS (ESI) m/z: 500.12981 $(M+H)^+$.

(Example 23)

2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-1,3,4-oxadiazole



N'-Acetyl-5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carbohydrazide (86.5 mg, 0.172 mmol) synthesized in Example (22a) was dissolved in acetonitrile (5 mL), (methoxycarbonysulfamoyl)triethylammonium hydroxide (60.7 mg, 0.258 mmol) and triethylamine (36 μL, 0.26 mmol) were added, and

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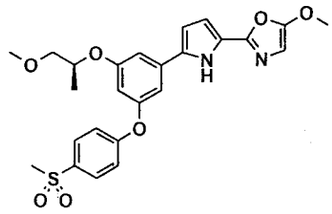
stirring was carried out at 80°C for 3 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, water (20 mL) was added to the reaction solution, and extraction was carried out with ethyl acetate (30 mL). The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=50%-75%) to afford the desired compound (49.1 mg, yield 59%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J=6.3 Hz), 2.58 (3H, s), 3.08 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J=3.9, 10.2 Hz), 3.60 (1H, dd, J=6.3, 10.2 Hz), 4.55-4.61 (1H, m), 6.57-6.60 (2H, m), 6.85-6.87 (2H, m), 7.02 (1H, s), 7.14 (2H, d, J=8.6 Hz), 7.91 (2H, d, J=8.6 Hz), 9.65 (1H, brs).

MS (ESI) m/z: 484.15505 $(M+H)^+$.

(Example 24)

5-Methoxy-2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-1,3-oxazole



(24a) Methyl N-[(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)carbonyl]glycinate

5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carboxylic acid (275 mg, 0.617 mmol) synthesized in Example (18a) was dissolved in dichloromethane (10 mL), and glycine methyl ester hydrochloride (120 mg, 0.956 mmol), WSCI·HCl (180 mg, 0.939 mmol) and 4-dimethylaminopyridine (150 mg, 1.23 mmol) were added, followed by stirring at room temperature for 2 hours under nitrogen atmosphere. 1N hydrochloric acid (10 mL) was added,

and the solution was separated with dichloromethane (15 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=20%-60%) to afford the desired product (270 mg, yield 85%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J=6.3 Hz), 3.07 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J= 3.9, 10.2 Hz), 3.59 (1H, dd, J=6.3, 10.2 Hz), 3.78 (3H, s), 4.56 (1H, m), 6.48 (1H, brt, J=3.9 Hz), 6.54-6.58 (2H, m), 6.69 (1H, dd, J=2.4, 3.9 Hz), 6.89 (1H, t, J=2.0 Hz), 7.02 (1H, t, J=2.0 Hz), 7.12 (2H, d, J=8.6 Hz), 7.89 (2H, d, J=8.9 Hz), 10.11 (1H, brs).

(24b) 5-Methoxy-2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-1,3-oxazole

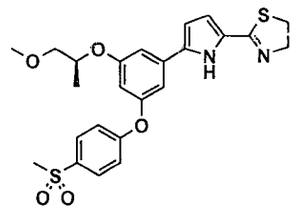
Methyl N-[(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)carbonyl]glycinate (270 mg, 0.523 mmol) synthesized in Example (24a) was dissolved in acetonitrile (10 mL), and triphenylphosphine (410 mg, 1.56 mmol), triethylamine (0.22 mL, 1.58 mmol) and carbon tetrachloride (0.33 mL, 3.42 mmol) were added, followed by stirring at room temperature for 15 hours under nitrogen atmosphere. Water (10 mL) was added, and the solution was separated with ethyl acetate (15 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=10%-40%) to afford the desired product (162 mg, yield 62%) as an orange solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J=6.3 Hz), 3.07 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J= 3.9, 10.2 Hz), 3.59 (1H, dd, J=6.3, 10.2 Hz), 3.92 (3H, s), 4.55 (1H, m), 6.08 (1H, s), 6.51-6.55 (2H, m), 6.70 (1H, dd, J=2.4, 3.9 Hz), 6.83 (1H, t, J=2.0

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Hz), 6.99 (1H, t, J=2.0 Hz), 7.12 (2H, d, J=9.0 Hz), 7.90 (2H, d, J=9.0 Hz), 9.77 (1H, brs).
MS (ESI) m/z: 499.15601 $(M+H)^+$.

(Example 25)
2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-thiazole



(25a) 2-(Tritylthio)ethaneamine

Hydrochloric acid 2-aminoethanethiol (5.16 g, 45.4 mmol) was dissolved in dichloromethane (80 mL), and trifluoroacetic acid (7.0 mL, 90.8 mmol) and triphenylmethyl chloride (13.29 g, 47.7 mmol) were added, followed by stirring at room temperature for 1 hour. A 1N aqueous sodium hydroxide solution (150 mL) was added, and extraction was carried out with dichloromethane (500 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, methanol (100 mL) was added to the resulting residue, and the deposited by-product was removed by filtration. 1N hydrochloric acid (300 mL) was added to make the solution acidic, and the deposit was filtered off. After the by-product was washed with dichloromethane (50 mL) to remove it, the solution was made alkaline with a 1N aqueous sodium hydroxide solution, and extraction was carried out with dichloromethane (600 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, to afford the desired product (8.77 g, yield 60%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.33 (2H, t, J=6.6 Hz), 2.59 (2H, t, J=6.6 Hz), 7.19-7.23 (3H, m), 7.26-7.30 (6H, m), 7.41-7.44 (6H,

m).

(25b) 5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-N-[2-(tritylthio)ethyl]-1H-pyrrole-2-carboxamide

To 5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carboxylic acid (940 mg, 2.1 mmol) synthesized in Example (18a), 2-(tritylthio)ethaneamine (1.01 g, 3.17 mmol) synthesized in Example (25a) and 4-dimethylaminopyridine (13 mg, 0.1 mmol) were added, followed by dissolution in dichloromethane (50 mL), and subsequently WSCI·HCl (445 mg, 2.3 mmol) was added at room temperature, and stirring was carried out for 1 hour under nitrogen atmosphere. The reaction solution was diluted with dichloromethane (150 mL), washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=10%-55%) to afford the desired product (1.08 g, yield 69%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J=6.3 Hz), 2.50 (2H, t, J=6.5 Hz), 3.07 (3H, s), 3.27 (2H, dt, J=5.9, 6.2 Hz), 3.42 (3H, s), 3.51 (1H, dd, J=4.0, 10.4 Hz), 3.59 (1H, dd, J=5.9, 10.4 Hz), 4.55-4.59 (1H, m), 5.99 (1H, brm), 6.48 (1H, dd, J=2.8, 3.9 Hz), 6.53 (1H, dd, J=2.5, 3.9 Hz), 6.57 (1H, t, J=2.3 Hz), 6.81 (1H, t, J=2.2 Hz), 6.98 (1H, t, J=2.1 Hz), 7.14 (2H, d, J=8.9 Hz), 7.19-7.30 (9H, m), 7.42 (6H, dd, J=1.6, 7.3 Hz), 7.91 (2H, d, J=8.9 Hz), 9.41 (1H, brs).

(25c) 2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-thiazole

Triphenylphosphine oxide (2.41 g, 8.7 mmol) was dissolved in dichloromethane (20 mL), and trifluoromethanesulfonic

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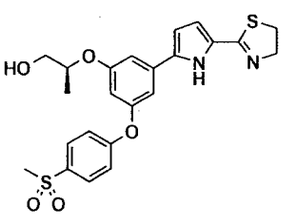
anhydride (0.73 mL, 4.3 mmol) was added dropwise slowly at 0°C. After stirring for 10 minutes, a dichloromethane (15 mL) solution of 5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-N-[2-(tritylthio)ethyl]-1H-pyrrole-2-carboxamide synthesized in Example (25b) was added. After reaction solution was stirred at room temperature for 30 minutes, the solvent was distilled off under reduced pressure, a saturated aqueous sodium hydrogencarbonate solution was added, and extraction was carried out with ethyl acetate (200 mL). The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=50%-80%) to afford the desired product (636 mg, yield 90%) as a white solid.

^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.33 (3H, d, J=6.3 Hz), 3.07 (3H, s), 3.39 (2H, t, J=8.4 Hz), 3.41 (3H, s), 3.50 (1H, dd, J=3.9, 10.3 Hz), 3.59 (1H, dd, J=5.9, 10.3 Hz), 4.33 (2H, t, J=8.7 Hz), 4.55-4.59 (1H, m), 6.50 (1H, d, J=3.9 Hz), 6.56 (1H, t, J=2.5 Hz), 6.64 (1H, d, J=3.9 Hz), 6.83 (1H, t, J=2.0 Hz), 7.00 (1H, t, J=2.4 Hz), 7.13 (2H, d, J=8.8 Hz), 7.90 (2H, d, J=8.8 Hz).

MS (ESI) m/z: 487.13595 $(M+H)^+$.

(Example 26)

(2S)-2-{3-[5-(4,5-Dihydro-1,3-thiazol-2-yl)-1H-pyrrol-2-yl]-5-[4-(methylsulfonyl)phenoxy]phenoxy}propan-1-ol



2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-thiazole (88 mg, 0.18 mmol) synthesized in Example (25c) was dissolved in dichloromethane (5 mL), and cooled to -78°C, a 1.0 mol/L boron tribromide dichloromethane solution (0.22 mL, 0.22

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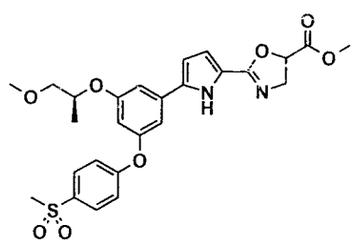
mmol) was added under nitrogen atmosphere. After the temperature was raised naturally and the solution was stirred at room temperature for 1 hour, subsequently a saturated aqueous sodium hydrogencarbonate solution was added to neutralize the reaction solution, followed by extraction with dichloromethane (60 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=40%-100%) to afford the desired product (46 mg, yield 54%) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.29 (3H, d, J=6.4 Hz), 3.27 (3H, s), 3.40 (2H, t, J=8.1 Hz), 3.76-3.78 (2H, m), 4.33 (2H, t, J=8.2 Hz), 4.55-4.59 (1H, m), 6.47 (1H, d, J=2.4 Hz), 6.49 (1H, d, J=3.7 Hz), 6.65 (1H, d, J=3.7 Hz), 6.82 (1H, s), 6.96 (1H, s), 7.11 (2H, d, J=8.7 Hz), 7.90 (2H, d, J=8.7 Hz).

MS (ESI) m/z: 473.12049 $(M+H)^+$.

(Example 27)

Methyl 2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-oxazole-5-carboxylate



(27a) Methyl 2-hydroxy-3-{[(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)carbonyl]amino}propanoate

5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carboxylic acid (420 mg, 0.943 mmol) synthesized in Example (18a) was dissolved in dichloromethane (10 mL), and DL-isoserine methyl ester

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hydrochloride (300 mg, 1.93 mmol), WSCI·HCl (270 mg, 1.41 mmol) and 4-dimethylaminopyridine (230 mg, 1.88 mmol) were added, followed by stirring at room temperature for 1.5 hours under nitrogen atmosphere. 1N hydrochloric acid (10 mL) was added, and the solution was separated with dichloromethane (15 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=50%-80%) to afford the desired product (400 mg, yield 78%) as a white solid.

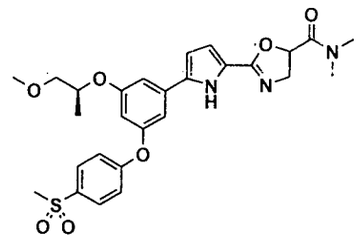
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J=6.3 Hz), 3.07 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J= 3.9, 10.2 Hz), 3.60 (1H, dd, J=6.3, 10.2 Hz), 3.72-3.85 (2H, m), 3.80 (3H, s), 4.38 (1H, brt, J=4.7 Hz), 4.58 (1H, m), 6.43 (1H, brs), 6.47 (1H, m), 6.56 (1H, t, J=2.0 Hz), 6.63 (1H, dd, J=2.4, 3.9 Hz), 6.86 (1H, t, J=2.0 Hz), 7.01 (1H, t, J=2.0 Hz), 7.12 (2H, d, J=9.0 Hz), 7.90 (2H, d, J=9.0 Hz), 9.85 (1H, brs).

(27b) Methyl 2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-oxazole-5-carboxylate

Methyl 2-hydroxy-3-{[(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)carbonyl]amino}propanoate (686 mg, 1.26 mmol) synthesized in Example (27a) was dissolved in tetrahydrofuran (15 mL), and methanesulfonic anhydride (330 mg, 1.89 mmol) and triethylamine (0.53 mL, 3.80 mmol) were added, followed by stirring at room temperature for 19 hours under nitrogen atmosphere. A saturated aqueous sodium hydrogencarbonate solution (10 mL) was added, and the solution was separated with ethyl acetate (20 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution

solvent: ethyl acetate/hexane=30%-70%) to afford the desired product (586 mg, yield 88%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J=6.3 Hz), 3.07 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J= 3.9, 10.2 Hz), 3.60 (1H, dd, J=6.3, 10.2 Hz), 4.10 (1H, dd, J=7.0, 14.5 Hz), 4.30 (1H, dd, J=10.6, 14.5 Hz), 4.56 (1H, m), 5.07 (1H, dd, J=7.0, 10.6 Hz), 6.52 (1H, d, J=3.9 Hz), 6.57 (1H, t, J=2.0 Hz), 6.83 (1H, t, J=2.0 Hz), 6.86 (1H, d, J=3.9 Hz), 7.00 (1H, t, J=2.0 Hz), 7.14 (2H, d, J=9.0 Hz), 7.90 (2H, d, J=9.0 Hz), 9.66 (1H, brs).
MS (ESI) m/z: 529.16412 $(M+H)^+$.

(Example 28)
2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-N,N-dimethyl-4,5-dihydro-1,3-oxazole-5-carboxamide



(28a) 2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-oxazole-5-carboxylic acid

Methyl 2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-oxazole-5-carboxylate (60.5 mg, 0.114 mmol) synthesized in Example (27b) was dissolved in ethanol (4 mL). An aqueous sodium hydroxide solution (5M, 2 mL) was added, and stirring was carried out at 70°C for 2.5 hours. After cooling to room temperature, hydrochloric acid (2M, 5 mL) and ethyl acetate (10 mL) were added, and the solution was separated. The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure to afford the desired compound (69.3 mg, yield ~100%) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.34 (3H, d, J=6.3 Hz), 3.07 (3H, s), 3.42 (3H, s), 3.55-3.63 (2H, m), 4.28-4.44 (2H, m), 4.78 (1H, m), 5.49 (1H, brs), 6.60-6.68 (2H, m), 7.10 (1H, brs), 7.14 (2H, d, J=8.3 Hz), 7.26 (1H, m), 7.39 (1H, brd, J=8.3 Hz), 7.89 (2H, d, J=8.3 Hz), 13.10 (1H, brs).
MS (ESI) m/z: 515.14638 $(M+H)^+$.

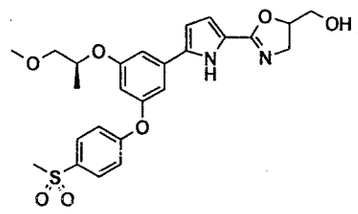
(28b) 2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-N,N-dimethyl-4,5-dihydro-1,3-oxazole-5-carboxamide

2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-oxazole-5-carboxylic acid (154 mg, 0.299 mmol) synthesized in Example (28a) was dissolved in dichloromethane (10 mL), and dimethylamine hydrochloride (75.0 mg, 0.920 mmol), WSCI·HCl (115 mg, 0.600 mmol) and 4-dimethylaminopyridine (110 mg, 0.900 mmol) were added, followed by stirring at room temperature for 2 days under nitrogen atmosphere. Water (10 mL) was added, and the solution was separated with dichloromethane (15 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=70%-100%) to afford the desired product (107 mg, yield 66%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J=6.3 Hz), 3.02 (3H, s), 3.07 (3H, s), 3.15 (3H, s), 3.42 (3H, s), 3.50 (1H, dd, J= 3.9, 10.2 Hz), 3.60 (1H, dd, J=5.9, 10.2 Hz), 4.19 (1H, ddd, J=1.2, 10.2, 14.1 Hz), 4.33 (1H, brdd, J=7.8, 14.1 Hz), 4.57 (1H, m), 5.27 (1H, dd, J=7.8, 10.2 Hz), 6.50 (1H, d, J=3.9 Hz), 6.56 (1H, d, J=2.0 Hz), 6.78 (1H, d, J=3.9 Hz), 6.83 (1H, t, J=2.0 Hz), 7.01 (1H, d, J=2.0 Hz), 7.13 (2H, d, J=8.6 Hz), 7.90 (2H, d, J=8.9 Hz), 9.80 (1H, brs).
MS (ESI) m/z: 542.19865 $(M+H)^+$.

(Example 29)

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[2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-oxazol-5-yl]methanol



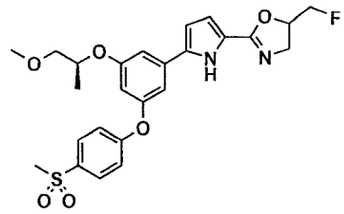
Lithium aluminum hydride (17.0 mg, 0.448 mmol) was suspended in tetrahydrofuran (2 mL). Methyl 2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-oxazole-5-carboxylate (77.0 mg, 0.146 mmol) synthesized in Example (27b) was dissolved in tetrahydrofuran (2 mL), followed by dropwise addition at 0°C under nitrogen atmosphere. After stirring at 0°C for 30 minutes, water (17 μL) and an aqueous sodium hydroxide solution (5M, 68 μL) were added dropwise slowly and sequentially. After filtration through Celite, the solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=50%-100%) to afford the desired compound (54.1 mg, yield 74%) as a white solid.

^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.29-1.33 (3H, m), 3.06 (3H, s), 3.41 (3H, s), 3.49 (1H, m), 3.58 (1H, m), 3.63-3.76 (2H, m), 3.83 (1H, m), 3.97 (1H, m), 4.59 (1H, m), 4.76 (1H, m), 6.46 (1H, m), 6.54 (1H, brs), 6.72 (1H, m), 6.69 (1H, brs), 7.05 (1H, m), 7.13 (2H, d, J=8.8 Hz), 7.89 (2H, d, J=8.8 Hz).

MS (ESI) m/z: 501.17097 $(M+H)^+$.

(Example 30)

5-(Fluoromethyl)-2-(5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-oxazole



[2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-oxazol-5-yl]methanol (100 mg, 0.20 mmol) synthesized in Example 29 was dissolved in dichloromethane (5 mL), and bis(2-methoxyethyl) aminosulfur trifluoride (81 μL, 0.44 mmol) was added at 0°C. After stirring at room temperature for 6 hours, a saturated aqueous sodium hydrogencarbonate solution was added, and extraction was carried out with dichloromethane (60 mL). The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=80%-100%) to afford the desired product (61 mg, yield 61%) as a white solid.

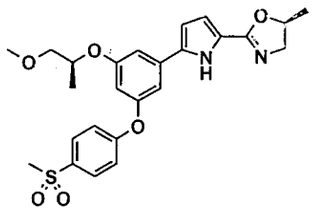
^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.33 (3H, d, J=6.3 Hz), 3.07 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J=4.1,10.3 Hz), 3.59 (1H, dd, J=6.3, 10.3 Hz), 3.82 (1H, dd, J=7.4, 14.5 Hz), 4.10 (1H, ddd, J=1.4, 10.1, 14.6 Hz), 4.49 (1H, ddd, J=5.5, 10.5, 37.9 Hz), 4.54-4.58 (1H, m), 4.62 (1H, ddd, J=3.0, 10.6, 33.3 Hz), 4.85-4.96 (1H, m), 6.51 (1H, d, J=3.9 Hz), 6.57 (1H, t, J=2.1 Hz), 6.80 (1H, d, J=3.6 Hz), 6.81 (1H, t, J=1.9 Hz), 6.98 (1H, t, J=1.8 Hz), 7.13 (2H, d, J=8.9 Hz), 7.91 (2H, d, J=8.9 Hz)

MS (ESI) m/z: 503.16398 $(M+H)^+$.

(Example 31)

(5S)-2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-4,5-dihydro-1,3-oxazole

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(31a) N-[(2R)-2-Hydroxypropyl]-5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carboxamide

5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carboxylic acid (204 mg, 0.458 mmol) synthesized in Example (18a) was dissolved in dichloromethane (10 mL), and (R)-(-)-1-amino-2-propanol (72.0μ mL, 0.914 mmol), WSCI·HCl (130 mg, 0.678 mmol) and 4-dimethylaminopyridine (115 mg, 0.941 mmol) were added, followed by stirring at room temperature for 18 hours under nitrogen atmosphere. 1N hydrochloric acid (10 mL) was added, and the solution was separated with dichloromethane (15 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=60%-100%) to afford the desired product (191 mg, yield 83%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.21 (3H, d, J=6.3 Hz), 1.31 (3H, d, J=6.3 Hz), 3.07 (3H, s), 3.24 (3H, s), 3.41 (3H, s), 3.51 (1H, dd, J= 3.9, 10.2 Hz), 3.57 (1H, m), 3.59 (1H, dd, J=6.3, 10.2 Hz), 3.98 (1H, m), 4.56 (1H, m), 6.47 (1H, dd, J=2.7, 3.9 Hz), 6.50 (1H, brs), 6.55 (1H, t, J=2.0 Hz), 6.64 (1H, dd, J=2.4, 3.9 Hz), 6.87 (1H, t, J=2.0 Hz), 7.00 (1H, t, J=2.0 Hz), 7.12 (2H, d, J=9.0 Hz), 7.89 (2H, d, J=9.0 Hz), 10.09 (1H, brs).

(31b) (5S)-2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-4,5-dihydro-1,3-oxazole

N-[(2R)-2-Hydroxypropyl]-5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-

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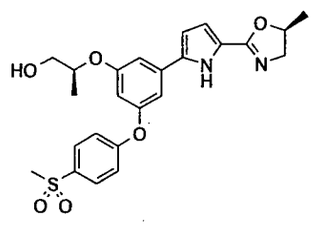
carboxamide (191 mg, 0.380 mmol) synthesized in Example (31a) was dissolved in tetrahydrofuran (10 mL), and anhydrous methanesulfonic acid (100 mg, 0.574 mmol) and triethylamine (0.16 mL, 1.15 mmol) were added, followed by stirring at room temperature for 18 hours under nitrogen atmosphere. A saturated aqueous sodium hydrogencarbonate solution (10 mL) was added, and the solution was separated with ethyl acetate (20 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=30%-70%) to afford the desired product (136 mg, yield 74%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J=6.3 Hz), 1.42 (3H, d, J=6.3 Hz), 3.07 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J= 4.3, 10.2 Hz), 3.52 (1H, dd, J=7.4, 14.1 Hz), 3.59 (1H, dd, J=6.3, 10.2 Hz), 4.06 (1H, dd, J=9.4, 14.1 Hz), 4.57 (1H, m), 4.82 (1H, m), 6.50 (1H, d, J=3.9 Hz), 6.55 (1H, t, J=2.0 Hz), 6.75 (1H, d, J=3.9 Hz), 6.83 (1H, t, J=2.0 Hz), 7.00 (1H, t, J=2.0 Hz), 7.13 (2H, d, J=9.0 Hz), 7.90 (2H, d, J=9.0 Hz).

MS (ESI) m/z: 485.17394 $(M+H)^+$.

(Example 32)

(2S)-2-(3-{5-[(5S)-5-Methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-[4-(methylsulfonyl)phenoxy]phenoxy)propan-1-ol

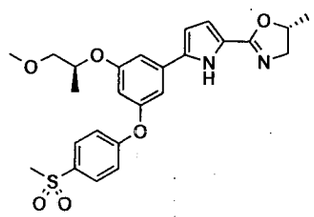


(5S)-2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-4,5-dihydro-1,3-oxazole (280 mg, 0.58 mmol) synthesized in Example(31b) was dissolved in dichloromethane (10 mL) and cooled to -78°C, and a 1.0 mol/l boron tribromide dichloromethane solution (0.61 mL, 0.61 mmol) was added under nitrogen

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atmosphere. After the temperature was raised naturally and the solution was stirred at room temperature for 30 minutes, a saturated aqueous sodium hydrogencarbonate solution was added to neutralize the reaction solution, followed by extraction with dichloromethane (60 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate) to afford the desired product (222 mg, yield 82%) as a white solid.
^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.28 (3H, d, J=6.3 Hz), 1.43 (3H, d, J=6.3 Hz), 3.07 (3H, s), 3.55 (1H, dd, J=7.3, 13.9 Hz), 3.79 (2H, d, J=5.4 Hz), 4.09 (1H, dd, J=9.2, 14.0 Hz), 4.60-4.64 (1H, m), 4.81-4.87 (1H, m), 6.36 (1H, t, J=2.3 Hz), 6.46 (1H, d, J=3.9 Hz), 6.75 (1H, d, J=3.9 Hz), 6.91 (1H, t, J=1.9 Hz), 7.08 (2H, d, J=8.9 Hz), 7.88 (2H, d, J=8.9 Hz).
MS (ESI) m/z: 471.15892 $(M+H)^+$.

(Example 33)
(5R)-2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-4,5-dihydro-1,3-oxazole



(33a) N-[(2S)-2-Hydroxypropyl]-5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carboxamide

5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carboxylic acid (305 mg, 0.685 mmol) synthesized in Example(18a) was dissolved in dichloromethane (10 mL), and (S)-(+)-1-amino-2-propanol (110μ mL, 1.40 mmol), WSCI·HCl (200 mg, 1.04 mmol) and 4-dimethylaminopyridine (170 mg, 1.39 mmol) were added, followed

by stirring at room temperature for 16 hours under nitrogen atmosphere. 1N hydrochloric acid (10 mL) was added, and the solution was separated with dichloromethane (15 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=60%-100%) to afford the desired product (285 mg, yield 83%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.24 (3H, d, J=6.3 Hz), 1.33 (3H, d, J=6.3 Hz), 3.07 (3H, s), 3.28 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J= 3.9, 10.2 Hz), 3.56-3.65 (2H, m), 4.01 (1H, m), 4.58 (1H, m), 6.35 (1H, brt, J=5.5 Hz), 6.49 (1H, dd, J=2.7, 3.9 Hz), 6.57 (1H, t, J=2.0 Hz), 6.62 (1H, dd, J=2.4, 3.9 Hz), 6.84 (1H, t, J=2.0 Hz), 7.00 (1H, t, J=2.0 Hz), 7.13 (2H, d, J=8.6 Hz), 7.90 (2H, d, J=8.6 Hz), 9.66 (1H, brs).

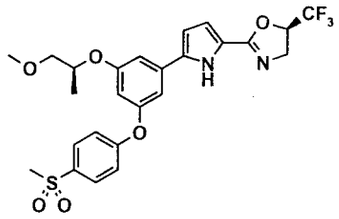
(33b) (5R)-2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-4,5-dihydro-1,3-oxazole

N-[(2S)-2-Hydroxypropyl]-5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carboxamide (285 mg, 0.567 mmol) synthesized in Example (33a) was dissolved in tetrahydrofuran (10 mL), and anhydrous methanesulfonic acid (130 mg, 0.746 mmol) and triethylamine (0.24 mL, 1.72 mmol) were added, followed by stirring at room temperature for 21 hours under nitrogen atmosphere. A saturated aqueous sodium hydrogencarbonate solution (10 mL) was added, and the solution was separated with ethyl acetate (20 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=30%-70%) to afford the desired product (155 mg, yield 56%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J=6.3 Hz), 1.41 (3H, d,

J=6.3 Hz), 3.06 (3H, s), 3.40 (3H, s), 3.50 (1H, dd, J= 3.9, 10.2 Hz), 3.51 (1H, dd, J=8.2, 14.1 Hz), 3.58 (1H, dd, J=5.9, 10.2 Hz), 4.04 (1H, dd, J=9.4, 14.1 Hz), 4.56 (1H, m), 4.80 (1H, m), 6.50 (1H, d, J=3.9 Hz), 6.55 (1H, t, J=2.0 Hz), 6.74 (1H, d, J=3.9 Hz), 6.84 (1H, t, J=2.0 Hz), 7.00 (1H, t, J=2.0 Hz), 7.12 (2H, d, J=9.0 Hz), 7.89 (2H, d, J=9.0 Hz).
MS (ESI) m/z: 485.17398 $(M+H)^+$.

(Example 34)
(5R)-2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5-(trifluoromethyl)-4,5-dihydro-1,3-oxazole



(34a) 5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-N-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-1H-pyrrole-2-carboxamide

5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carboxylic acid (408 mg, 0.94 mmol) synthesized in Example (18a), (2S)-3-amino-1,1,1-trifluoro-2-propanol (177 mg, 1.37 mmol) and 4-dimethylaminopyridine (224 mg, 1.87 mmol) were dissolved in dichloromethane (20 mL), and WSCI·HCl (193 mg, 1.01 mmol) was added at room temperature, followed by stirring for 2 hours under nitrogen atmosphere. The reaction solution was diluted with dichloromethane (200 mL), washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=50%-70%) to afford the desired product (339 mg, yield 67%) as a white amorphous substance.

^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.31 (3H, d, J=6.3 Hz), 3.08 (3H, s), 3.42 (3H, s), 3.52 (1H, dd, J=3.9, 10.3 Hz), 3.60 (1H, dd, J=6.2, 10.2 Hz), 3.58-3.65 (1H, m), 3.85 (1H, ddd, J=2.7, 6.6, 14.9 Hz), 4.08-4.15 (1H, brm), 4.53-4.60 (1H, m), 4.74 (1H, d, J=5.5 Hz), 6.37 (1H, t, J=6.1 Hz), 6.50 (1H, dd, J=3.0, 4.0 Hz), 6.58 (1H, t, J=2.2 Hz), 6.67 (1H, dd, J=2.7, 4.0 Hz), 6.84 (1H, t, J=1.7 Hz), 6.99 (1H, t, J=2.0 Hz), 7.13 (2H, d, J=8.9 Hz), 7.91 (2H, d, J=8.9 Hz), 9.82 (1H, brs).

(34b) (5R)-2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5-(trifluoromethyl)-4,5-dihydro-1,3-oxazole

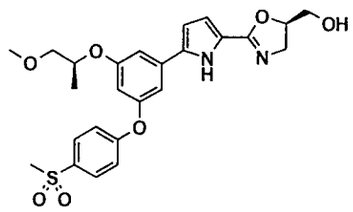
5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-N-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-1H-pyrrole-2-carboxamide (339 mg, 0.61 mmol) synthesized in Example (34a) was dissolved in tetrahydrofuran (10 mL), and triethylamine (0.51 mL, 3.66 mmol) and anhydrous methanesulfonic acid (296 mg, 1.71 mmol) were added at 0°C, followed by heating at 120°C for 30 hours. To the reaction solution, a saturated aqueous sodium hydrogencarbonate solution was added, and extraction was carried out with ethyl acetate (60 mL). After washing with saturated brine, drying was carried out over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=30%-50%) to afford the desired product (328 mg, yield 84%) as a white solid.

^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.33 (3H, d, J=6.3 Hz), 3.08 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J=3.9, 10.4 Hz), 3.59 (1H, dd, J=6.3, 10.1 Hz), 4.15 (1H, dd, J=6.5, 15.4 Hz), 4.22 (1H, dd, 10.0, 15.4 Hz), 4.55-4.59 (1H, m), 4.88-4.92 (1H, m), 6.52 (1H, dd, J=2.4,4.0 Hz), 6.58 (1H, t, J=2.2 Hz), 6.82 (1H, t, J=1.8 Hz), 6.84 (1H, dd, J=2.3, 3.9 Hz), 6.98 (1H, t, J=2.0 Hz), 7.13 (2H, d, J=8.8 Hz), 7.91 (2H, d, J=8.8 Hz), 9.25 (1H, brs).

MS (ESI) m/z: 539.14603 $(M+H)^+$.

(Example 35)

[(5R)-2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-oxazol-5-yl]methanol



(35a) N-[(2S)-2,3-Dihydroxypropyl]-5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carboxamide

5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carboxylic acid (338 mg, 0.759 mmol) synthesized in Example (18a) was dissolved in dichloromethane (10 mL), and (S)-(-)-3-amino-1,2-propanediol (105 mg, 1.15 mmol), WSCI·HCl (220 mg, 1.15 mmol) and 4-dimethylaminopyridine (185 mg, 1.51 mmol) were added, followed by stirring at room temperature for 3 days under nitrogen atmosphere. 1N hydrochloric acid (10 mL) was added, and the solution was separated with dichloromethane (15 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=70%-100%) to afford the desired product (265 mg, yield 68%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J=6.3 Hz), 3.07 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J= 3.9, 10.2 Hz), 3.553-3.64 (4H, m), 3.85 (1H, m), 4.57 (1H, m), 6.38 (1H, m), 6.50 (1H, dd, J=2.7, 3.9 Hz), 6.58 (1H, t, J=2.0 Hz), 6.64 (1H, dd, J=2.4, 3.9 Hz), 6.84 (1H, t, J=2.0 Hz), 7.00 (1H, t, J=2.0 Hz), 7.13 (2H, d, J=9.0 Hz), 7.91 (2H, d, J=9.0 Hz), 9.59 (1H, brs).

(35b) N-{(2S)-2-Hydroxy-3-[(triisopropylsilyl)oxy]propyl}-5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-

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(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carboxamide

N-[(2S)-2,3-Dihydroxypropyl]-5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carboxamide (265 mg, 0.514 mmol) synthesized in Example (35a) was dissolved in dichloromethane (10 mL), and triisopropylsilyl chloride (0.12 mL, 0.691 mmol), triethylamine (0.21 mL, 1.51 mol) and 4-dimethylaminopyridine (6.0 mg, 0.049 mmol) were added, followed by stirring at room temperature for 24 hours under nitrogen atmosphere. Water (10 mL) was added, and the solution was separated with dichloromethane (20 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=20%-50%) to afford the desired product (177 mg, yield 51%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.04-1.13 (21H, m), 1.32 (3H, d, J=6.3 Hz), 3.07 (3H, s), 3.21 (1H, d, J=4.3 Hz), 3.38 (1H, m), 3.42 (3H, s), 3.51 (1H, dd, J=3.9, 10.2 Hz), 3.60 (1H, dd, J=6.3, 10.2 Hz), 3.67 (1H, dd, J=6.3, 9.8 Hz), 3.73 (1H, m), 3.76 (1H, dd, J=5.0, 9.8 Hz), 3.86 (1H, m), 4.58 (1H, m), 6.43 (1H, brt, J=5.9 Hz), 6.48 (1H, dd, J=2.8, 3.9 Hz), 6.56 (1H, t, J=2.0 Hz), 6.61 (1H, dd, J=2.4, 3.9 Hz), 6.85 (1H, t, J=2.0 Hz), 7.00 (1H, t, J=2.0 Hz), 7.13 (2H, d, J=8.6 Hz), 7.90 (2H, d, J=8.6 Hz), 9.80 (1H, brs).

(35c) (5S)-2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5-{[(triisopropylsilyl)oxy]methyl}-4,5-dihydro-1,3-oxazole

N-{(2S)-2-Hydroxy-3-[(triisopropylsilyl)oxy]propyl}-5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carboxamide (177 mg, 0.262 mmol) synthesized in Example (35b) was dissolved in tetrahydrofuran (10 mL), and anhydrous methanesulfonic acid (70.0 mg, 0.402 mmol) and triethylamine (0.22 mL, 1.58 mmol) were added, followed by stirring at 70°C for 3 days under

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nitrogen atmosphere. A saturated aqueous sodium hydrogencarbonate solution (10 mL) was added, and the solution was separated with ethyl acetate (20 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=30%-60%) to afford the desired product (180 mg, yield ~100%) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.02-1.10 (21H, m), 1.33 (3H, d, J=6.3 Hz), 3.07 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J= 4.3, 10.2 Hz), 3.59 (1H, dd, J=6.3, 10.2 Hz), 3.82-3.90 (3H, m), 4.00 (1H, dd, J=9.8, 14.1 Hz), 4.58 (1H, m), 4.75 (1H, m), 6.49 (1H, d, J=3.9 Hz), 6.55 (1H, t, J=2.0 Hz), 6.73 (1H, d, J=3.9 Hz), 6.83 (1H, t, J=2.0 Hz), 7.00 (1H, t, J=2.0 Hz), 7.13 (2H, d, J=9.0 Hz), 7.90 (2H, d, J=9.0 Hz), 9.59 (1H, brs).

(35d) [(5R)-2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-oxazol-5-yl]methanol

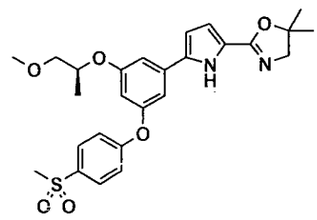
(5S)-2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5-{[(triisopropylsilyl)oxy]methyl}-4,5-dihydro-1,3-oxazole (180 mg, 0.262 mmol) synthesized in Example (35c) was dissolved in tetrahydrofuran (10 mL), and tetrabutylammonium fluoride (1M tetrahydrofuran solution, 0.53 mL, 0.53 mmol) was added, followed by stirring at room temperature for 30 minutes under nitrogen atmosphere. Water (10 mL) was added, and extraction was carried out with ethyl acetate (20 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=60%-100%) to afford the desired compound (103 mg, yield 79%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.27 (3H, d, J=6.3 Hz), 3.07 (3H, s),

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3.42 (3H, s), 3.49 (1H, dd, J= 3.9, 10.2 Hz), 3.58 (1H, dd, J=6.3, 10.2 Hz), 3.67 (1H, dd, J=5.1, 12.5 Hz), 3.74 (1H, dd, J=7.4, 14.5 Hz), 3.84 (1H, dd, J=3.1, 12.5 Hz), 4.00 (1H, dd, J=9.8, 14.5 Hz), 4.54 (1H, m), 4.78 (1H, m), 6.46 (1H, d, J=3.9 Hz), 6.55 (1H, t, J=2.0 Hz), 6.71 (1H, d, J=3.9 Hz), 6.85 (1H, t, J=2.0 Hz), 6.98 (1H, t, J=2.0 Hz), 7.14 (2H, d, J=8.6 Hz), 7.90 (2H, d, J=9.0 Hz), 9.59 (1H, brs).
MS (ESI) m/z: 501.16898 $(M+H)^+$.

(Example 36)
2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5,5-dimethyl-4,5-dihydro-1,3-oxazole



(36a) N-(2-Hydroxy-2-methylpropyl)-5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carboxamide

5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carboxylic acid (300 mg, 0.673 mmol) synthesized in Example (18a) was dissolved in dichloromethane (10 mL), and 1-amino-2-methyl-2-propanol (150 mg, 1.68 mmol), WSCI·HCl (185 mg, 0.965 mmol) and 4-dimethylaminopyridine (165 mg, 1.35 mmol) were added, followed by stirring at room temperature for 17 hours under nitrogen atmosphere. 1N hydrochloric acid (10 mL) was added, and the solution was separated with dichloromethane (15 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=60%-100%) to afford the desired product (307 mg, yield 88%) as a white solid.

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^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.26 (6H, s), 1.32 (3H, d, J=6.3 Hz), 3.07 (3H, s), 3.41 (3H, s), 3.41 (2H, m), 3.51 (1H, dd, J= 3.9, 10.2 Hz), 3.59 (1H, dd, J= 6.3, 10.2 Hz), 4.58 (1H, m), 4.46 (1H, brs), 6.48 (1H, dd, J=2.7, 3.9 Hz), 6.56 (1H, t, J=2.0 Hz), 6.65 (1H, dd, J=2.4, 3.9 Hz), 6.86 (1H, t, J=2.0 Hz), 7.00 (1H, t, J=2.0 Hz), 7.12 (2H, d, J=9.0 Hz), 7.90 (2H, d, J=9.0 Hz), 9.86 (1H, brs).

(36b) 2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5,5-dimethyl-4,5-dihydro-1,3-oxazole

N-(2-Hydroxy-2-methylpropyl)-5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carboxamide (307 mg, 0.594 mmol) synthesized in Example (36a) was dissolved in tetrahydrofuran (10 mL), and anhydrous methanesulfonic acid (160 mg, 0.918 mmol) and triethylamine (0.25 mL, 1.79 mol) were added, followed by stirring at room temperature for 4 days under nitrogen atmosphere. A saturated aqueous sodium hydrogencarbonate solution (10 mL) was added, and the solution was separated with ethyl acetate (20 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=30%-70%) to afford the desired product (187 mg, yield 63%) as a white solid.

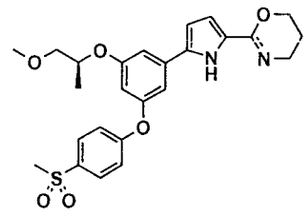
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J=6.3 Hz), 1.47 (6H, s), 3.07 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J= 3.9, 10.2 Hz), 3.59 (1H, dd, J=6.3, 10.2 Hz), 3.69 (1H, s), 4.57 (1H, m), 6.50 (1H, d, J=3.9 Hz), 6.55 (1H, t, J=2.0 Hz), 6.74 (1H, d, J=3.9 Hz), 6.83 (1H, t, J=2.0 Hz), 7.00 (1H, t, J=2.0 Hz), 7.13 (2H, d, J=9.0 Hz), 7.90 (2H, d, J=9.0 Hz).

MS (ESI) m/z: 499.18990 $(M+H)^+$.

(Example 37)

2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-

(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5,6-dihydro-4H-1,3-oxazine



(37a) N-(3-Hydroxypropyl)-5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carboxamide

5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carboxylic acid (250 mg, 0.561 mmol) synthesized in Example (18a) was dissolved in dichloromethane (10 mL), and 3-amino-1-propanol (90.0 μL, 1.18 mmol), WSCI·HCl (165 mg, 0.861 mmol) and 4-dimethylaminopyridine (140 mg, 1.15 mmol) were added, followed by stirring at room temperature for 16 hours under nitrogen atmosphere. 1N hydrochloric acid (10 mL) was added, and the solution was separated with dichloromethane (15 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=60%-100%) to afford the desired product (216 mg, yield 77%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J=6.3 Hz), 1.78 (2H, m), 3.07 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J= 3.9, 10.2 Hz), 3.56-3.62 (3H, m), 3.71 (2H, m), 4.58 (1H, m), 6.32 (1H, brs), 6.49 (1H, dd, J=2.7, 3.9 Hz), 6.56-6.60 (2H, m), 6.84 (1H, t, J=2.0 Hz), 6.99 (1H, t, J=2.0 Hz), 7.13 (2H, d, J=9.0 Hz), 7.91 (2H, d, J=9.0 Hz), 9.63 (1H, brs).

(37b) 2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrol-2-yl)-5,6-dihydro-4H-1,3-oxazine

N-(3-Hydroxypropyl)-5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[4-(methylsulfonyl)phenoxy]phenyl}-1H-pyrrole-2-carboxamide

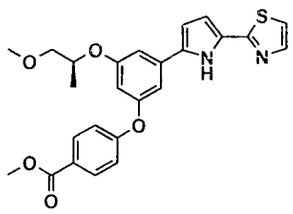
(216 mg, 0.430 mmol) synthesized in Example (37a) was dissolved in tetrahydrofuran (10 mL), and anhydrous methanesulfonic acid (115 mg, 0.660 mmol) and triethylamine (0.18 mL, 1.29 mol) were added, followed by stirring at room temperature for 4 days, further at 80°C for 17 hours, under nitrogen atmosphere. A saturated aqueous sodium hydrogencarbonate solution (10 mL) was added, and the solution was separated with ethyl acetate (20 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=50%-90%) to afford the desired product (150 mg, yield 72%) as a pale brownish solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J=6.3 Hz), 1.98 (2H, m), 3.06 (3H, s), 3.41 (3H, s), 3.48-3.54 (3H, m), 3.59 (1H, dd, J=6.3, 10.2 Hz), 4.32 (2H, brt, J=5.5 Hz), 4.56 (1H, m), 6.46 (1H, d, J=3.9 Hz), 6.53 (1H, t, J=2.0 Hz), 6.62 (1H, d, J=3.9 Hz), 6.82 (1H, t, J=2.0 Hz), 6.99 (1H, t, J=2.0 Hz), 7.12 (2H, d, J=9.0 Hz), 7.89 (2H, d, J=9.0 Hz).

MS (ESI) m/z: 485.17572 $(M+H)^+$.

(Example 38)

Methyl 4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}benzoate



(38a) 1-Bromo-3-methoxy-5-[(1S)-2-methoxy-1-methylethoxy]benzene

3-Bromo-5-methoxyphenol (7.60 g, 37.4 mmol) synthesized in Example (1a) was dissolved in toluene (100 mL), and R-(-)1-methoxy-2-propanol (4.40 mL, 44.9 mmol) and triphenylphosphine (13.8 g, 52.6 mmol) were added, followed by dropwise addition of

diethyl azodicarboxylate (2.2 mol/l toluene solution, 24 mL, 52.8 mmol) at 0°C and stirring at room temperature for 1.5 hours under nitrogen atmosphere. The solvent was distilled off under reduced pressure, diethyl ether (100 mL) was added, and the deposit was filtered to be removed. The mother liquor was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=10%-20%) to afford the desired compound (9.22 g, yield 89%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.30 (3H, d, J=6.3 Hz), 3.40 (3H, s), 3.47 (1H, dd, J=10.6, 4.3 Hz), 3.55 (1H, dd, J=10.4, 6.1 Hz), 3.76 (3H, s), 4.46-4.52 (1H, m), 6.42 (1H, t, J=2.2 Hz), 6.65 (1H, dd, J=2.3, 1.6 Hz), 6.69 (1H, t, J=2.0 Hz).

MS (EI) m/z: 274 $(M)^+$.

(38b) 3-Bromo-5-[(1S)-2-methoxy-1-methylethoxy]phenol

1-Bromo-3-methoxy-5-[(1S)-2-methoxy-1-methylethoxy]benzene (9.21 g, 33.5 mmol) synthesized in Example (38a) was dissolved in 1-methyl-2-pyrrolidone (100 mL), and sodium thiomethoxide (2.75 g, 37.3 mmol) was added, followed by stirring at 130°C for 3 for hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, 2N hydrochloric acid (500 mL) was added, and extraction was carried out with diethyl ether (300 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=20%-25%) to afford the desired compound (8.30 g, yield 95%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.29 (3H, d, J=6.3 Hz), 3.41 (3H, s), 3.46 (1H, dd, J=10.2, 4.3 Hz), 3.55 (1H, dd, J=10.6, 5.9 Hz), 4.45-4.51 (1H, m), 4.96 (1H, br s), 6.36 (1H, t, J= 2.0 Hz), 6.59 (1H, t, J= 2.0 Hz), 6.68 (1H, t, J= 2.0 Hz).

MS (EI) m/z: 260 $(M)^+$.

(38c) 3-[(1S)-2-Methoxy-1-methylethoxy]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol

3-Bromo-5-[(1S)-2-methoxy-1-methylethoxy]phenol (8.30 g, 31.8 mmol) synthesized in Example (38b) was dissolved in N,N-dimethylformamide (100 mL), and bis(pinacolate)diboron (10.50 g, 41.3 mmol), [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloride dichloromethane complex (810 mg, 0.992 mmol) and potassium acetate (15.50 g, 158 mmol) were added, followed by stirring at 90°C for 3 hours under nitrogen atmosphere. After the reaction solution was cooled to room temperature, water (500 mL) was added, and extraction was carried out with diethyl ether (300 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=20%-30%) to afford the desired compound (8.75 g, yield 89%) as a brownish oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.26 (3H, d, J=4.1 Hz), 1.33 (12H, s), 3.41 (1H, s), 3.47 (1H, dd, J=10.2, 4.7 Hz), 3.57 (1H, dd, J=10.6, 5.9 Hz), 4.52-4.58 (1H, m), 4.80 (1H, brs), 6.55 (1H, t, J=2.4 Hz), 6.83 (1H, d, J=2.4 Hz), 6.95 (1H, d, J=2.4 Hz).
MS (FAB) m/z: 309 $(M+H)^+$.

(38d) t-Butyl 2-{3-hydroxy-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-5-(1,3-thiazol-2-yl)-1H-pyrrole-1-carboxylate

3-[(1S)-2-Methoxy-1-methylethoxy]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (3.30 g, 10.7 mmol) synthesized in Example (38c) and t-butyl 2-bromo-5-(1,3-thiazol-2-yl)-1H-pyrrole-1-carboxylate (4.10 g, 12.5 mmol) synthesized in Example (1g) were dissolved in a mixed solvent of 1,4-dioxane (100 mL) and water (25 mL), and [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloride dichloromethane complex (400 mg, 0.490 mmol) and potassium carbonate (7.20 g, 52.1 mmol) were added, followed by stirring

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at 50°C for 4 hours under nitrogen atmosphere. After the reaction solution was cooled to room temperature, water (200 mL) was added, and extraction was carried out with ethyl acetate (400 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=25%-40%) to afford the desired compound (3.72 g, yield 81%) as a pale yellow oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.24-1.29 (12H, m), 3.40 (3H, s), 3.47 (1H, dd, J= 4.4, 10.3 Hz), 3.57 (1H, dd, J=5.9, 10.3 Hz), 4.48-4.54 (1H, m), 5.74 (1H, brs), 6.19 (1H, brs), 6.39-6.44 (2H, brs), 6.55 (1H, brs), 6.60 (1H, d, J=3.9 Hz), 7.31 (1H, d, J=3.0 Hz), 7.81 (1H, d, J=3.4 Hz).

(38e) t-Butyl 2-{3-[4-(methoxycarbonyl)phenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-5-(1,3-thiazol-2-yl)-1H-pyrrole-1-carboxylate

t-Butyl 2-{3-hydroxy-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-5-(1,3-thiazol-2-yl)-1H-pyrrole-1-carboxylate (117 mg, 0.272 mmol) synthesized in Example (38d) was dissolved in dichloromethane (20 mL), and 4-methoxycarbonylphenyl boronic acid (100 mg, 0.556 mmol), copper (II) acetate (80 mg, 0.440 mmol), triethylamine (0.20 mL, 1.435 mmol) and molecular sieves 4A (100 mg) were added, followed by stirring at room temperature for 3 days under nitrogen atmosphere. The deposit of this reaction solution was Celite filtered. This mother liquor was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=15%-25%) to afford the desired compound (70 mg, yield 46%) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.31 (12H, m), 3.40 (3H, s), 3.48 (1H, dd, J=10.2, 4.3 Hz), 3.57 (1H, dd, J=10.2, 5.9 Hz), 3.90 (3H, s), 4.48-4.58 (1H, m), 6.25 (1H, d, J=3.5 Hz), 6.58 (1H, d, J=3.5

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Hz), 6.63 (1H, t, J=2.4 Hz), 6.70 (1H, dd, J=2.4, 1.2 Hz), 6.84 (1H, dd, J=2.4, 1.6 Hz), 7.04 (2H, d, J=9.0 Hz), 7.33 (1H, d, J=3.1 Hz), 7.80 (1H, d, J=3.5 Hz), 8.00 (2H, d, J=9.0 Hz).

(38f) Methyl 4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy} benzoate

t-Butyl 2-{3-[4-(methoxycarbonyl)phenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-5-(1,3-thiazol-2-yl)-1H-pyrrole-1-carboxylate (70 mg, 0.124 mmol) synthesized in Example (38e) was dissolved in dichloromethane (1.0 mL). Trifluoroacetic acid (2.0 mL) was added dropwise with stirring under nitrogen atmosphere, and stirring was carried out at room temperature for 2 hours. The solvent was distilled off under reduced pressure, followed by dilution with ethyl acetate (30 mL), a saturated aqueous sodium hydrogencarbonate solution (20 mL) was added, and the solution was separated. The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=30%-50%) to afford the desired compound (65 mg, yield ~100%) as a pale yellow liquid.

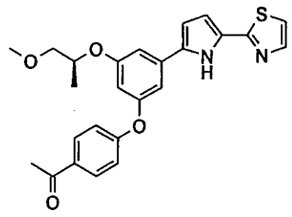
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J=6.3 Hz), 3.42 (3H, s), 3.52 (1H, dd, J=3.9, 10.2 Hz), 3.60 (1H, dd, J=5.9, 10.2 Hz), 3.91 (3H, s), 4.60-4.70 (1H, m), 6.56-6.59 (2H, m), 6.86 (1H, brs), 6.93 (1H, brs), 7.05 (2H, d, J=9.0 Hz), 7.15 (1H, brs), 7.70 (1H, brs), 8.02 (2H, d, J=9.0 Hz).

MS (ESI) m/z: 465.19025 $(M+H)^+$.

(Example 39)

1-(4-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}phenyl)ethanone

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(39a) t-Butyl 2-{3-(4-acetylphenoxy)-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-5-(1,3-thiazol-2-yl)-1H-pyrrole-1-carboxylate

t-Butyl 2-{3-hydroxy-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-5-(1,3-thiazol-2-yl)-1H-pyrrole-1-carboxylate (92 mg, 0.214 mmol) synthesized in Example (38d) was dissolved in dichloromethane (10 mL), and 4-acetylphenylboronic acid (70 mg, 0.427 mmol), copper (II) acetate (60 mg, 0.330 mmol), triethylamine (0.15 mL, 1.08 mmol) and molecular sieves 4A (90 mg) were added, followed by stirring at room temperature for 1 day under nitrogen atmosphere. The deposit of this reaction solution was Celite filtered. This mother liquor was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=15%-25%) to afford the desired compound (73 mg, yield 62%) as a yellow oil.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.32 (12H, m), 2.57 (3H, s), 3.40 (3H, s), 3.48 (1H, dd, J=10.2, 4.3 Hz), 3.57 (1H, dd, J=10.2, 5.9 Hz), 4.53-4.54 (1H, m), 6.26 (1H, d, J=3.9 Hz), 6.59 (1H, d, J=3.5 Hz), 6.63 (1H, t, J=2.3 Hz), 6.71 (1H, t, J=1.8 Hz), 6.85 (1H, dd, J=2.2, 1.4 Hz), 7.06 (2H, dt, J=9.4, 2.4 Hz), 7.30 (1H, d, J=3.1 Hz), 7.80 (1H, d, J=3.1 Hz), 7.94 (2H, dt, J=9.4, 2.4 Hz).

(39b) 1-(4-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}phenyl)ethanone

t-Butyl 2-{3-(4-acetylphenoxy)-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-5-(1,3-thiazol-2-yl)-1H-pyrrole-1-carboxylate (73 mg, 0.133 mmol) synthesized in Example (39a) was dissolved in dichloromethane (1.0 mL). Trifluoroacetic acid (2.0 mL) was added dropwise with stirring under nitrogen atmosphere, and stirring was carried out at room temperature for

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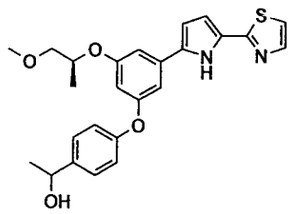
2.5 hours. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=30%-40%) to afford the desired compound (56 mg, yield 94%) as a pale yellow liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J=6.3 Hz), 2.59 (3H, s), 3.42 (3H, s), 3.52 (1H, dd, J=10.3, 3.9 Hz), 3.59 (1H, dd, J=10.3, 5.9 Hz), 4.61-4.68 (1H, m), 6.54-6.59 (2H, m), 6.82 (1H, d, J=2.9 Hz), 6.91 (1H, s), 7.06-7.11 (3H, br m), 7.18-7.20 (1H, br m), 7.68-7.70 (1H, br m), 7.96 (2H, d, J=8.8 Hz), 10.51 (1H, br s).

MS (ESI) m/z: 449.15388 $(M+H)^+$.

(Example 40)

1-(4-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}phenyl)ethanol

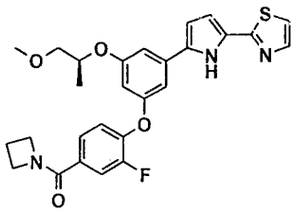


1-(4-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}phenyl)ethanone (30 mg, 0.067 mmol) synthesized in Example (39b) was dissolved in a mixed solvent of tetrahydrofuran (3.0 mL) and methanol (1.0 mL), and sodium borohydride (10 mg, 0.264 mmol) was added, followed by stirring at room temperature for 3 hours under nitrogen atmosphere. To this reaction solution, a saturated aqueous ammonium chloride solution (10 mL) was added, and extraction was carried out with ethyl acetate (10 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=40%-60%) to afford the desired compound (27.5 mg, yield 91%) as a white solid.

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^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J=6.3 Hz), 1.53 (3H, d, J=6.3 Hz), 3.42 (3H, s), 3.49 (1H, dd, J=9.4, 5.1 Hz), 3.59 (1H, dd, J=10.2, 5.9 Hz), 4.52-4.59 (1H, m), 4.92 (1H, q, J=6.3 Hz), 6.47-6.52 (2H, m), 6.72 (1H, t, J=2.7 Hz), 6.92 (1H, s), 7.04 (2H, d, J=8.2 Hz), 7.16 (1H, d, J=3.1 Hz), 7.37 (2H, d, J=9.0 Hz), 7.67 (1H, d, J=3.1 Hz), 9.72 (1H, br s).
MS (ESI) m/z: 451.16915 $(M+H)^+$.

(Example 41)
2-(5-{3-[4-(Azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl-1,3-thiazole



(41a) 1-(3,4-Difluorobenzoyl)azetidine

Commercially available 3,4-difluorobenzoic acid (3.00 g, 19.0 mmol) was dissolved in dichloromethane (50 mL), and N,N-dimethylformamide (0.10 mL) was added, followed by dropwise addition of oxalyl chloride (1.98 mL, 22.8 mmol) and stirring at room temperature overnight under nitrogen atmosphere. The solvent was distilled off under reduced pressure, and the resulting residue was dissolved in dichloromethane (100 mL), and azetidine hydrochloride (2.27 g, 24.2 mmol) and triethylamine (6.60 mL, 47.4 mmol) were added, followed by stirring at room temperature for 4.5 hours under nitrogen atmosphere. 0.5N hydrochloric acid (100 mL) was added, and extraction was carried out with dichloromethane (100 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=40%-50%) to afford the desired compound (600 mg, yield 16%) as a colorless liquid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.37 (2H, m), 4.23 (2H, t, J=7.4 Hz),

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4.32 (2H, t, J=7.4 Hz), 7.20 (1H, m), 7.40 (1H, m), 7.50 (1H, m).

(41b) 2-(5-{3-[4-(Azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl-1,3-thiazole

t-Butyl 2-{3-hydroxy-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-5-(1,3-thiazol-2-yl)-1H-pyrrole-1-carboxylate (70 mg, 0.163 mmol) synthesized in Example (38d) and 1-(3,4-difluorobenzoyl)azetidine (68 mg, 0.345 mmol) synthesized in Example (41a) were dissolved in dimethyl sulfoxide (3.0 mL), and sodium hydride (60%, 25 mg, 0.63 mmol) was added, followed by stirring at 100°C for 5 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, 2N hydrochloric acid (30 mL) was added, and extraction was carried out with diethyl ether (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=60%-80%) to afford the desired compound (54 mg, yield 65%) as a yellow solid.

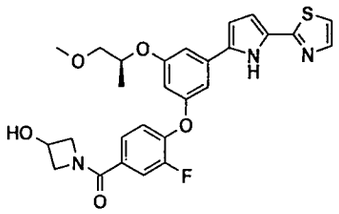
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J=6.3 Hz), 2.38 (2H, m), 3.41 (3H, s), 3.50 (1H, dd, J=3.9, 10.2 Hz), 3.58 (1H, dd, J=6.3, 10.2 Hz), 4.20-4.26 (2H, brs), 4.33-4.40 (2H, brs), 4,57 (1H, m), 6.49-6.52 (2H, m), 6.71 (1H, dd, J=2.4, 3.9 Hz), 6.82 (1H, dd, J=1.6, 2.4 Hz), 6.94 (1H, dd, J=1.6, 2.4 Hz), 7.07 (1H, t, J=8.2 Hz), 7.16 (1H, d, J=3.5 Hz), 7.40 (1H, ddd, J=1.2, 2.4, 8.6 Hz), 7.52 (1H, dd, J=2.0, 11.0 Hz), 7.68 (1H, d, J=3.2 Hz), 9.62 (1H, brs).

MS (ESI) m/z: 508.17094 $(M+H)^+$.

(Example 42)

1-(3-Fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}benzoyl)azetidin-3-ol

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(42a) 1-(3,4-difluorobenzoyl)-3-(tetrahydro-2H-pyran-2-yloxy)azetidine

Commercially available 3,4-difluorobenzoic acid (1.00 g, 6.33 mmol) was dissolved in methanol (10 mL), and 3-hydroxyazetidine hydrochloride (830 mg, 7.58 mmol), 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride n hydrate (2.10 g, 7.59 mmol) and N-methylmorpholine (0.85 mL, 2.83 mmol) were added, followed by stirring at room temperature for 2.5 hours under nitrogen atmosphere. The insolubles were removed by Celite filtration, and the solvent was distilled off under reduced pressure. The resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=50%-70%).

The resulting compound was dissolved in dichloromethane (20 mL), and 3,4-dihydro-2H-pyrane (1.00 mL, 11.1 mmol) and pyridinium p-toluenesulfonate (250 mg, 0.99 mmol) were added, followed by stirring at room temperature overnight under nitrogen atmosphere. To the reaction solution, triethylamine (0.5 mL) was added, the solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=35%-50%) to afford the desired compound (2.24 g, yield ~100%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.48-1.65 (4H, br m), 1.68-1.89 (2H, br m), 3.46-3.55 (2H, br m), 3.83-3.88 (2H, br m), 4.02-4.47 (2H, br m), 4.55-4.66 (2H, br m), 7.18-7.21 (1H, m), 7.38-7.42 (1H, m), 7.47-7.52 (1H, m).

(42b) 2-(5-{3-(2-Fluoro-4-{[3-(tetrahydro-2H-pyran-2-yloxy)azetidin-1-yl]carbonyl}phenoxy)-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole

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t-Butyl 2-{3-hydroxy-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-5-(1,3-thiazol-2-yl)-1H-pyrrole-1-carboxylate (150 mg, 0.348 mmol) synthesized in Example (38d) and 1-(3,4-difluorobenzoyl)-3-(tetrahydro-2H-pyran-2-yloxy)azetidine (220 mg, 0.740 mmol) synthesized in Example (42a) were dissolved in dimethyl sulfoxide (5.0 mL), and sodium hydride (60%, 70 mg, 1.75 mmol) was added, followed by stirring at 100°C for 1.5 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, saturated brine (30 mL) was added, and extraction was carried out with ethyl acetate (30 mL). Subsequently, drying was carried out over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=65%-85%) to afford the desired compound (158 mg, yield 75%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J=6.3 Hz), 1.48-1.90 (6H, m), 3.41 (3H, s), 3.46-3.55 (2H, m), 3.50 (1H, dd, J=10.2, 4.3 Hz), 3.59 (1H, dd, J=10.4, 6.1 Hz), 3.80-3.89 (2H, m), 4.40-4.64 (4H, m), 6.51-6.52 (2H, m), 6.72 (1H, dd, J=3.5, 2.7 Hz), 6.82 (1H, br s), 6.94 (1H, br s), 7.06 (1H, t, J=8.4 Hz), 7.17 (1H, d, J=3.5 Hz), 7.34-7.44 (1H, m), 7.52 (1H, dd, J=10.0, 5.0 Hz), 7.68 (1H, d, J=3.1 Hz), 9.52 (1H, br s).

MS (ESI) m/z: 608.22267 $(M+H)^+$.

(42c) 1-(3-Fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}benzoyl)azetidin-3-ol

2-(5-{3-(2-Fluoro-4-{[3-(tetrahydro-2H-pyran-2-yloxy)azetidin-1-yl]carbonyl}phenoxy)-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole (110 mg, 0.181 mmol) synthesized in Example (42b) was dissolved in methanol (10 mL), and 10-camphorsulfonic acid (20 mg, 0.086 mmol) was added, followed by stirring at room temperature overnight under nitrogen atmosphere. To the reaction solution, triethylamine (0.1 mL) was added, and the solvent was distilled off under reduced pressure. The resulting residue was purified using

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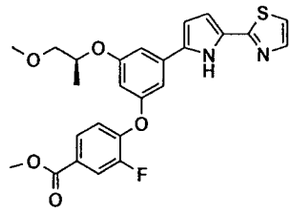
silica gel column chromatography (elution solvent: ethyl acetate/hexane=90%-100%) to afford the desired compound (62 mg, yield 65%) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J=6.3 Hz), 2.28 (1H, br s), 3.41 (3H, s), 3.50 (1H, dd, J=10.4, 4.1 Hz), 3.59 (1H, dd, J=10.2, 5.9 Hz), 4.08 (1H, br s), 4.23 (1H, br s), 4.45-4.58 (2H, m), 4.52-4.60 (1H, m), 4.71-4.80 (2H, m), 6.50-6.53 (2H, m), 6.73 (1H, dd, J=3.5, 2.7 Hz), 6.83 (1H, t, J=1.8 Hz), 6.95-6.97 (1H, m), 7.06 (1H, t, J=8.2 Hz), 7.17 (1H, d, J=3.1 Hz), 7.37-7.40 (1H, m), 7.50-7.53 (1H, m), 7.68 (1H, d, J=3.1 Hz), 9.61 (1H, br s).

MS (ESI) m/z: 524.16841 $(M+H)^+$.

(Example 43)

Methyl 3-fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}benzoate



t-Butyl 2-{3-hydroxy-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-5-(1,3-thiazol-2-yl)-1H-pyrrole-1-carboxylate (485 mg, 1.127 mmol) synthesized in Example (38d) and commercially available methyl 3,4-difluorobenzoate (540 mg, 3.137 mmol) were dissolved in dimethyl sulfoxide (10 mL), and sodium hydride (60%, 180 mg, 4.50 mmol) was added, followed by stirring at 100°C for 2.5 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, water (50 mL) was added, and extraction was carried out with diethyl ether (50 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=10%-30%) to afford the desired compound (97 mg, yield 18%) as a white

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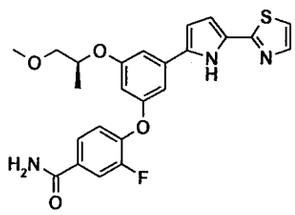
solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J=6.3 Hz), 3.39 (3H, s), 3.48 (1H, dd, J=10.2, 3.9 Hz), 3.57 (1H, dd, J=10.2, 5.9 Hz), 3.91 (3H, s), 4.51-4.59 (1H, m), 6.49-6.52 (2H, m), 6.71 (1H, dd, J=3.9, 2.3 Hz), 6.82-6.85 (1H, br m), 6.98 (1H, br s), 7.05 (1H, t, J=8.2 Hz), 7.15 (1H, d, J=3.1 Hz), 7.66 (1H, d, J=3.1 Hz), 7.78 (1H, d, J=9.8 Hz), 7.85 (1H, dd, J=11.1, 2.2 Hz), 9.78-9.87 (1H, m).

MS (ESI) m/z: 483.13782 $(M+H)^+$.

(Example 44)

3-Fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}benzamide



(44a) 3-Fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}benzoic acid

Methyl 3-fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}benzoate (611 mg, 1.42 mmol) synthesized in Example 43 was dissolved in methanol (18 mL), and water (3 mL) and lithium hydroxide monohydrate (298 mg, 7.10 mmol) were added, followed by stirring at 60°C for 4 hours under nitrogen atmosphere. To the reaction solution, water (50 mL) was added, and extraction was carried out twice with ethyl acetate (40 mL), followed by drying over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=30%-75%) to afford the desired compound (519 mg, yield 88%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.38 (3H, d, J=6.3 Hz), 3.45 (3H, s), 3.55 (1H, dd, J=10.2, 4.3 Hz), 3.64 (1H, dd, J=10.2, 5.9 Hz), 4.60-4.67 (1H, m), 6.63 (1H, dd, J=3.9, 2.7 Hz), 6.74 (1H, t,

J=2.2 Hz), 6.84 (1H, dd, J=3.9, 2.3 Hz), 6.99 (1H, t, J=8.2 Hz), 7.16-7.14 (2H, m), 7.41 (1H, t, J=1.8 Hz), 7.55 (1H, dt, J=8.6, 1.0 Hz), 7.61 (1H, d, J=3.1 Hz), 7.72 (1H, dd, J=10.6, 2.0 Hz), 11.85 (1H, s).

(44b) 3-Fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}benzamide

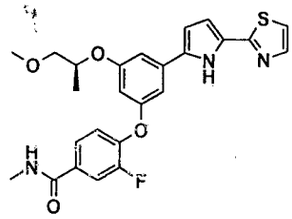
3-Fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}benzoic acid (40.0 mg, 0.163 mmol) synthesized in Example (44a) was dissolved in dichloromethane (5 mL), and 28% aqueous ammonia solution (0.50 mL), WSCI·HCl (19.6 mg, 0.102 mmol) and HOBt·H_2O (13.1 mg, 0.086 mmol) were added, followed by stirring at room temperature for 7 hours under nitrogen atmosphere. To the reaction solution, water (10 mL) was added, and extraction was carried out with ethyl acetate (20 mL). The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-75%) to afford the desired compound (11.3 mg, yield 28%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J=6.3 Hz), 3.42 (3H, s), 3.51 (1H, dd, J=10.3, 5.4 Hz), 3.59 (1H, dd, J=10.3, 5.9 Hz), 4.54-4.61 (1H, m), 6.51-6.54 (2H, m), 6.73 (1H, dd, J=3.4, 2.4 Hz), 6.84 (1H, s), 6.97 (1H, s), 7.09 (1H, t, J=8.1 Hz), 7.18 (1H, d, J=2.9 Hz), 7.53 (1H, d, J=8.8 Hz), 7.67-7.73 (2H, m), 9.60 (1H, br s).

MS (ESI) m/z: 468.13800 $(M+H)^+$.

(Example 45)

3-Fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}-N-methylbenzamide



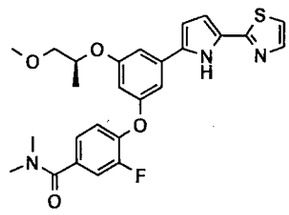
3-Fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}benzoic acid (40.0 mg, 0.163 mmol) synthesized in Example (44a) was dissolved in tetrahydrofuran (5 mL), and methylamine hydrochloride (17.3 mg, 0.256 mmol), HATU (64.5 mg, 0.170 mmol) and N,N-diisopropylethylamine (89 μL, 0.51 mmol) were added, followed by stirring at room temperature for 4 hours under nitrogen atmosphere. To the reaction solution, saturated brine (15 mL) was added, and extraction was carried out twice with ethyl acetate (15 mL), followed by drying over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-55%) to afford the desired compound (41 mg, yield ~100%) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J=6.3 Hz), 3.03 (3H, d, J=4.7 Hz), 3.41 (3H, s), 3.50 (1H, dd, J=10.2, 3.9 Hz), 3.58 (1H, dd, J=10.2, 6.3 Hz), 4.52-4.60 (1H, m), 6.49-6.53 (2H, m), 6.72 (1H, dd, J=3.9, 2.3 Hz), 6.79 (1H, t, J=2.0 Hz), 6.94 (1H, t, J=2.0 Hz), 7.08 (1H, t, J=8.0 Hz), 7.17 (1H, d, J=3.5 Hz), 7.47 (1H, d, J=8.6 Hz), 7.65 (1H, dd, J=10.9, 2.0 Hz), 7.68 (1H, d, J=3.9 Hz), 9.48 (1H, br s).

MS (ESI) m/z: 482.15436 $(M+H)^+$.

(Example 46)

3-Fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}-N,N-dimethylbenzamide



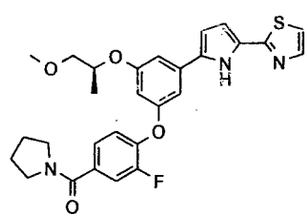
3-Fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}benzoic acid (40.0 mg, 0.163 mmol) synthesized in Example (44a) was dissolved in tetrahydrofuran (5 mL), and dimethylamine hydrochloride (20.1 mg, 0.246 mmol), HATU (64.5 mg, 0.170 mmol) and N,N-diisopropylethylamine (89 µL, 0.51 mmol) were added, followed by stirring at room temperature for 4 hours under nitrogen atmosphere. To the reaction solution, saturated brine (15 mL) was added, and extraction was carried out twice with ethyl acetate (15 mL), followed by drying over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-75%) to afford the desired compound (45 mg, yield 99%) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J=6.3 Hz), 3.02-3.14 (6H, br m), 3.41 (3H, s), 3.50 (1H, dd, J=10.2, 3.9 Hz), 3.58 (1H, dd, J=10.2, 5.9 Hz), 4.52-4.61 (1H, m), 6.49-6.54 (2H, m), 6.73 (1H, dd, J=3.7, 1.9 Hz), 6.85 (1H, t, J=1.6 Hz), 6.95 (1H, t, J=1.6 Hz), 7.08 (1H, t, J=8.0 Hz), 7.16-7.20 (2H, m), 7.29 (1H, dd, J=10.8, 1.8 Hz), 7.68 (1H, d, J=3.1 Hz), 9.65 (1H, br s).

MS (ESI) m/z: 496.17025 $(M+H)^+$.

(Example 47)

2-(5-{3-[2-Fluoro-4-(pyrrolidin-1-ylcarbonyl)phenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole



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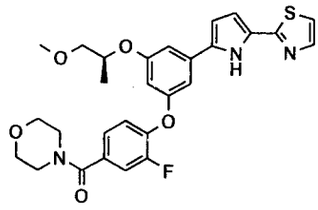
3-Fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}benzoic acid (40.0 mg, 0.085 mmol) synthesized in Example (44a) was dissolved in tetrahydrofuran (5 mL), and pyrrolidine (21 μL, 0.26 mmol), HATU (64.9 mg, 0.171 mmol) and N,N-diisopropylethylamine (89 μL, 0.51 mmol) were added, followed by stirring at room temperature for 20 hours under nitrogen atmosphere. To the reaction solution, saturated brine (15 mL) was added, and extraction was carried out twice with ethyl acetate (15 mL), followed by drying over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-75%) to afford the desired compound (32 mg, yield 72%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.29 (3H, d, J=6.3 Hz), 1.84-1.98 (4H, m), 3.38 (3H, s), 3.41-3.49 (3H, m), 3.55 (1H, dd, J=10.2, 5.9 Hz), 3.61 (2H, t, J=6.8 Hz), 4.48-4.56 (1H, m), 6.46-6.49 (2H, m), 6.68 (1H, dd, J=3.9, 2.7 Hz), 6.78 (1H, t, J=1.8 Hz), 6.89 (1H, t, J=2.0 Hz), 7.04 (1H, t, J=8.2 Hz), 7.13 (1H, d, J=3.1 Hz), 7.25-7.29 (1H, m), 7.38 (1H, dd, J=10.9, 2.0 Hz), 7.64 (1H, d, J=3.5 Hz), 9.51 (1H, br s).

MS (ESI) m/z: 522.18695 $(M+H)^+$.

(Example 48)

4-(3-Fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}benzoyl)morpholine



3-Fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}benzoic acid (49.0 mg, 0.105 mmol) synthesized in Example (44a) was dissolved in tetrahydrofuran (5 mL), and morpholine (22 μL, 0.26 mmol), HATU (64.5 mg, 0.170 mmol) and N,N-diisopropylethylamine (89 μL, 0.51

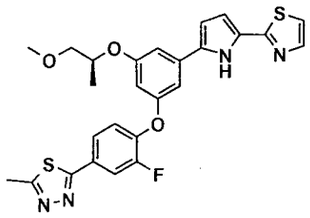
mmol) were added, followed by stirring at room temperature for 4 hours under nitrogen atmosphere. To the reaction solution, saturated brine (15 mL) was added, and extraction was carried out twice with ethyl acetate (15 mL), followed by drying over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-75%) to afford the desired compound (39 mg, yield 70%) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J=6.3 Hz), 3.42 (3H, s), 3.51 (1H, dd, J=10.2, 4.3 Hz), 3.59 (1H, dd, J=10.2, 5.9 Hz), 3.72 (8H, br s), 4.52-4.61 (1H, m), 6.49-6.54 (2H, m), 6.72 (1H, dd, J=3.7, 2.5 Hz), 6.82 (1H, t, J=1.8 Hz), 6.93 (1H, t, J=1.8 Hz), 7.09 (1H, t, J=8.2 Hz), 7.16-7.19 (2H, m), 7.30 (1H, dd, J=10.6, 2.0 Hz), 7.69 (1H, d, J=3.1 Hz), 9.45 (1H, br s).

MS (ESI) m/z: 538.18048 $(M+H)^+$.

(Example 49)

2-(3-Fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}phenyl)-5-methyl-1,3,4-thiadiazole



(49a) N'-Acetyl-3-fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}benzohydrazide

3-Fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}benzoic acid (84 mg, 0.179 mmol) synthesized in Example (44a) was dissolved in dichloromethane (5.0 mL), and acetohydrazide (40 mg, 0.540 mmol), HATU (200 mg, 0.526 mmol) and N,N-diisopropylethylamine (0.15 mL, 0.861 mmol) were added, followed by stirring at room temperature overnight under nitrogen atmosphere. The solvent was distilled off under reduced pressure, and the resulting residue was

purified using silica gel column chromatography (elution solvent: ethyl acetate) to afford the desired compound (110 mg, yield ~100%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.44 (3/2H, d, J=6.3 Hz), 1.49 (3/2H, d, J=6.3 Hz), 2.05 (3H, s), 3.46 (3H, s), 3.55 (1H, dd, J=10.8, 4.1 Hz), 3.65 (1H, dd, J=10.0, 6.1 Hz), 4.58-4.69 (1H, m), 6.69 (1H, d, J=2.3 Hz), 6.73 (1H, s), 6.77 (1H, d, J=2.7 Hz), 7.12 (1H, br s), 7.16 (1H, br s), 7.29 (1H, br s), 7.34 (1H, br s), 7.37 (1H, br s), 7.45 (1H, d, J=8.2 Hz), 7.62 (1H, br s), 11.51 (1H, br s), 11.79 (1H, br s), 12.56 (1H, br s).

MS (ESI) m/z: 547.14358 $(M+Na)^+$.

(49b) 2-(3-Fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}phenyl)-5-methyl-1,3,4-thiadiazole

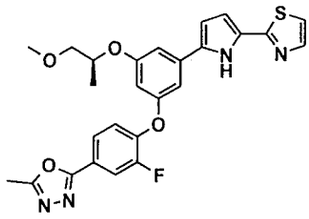
N'-Acetyl-3-fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}benzohydrazide (40 mg, 0.076 mmol) synthesized in Example (49a) was dissolved in a mixed solvent of toluene (4.0 mL) and acetonitrile (2.0 mL), and 2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (45 mg, 0.111 mmol) and pyridine (0.03 mL, 0.372 mmol) were added, followed by stirring at 100°C for 4 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, the solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=60%-80%) to afford the desired compound (28 mg, yield 70%) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J=6.3 Hz), 2.83 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J=10.3, 4.4 Hz), 3.60 (1H, dd, J=10.3, 5.9 Hz), 4.57-4.63 (1H, m), 6.54-6.54 (2H, m), 6.77 (1H, s), 6.87 (1H, s), 7.00 (1H, s), 7.14-7.17 (2H, m), 7.64 (1H, dd, J=8.3, 1.0 Hz), 7.68 (1H, d, J=3.4 Hz), 7.84 (1H, dd, J=11.2, 2.0 Hz), 10.01 (1H, br s).

MS (ESI) m/z: 523.12785 $(M+H)^+$.

(Example 50)

2-(3-Fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}phenyl)-5-methyl-1,3,4-oxadiazole



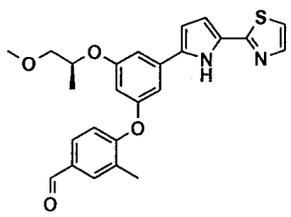
N'-Acetyl-3-fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}benzohydrazide (45 mg, 0.086 mmol) synthesized in Example (49a) was dissolved in acetonitrile (3.0 mL), and (methoxycarbonysulfamoyl)triethylammonium hydroxide (50 mg, 0.210 mmol) and triethylamine (0.05 mL, 0.359 mmol) were added, followed by stirring at 100°C for 1 day under nitrogen atmosphere. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=80%-100%) to afford the desired compound (26 mg, yield 60%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J=6.3 Hz), 2.63 (3H, s), 3.42 (3H, s), 3.50 (1H, dd, J=10.2, 4.3 Hz), 3.60 (1H, dd, J=10.2, 5.9 Hz), 4.54-4.62 (1H, m), 6.50-6.55 (2H, m), 6.72 (1H, dd, J=3.5, 2.0 Hz), 6.86 (1H, s), 6.99 (1H, s), 7.12-7.19 (2H, m), 7.67 (1H, d, J=3.1 Hz), 7.78 (1H, d, J=9.0 Hz), 7.87 (1H, dd, J=10.8, 1.4 Hz), 9.94 (1H, br s).

MS (ESI) m/z: 507.14909 $(M+H)^+$.

(Example 51)

4-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}-3-methylbenzaldehyde



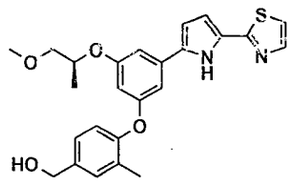
t-Butyl 2-{3-hydroxy-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-5-(1,3-thiazol-2-yl)-1H-pyrrole-1-carboxylate (150 mg, 0.348 mmol) synthesized in Example (38d) and commercially available 4-fluoro-3-methylbenzaldehyde (0.14 mL, 1.148 mmol) were dissolved in dimethyl sulfoxide (5.0 mL), and sodium hydride (60%, 40 mg, 1.00 mmol) was added, followed by stirring at 100°C for 4 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, a saturated aqueous ammonium chloride solution (30 mL) was added, and extraction was carried out with diethyl ether (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=25%-30%) to afford the desired compound (84 mg, yield 54%) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J=6.3 Hz), 2.39 (3H, s), 3.42 (3H, s), 3.50 (1H, dd, J=10.2, 3.9 Hz), 3.60 (1H, dd, J=10.4, 6.1 Hz), 4.55-4.64 (1H, m), 6.50 (1H, t, J=2.2 Hz), 6.53 (1H, dd, J=3.7, 2.9 Hz), 6.74 (1H, t, J=2.5 Hz), 6.83 (1H, t, J=2.0 Hz), 6.96 (1H, d, J=8.2 Hz), 7.00-7.02 (1H, m), 7.17 (1H, d, J=3.1 Hz), 7.65 (1H, d, J=2.3 Hz), 7.68 (1H, d, J=3.1 Hz), 7.81 (1H, d, J=1.2 Hz), 9.90 (1H, br s), 9.92 (1H, s).

MS (ESI) m/z: 449.15343 $(M+H)^+$.

(Example 52)

(4-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}-3-methylphenyl)methanol



4-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}-3-methylbenzaldehyde (32 mg, 0.071 mmol) synthesized in Example 51 was dissolved in methanol (3.0 mL), and sodium borohydride (5 mg, 0.132 mmol) was added, followed by stirring at 0°C for 4 hours under nitrogen atmosphere. The reaction solution was brought to room temperature, a saturated aqueous ammonium chloride solution (10 mL) was added, and extraction was carried out with ethyl acetate (10 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=50%-75%) to afford the desired compound (26 mg, yield 81%) as a white solid.

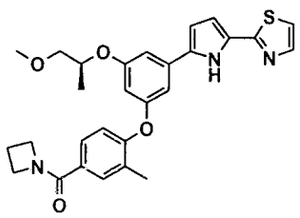
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J=6.3 Hz), 2.26 (3H, s), 3.41 (3H, s), 3.49 (1H, dd, J=10.2, 4.3 Hz), 3.58 (1H, dd, J=10.2, 5.9 Hz), 4.51-4.60 (1H, m), 4.67 (2H, br s), 6.40 (1H, t, J=2.2 Hz), 6.49 (1H, dd, J=3.5, 2.7 Hz), 6.70-6.72 (2H, m), 6.86 (1H, dd, J=3.5, 1.6 Hz), 6.96 (1H, d, J=8.2 Hz), 7.15 (1H, d, J=3.5 Hz), 7.19 (1H, dd, J=8.2, 2.0 Hz), 7.28 (1H, d, J=2.3 Hz), 7.66 (1H, d, J=3.5 Hz), 9.72 (1H, br s).

MS (ESI) m/z: 451.16757 $(M+H)^+$.

(Example 53)

2-(5-{3-[4-(Azetidin-1-ylcarbonyl)-2-methylphenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole

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(53a) 4-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}-3-methylbenzoic acid

4-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}-3-methylbenzaldehyde (50 mg, 0.11 mmol) synthesized in Example 51 was dissolved in a mixed solvent of t-butanol (5.0 mL) and water (2.0 mL), and 2-methyl-2-butene (0.15 mL, 1.42 mmol) and sodium dihydrogen phosphate dihydrate (80 mg, 0.51 mmol) were added, followed by slow addition of sodium chlorite (25 mg, 0.28 mmol) at 0°C and stirring at 0°C for 2 hours under nitrogen atmosphere. An aqueous sodium hydrogen sulfite solution (5 mL) was added at 0°C, and stirring was carried out at room temperature for 10 minutes. An aqueous sodium hydrogen sulfite solution (15 mL) was added, and extraction was carried out with ethyl acetate (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure to afford the desired compound (58 mg, yield ~100%) as a yellow solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J=6.3 Hz), 2.33 (3H, s), 3.41 (3H, s), 3.52 (1H, dd, J=10.6, 4.3 Hz), 3.60 (1H, dd, J=10.2, 5.9 Hz), 4.62-4.71 (1H, m), 6.54-6.57 (2H, m), 6.85-6.87 (2H, m), 7.08-7.16 (2H, m), 7.15 (1H, d, J=3.5 Hz), 7.64 (1H, s), 7.64 (1H, d, J=3.5 Hz), 7.87 (1H, s).

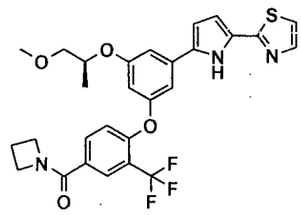
(53b) 2-(5-{3-[4-(Azetidin-1-ylcarbonyl)-2-methylphenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole

4-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}-3-methylbenzoic acid (58 mg, 0.125 mmol) synthesized in Example (53a) and azetidine hydrochloride (29 mg, 0.310 mmol) were dissolved in dichloromethane (10.0 mL),

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and HATU (95 mg, 0.250 mmol) and N,N-diisopropylethylamine (0.15 mL, 0.861 mmol) were added, followed by stirring at room temperature overnight under nitrogen atmosphere. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=75%-90%) to afford the desired compound (58 mg, yield 92%) as a yellow solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J=6.3 Hz), 2.30 (3H, s), 2.31-2.39 (2H, m), 3.41 (3H, s), 3.49 (1H, dd, J=10.4, 4.1 Hz), 3.59 (1H, dd, J=10.2, 5.9 Hz), 4.22-4.25 (2H, br m), 4.33-4.36 (2H, br m), 4.52-4.60 (1H, m), 6.43 (1H, t, J=2.3 Hz), 6.50 (1H, dd, J=3.7, 2.9 Hz), 6.72 (1H, dd, J=3.9, 2.3 Hz), 6.76 (1H, t, J=1.8 Hz), 6.90 (1H, s), 6.92-6.93 (1H, m), 7.16 (1H, d, J=3.1 Hz), 7.42 (1H, dd, J=8.2, 2.0 Hz), 7.59 (1H, d, J=1.6 Hz), 7.67 (1H, d, J=3.1 Hz), 9.73 (1H, br s).
MS (ESI) m/z: 504.19979 $(M+H)^+$.

(Example 54)
2-(5-{3-[4-(Azetidin-1-ylcarbonyl)-2-(trifluoromethyl)phenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole



(54a) 1-[4-Fluoro-3-(trifluoromethyl)benzoyl]azetidine

Commercially available 4-fluoro-3-(trifluoromethyl)benzoic acid (230 mg, 1.10 mmol) was dissolved in dichloromethane (50 mL), and azetidine hydrochloride (120 mg, 1.28 mmol), HATU (550 mg, 1.45 mmol) and N,N-diisopropylethylamine (0.50 mL, 2.87 mmol) were added, followed by stirring at room temperature for 4 hours under nitrogen atmosphere. 0.5N hydrochloric acid (100 mL) was added, and extraction was carried out with dichloromethane (100 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium

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sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=60%-80%) to afford the desired compound (211 mg, yield 78%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.35-2.43 (2H, m), 4.25 (2H, t, J=7.6 Hz), 4.33 (2H, t, J=7.4 Hz), 7.83-7.87 (1H, m), 7.93 (1H, dd, J=6.6, 2.0 Hz).

(54b) 2-(5-{3-[4-(Azetidin-1-ylcarbonyl)-2-(trifluoromethyl)phenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole

t-Butyl 2-{3-hydroxy-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-5-(1,3-thiazol-2-yl)-1H-pyrrole-1-carboxylate (119 mg, 0.276 mmol) synthesized in Example (38d) and 1-[4-fluoro-3-(trifluoromethyl)benzoyl]azetidine (145 mg, 0.587 mmol) synthesized in Example (54a) were dissolved in dimethyl sulfoxide (8.0 mL), and sodium hydride (60%, 39 mg, 0.97 mmol) was added, followed by stirring at 100°C for 2 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, a saturated aqueous ammonium chloride solution (30 mL) was added, and extraction was carried out with ethyl acetate (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=45%-60%) to afford the desired compound (105 mg, yield 68%) as a yellow solid.

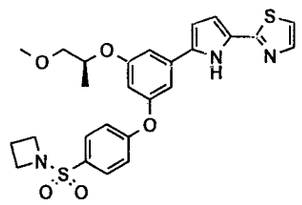
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J=6.3 Hz), 2.34-2.42 (2H, m), 3.42 (3H, s), 3.50 (1H, dd, J=10.2, 4.3 Hz), 3.60 (1H, dd, J=10.2, 5.9 Hz), 4.25 (2H, t, J=6.8 Hz), 4.36 (2H, t, J=6.6 Hz), 4.56-4.60 (1H, m), 6.54-6.55 (2H, m), 6.73 (1H, dd, J=3.7, 2.5 Hz), 6.87 (1H, t, J=1.6 Hz), 6.99 (1H, d, J=8.6 Hz), 7.03 (1H, t, J=1.8 Hz), 7.17 (1H, d, J=3.1 Hz), 7.68 (1H, d, J=3.1 Hz), 7.74 (1H, dd, J=8.6, 2.3 Hz), 8.00 (1H, d, J=2.0 Hz), 9.73 (1H, br s).

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MS (ESI) m/z: 558.16727 $(M+H)^+$.

(Example 55)

2-(5-{3-[4-(Azetidin-1-ylsulfonyl)phenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole



(55a) 1-[(4-Fluorophenyl)sulfonyl]azetidine

Commercially available 4-fluorophenylsulfonylchloride (225 mg, 1.15 mmol) was suspended in water (8 mL), and azetidine hydrochloride (90.0 mg, 0.96 mmol) and potassium carbonate (293 mg, 2.12 mmol) were added, followed by stirring at room temperature for 16 hours. To the reaction solution, water (15 mL) was added, followed by extraction twice with diethyl ether (15 mL), and washing was carried out with saturated brine (15 mL), followed by drying over sodium sulfate. The solvent was distilled off under reduced pressure, followed by vacuum drying, to afford the desired compound (170 mg, yield 82%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.10-2.17 (2H, m), 3.82 (4H, t, J=7.8 Hz), 7.28-7.30 (2H, m), 7.88-7.92 (2H, m).

(55b) 2-(5-{3-[4-(Azetidin-1-ylsulfonyl)phenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole

t-Butyl 2-{3-hydroxy-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-5-(1,3-thiazol-2-yl)-1H-pyrrole-1-carboxylate (60.0 mg, 0.139 mmol) synthesized in Example (38d) and 1-[(4-fluorophenyl)sulfonyl]azetidine (60.0 mg, 0.279 mmol) synthesized in Example (55a) were dissolved in N-methylpyrrolidone (5.0 mL), and sodium hydride (60%, 24 mg, 0.60 mmol) was added, followed by stirring at 100°C for 6 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, water (20 mL) was added, and extraction was carried

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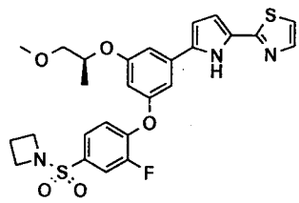
out with ethyl acetate (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-35%) to afford the desired compound (42 mg, yield 57%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.37 (3H, d, J=6.8 Hz), 2.12-2.18 (2H, m), 3.45 (3H, s), 3.54 (1H, dd, J=10.3, 4.4 Hz), 3.64 (1H, dd, J=10.0, 6.1 Hz), 3.83 (4H, t, J=7.6 Hz), 4.59-4.65 (1H, m), 6.57 (1H, t, J=3.4 Hz), 6.60 (1H, t, J=2.0 Hz), 6.76 (1H, t, J=3.7 Hz), 6.92 (1H, s), 7.07 (1H, s), 7.18 (2H, d, J=8.3 Hz), 7.21 (1H, d, J=2.9 Hz), 7.71 (1H, d, J=2.9 Hz), 7.84 (2H, d, J=8.8 Hz), 9.76 (1H, br s).

MS (ESI) m/z: 526.14773 $(M+H)^+$.

(Example 56)

2-(5-{3-[4-(Azetidin-1-ylsulfonyl)-2-fluorophenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole



(56a) 1-[(3,4-Difluorophenyl)sulfonyl]azetidine

Commercially available 3,4-difluorophenylsulfonylchloride (117 μL, 0.87 mmol) was dissolved in dichloromethane (5 mL), and azetidine hydrochloride (68 mg, 0.73 mmol) and triethylamine (203 μL, 1.45 mmol) were added, followed by stirring at room temperature for 2 hours. To the reaction solution, water (15 mL) was added, and extraction was carried out twice with dichloromethane (15 mL). Washing was carried out with saturated brine (15 mL), followed by drying over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=10%-50%)

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to afford the desired compound (132 mg, yield 78%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.10-2.18 (2H, m), 3.82 (4H, t, J=7.6 Hz), 7.35-7.41 (1H, m), 7.66-7.62 (1H, m), 7.72-7.68 (1H, m).

(56b) 2-(5-{3-[4-(Azetidin-1-ylsulfonyl)-2-fluorophenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl)-1,3-thiazole

t-Butyl 2-{3-hydroxy-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-5-(1,3-thiazol-2-yl)-1H-pyrrole-1-carboxylate (65.0 mg, 0.151 mmol) synthesized in Example (38d) and 1-[(3,4-difluorophenyl)sulfonyl]azetidine (42.3 mg, 0.181 mmol) synthesized in Example (56a) were dissolved in N-methylpyrrolidone (5.0 mL), and sodium hydride (55%, 20 mg, 0.45 mmol) was added, followed by stirring at 100°C for 4 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, a saturated aqueous ammonium chloride solution (20 mL) was added, and extraction was carried out with ethyl acetate (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified twice using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-35%) to afford the desired compound (35.6 mg, yield 43%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J=6.3 Hz), 2.11-2.20 (2H, m), 3.42 (3H, s), 3.51 (1H, dd, J=10.4, 4.1 Hz), 3.60 (1H, dd, J=10.4, 6.1 Hz), 3.84 (4H, t, J=7.6 Hz), 4.55-4.63 (1H, m), 6.53-6.56 (2H, m), 6.73 (1H, dd, J=3.9, 2.3 Hz), 6.89 (1H, t, J=2.0 Hz), 7.03 (1H, t, J=1.8 Hz), 7.14 (1H, t, J=8.0 Hz), 7.18 (1H, d, J=3.5 Hz), 7.57 (1H, d, J=8.6 Hz), 7.67-7.71 (2H, m), 9.79 (1H, br s).

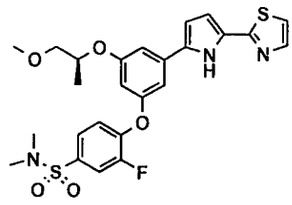
MS (ESI) m/z: 544.13720 $(M+H)^+$.

(Example 57)

3-Fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-

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2-yl)-1H-pyrrol-2-yl]phenoxy}-N,N-dimethylbenzenesulfonamide



(57a) 3,4-Difluoro-N,N-dimethylbenzenesulfonamide

Commercially available 3,4-difluorophenylsulfonylchloride (117 μL, 0.87 mmol) was dissolved in dichloromethane (5 mL), and dimethylamine hydrochloride (59 mg, 0.73 mmol) and triethylamine (203 μL, 1.45 mmol) were added, followed by stirring at room temperature for 2 hours. To the reaction solution, water (15 mL) was added, followed by extraction twice with dichloromethane (15 mL), and washing was carried out with saturated brine (15 mL), followed by drying over sodium sulfate. The solvent was distilled off under reduced presure, followed by vacuum drying, to afford the desired compound (41.0 mg, yield 26%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.74 (6H, s), 7.32-7.38 (1H, m), 7.59-7.55 (1H, m), 7.61-7.66 (1H, m).

(57b) 3-Fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}-N,N-dimethylbenzenesulfonamide

t-Butyl 2-{3-hydroxy-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-5-(1,3-thiazol-2-yl)-1H-pyrrole-1-carboxylate (65.0 mg, 0.151 mmol) synthesized in Example (38d) and 3,4-difluoro-N,N-dimethylbenzenesulfonamide (40.1 mg, 0.181 mmol) synthesized in Example (57a) were dissolved in N-methylpyrrolidone (5.0 mL), and sodium hydride (55%, 20 mg, 0.45 mmol) was added, followed by stirring at 100°C for 4 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, a saturated aqueous ammonium chloride solution (20 mL) was added, and extraction was carried out with ethyl acetate (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The

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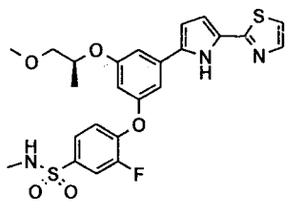
solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-35%) to afford the desired compound (31.0 mg, yield 39%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J=6.3 Hz), 2.76 (6H, s), 3.42 (3H, s), 3.51 (1H, dd, J=10.4, 4.1 Hz), 3.60 (1H, dd, J=10.4, 6.1 Hz), 4.55-4.62 (1H, m), 6.53-6.55 (2H, m), 6.73 (1H, dd, J=3.7, 2.5 Hz), 6.87 (1H, t, J=1.8 Hz), 7.02 (1H, t, J=1.8 Hz), 7.12 (1H, t, J=8.0 Hz), 7.18 (1H, d, J=3.5 Hz), 7.52-7.49 (1H, m), 7.63 (1H, dd, J=9.8, 2.0 Hz), 7.68 (1H, d, J=3.1 Hz), 9.79 (1H, s).

MS (ESI) m/z: 532.13886 $(M+H)^+$.

(Example 58)

3-Fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}-N-methylbenzenesulfonamide



(58a) 3,4-Difluoro-N-methylbenzenesulfonamide

Commercially available 3,4-difluorophenylsulfonylchloride (117 μL, 0.87 mmol) was dissolved in dichloromethane (5 mL), and methylamine hydrochloride (49 mg, 0.73 mmol) and triethylamine (203 μL, 1.45 mmol) were added, followed by stirring at room temperature for 2 hours. To the reaction solution, water (15 mL) was added, extraction was carried out twice with dichloromethane (15 mL), and washing was carried out with saturated brine (15 mL), followed by drying over sodium sulfate. The solvent was distilled off under reduced presure, followed by vacuum drying, to afford the desired compound (44.7 mg, yield 30%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.70 (3H, d, J=5.5 Hz), 4.43 (1H, br s), 7.36-7.30 (1H, m), 7.64-7.68 (1H, m), 7.69-7.74 (1H, m).

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(58b) 3-Fluoro-4-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}-N-methylbenzenesulfonamide

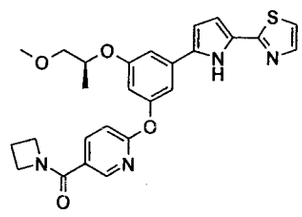
t-Butyl 2-{3-hydroxy-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-5-(1,3-thiazol-2-yl)-1H-pyrrole-1-carboxylate (60.0 mg, 0.139 mmol) synthesized in Example (38d) and 3,4-difluoro-N-methylbenzenesulfonamide (47.4 mg, 0.229 mmol) synthesized in Example (58a) were dissolved in N,N-dimethylformamide (5.0 mL), and potassium carbonate (77.0 mg, 0.557 mmol) was added, followed by stirring at 100°C for 19 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, water (20 mL) was added, and extraction was carried out with ethyl acetate (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-25%) to afford the desired compound (21.1 mg, yield 30%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (4H, d, J=5.9 Hz), 2.69 (3H, d, J=5.4 Hz), 3.42 (3H, s), 3.51 (1H, dd, J=10.3, 4.4 Hz), 3.60 (1H, dd, J=10.3, 5.9 Hz), 4.55-4.61 (1H, m), 5.22 (1H, s), 6.55 (2H, dt, J=8.3, 2.7 Hz), 6.74 (1H, t, J=2.9 Hz), 6.89 (1H, s), 7.01 (1H, t, J=1.7 Hz), 7.12 (1H, t, J=8.1 Hz), 7.16-7.18 (1H, m), 7.56-7.61 (2H, m), 7.69 (1H, d, J=9.8 Hz), 9.96 (1H, br s).

MS (ESI) m/z: 518.12006 $(M+H)^+$.

(Example 59)

5-(Azetidin-1-ylcarbonyl)-2-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}pyridine



(59a) 5-(Azetidin-1-ylcarbonyl)-2-chloropyridine

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Commercially available 6-chloronicotinic acid (160 mg, 1.01 mmol) was dissolved in dichloromethane (5 mL), and azetidine hydrochloride (130 mg, 1.39 mmol), HATU (420 mg, 1.10 mmol) and N,N-diisopropylethylamine (0.50 mL, 2.87 mmol) were added, followed by stirring at room temperature overnight under nitrogen atmosphere. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=40%-50%) to afford the desired compound (210 mg, yield ~100%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.40 (2H, m), 4.25 (2H, t, J=7.6 Hz), 4.35 (2H, t, J=7.6 Hz), 7.40 (1H, dd, J=0.8, 8.6 Hz), 7.97 (1H, dd, J=2.4, 8.2 Hz), 8.62 (1H, dd, J=0.8, 2.4 Hz).

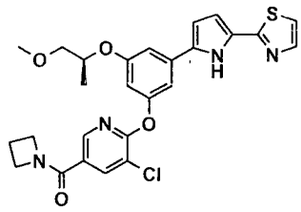
(59b) 5-(Azetidin-1-ylcarbonyl)-2-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}pyridine

t-Butyl 2-{3-hydroxy-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-5-(1,3-thiazol-2-yl)-1H-pyrrole-1-carboxylate (84 mg, 0.195 mmol) synthesized in Example (38d) and 5-(azetidin-1-ylcarbonyl)-2-chloropyridine (110 mg, 0.559 mmol) synthesized in Example (59a) were dissolved in dimethyl sulfoxide (3.0 mL), and sodium hydride (60%, 30 mg, 0.75 mmol) was added, followed by stirring at 100°C for 2 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, 2N hydrochloric acid (30 mL) was added, and extraction was carried out with ethyl acetate (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=75%-90%) to afford the desired compound (56 mg, yield 59%) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J=6.3 Hz), 2.38 (2H, m), 3.42 (3H, s), 3.50 (1H, dd, J=4.3, 10.2 Hz), 3.60 (1H, dd, J=5.9, 10.2 Hz), 4.24 (2H, t, J=7.4 Hz), 4.36 (2H, t, J=6.6 Hz), 4,57

(1H, m), 6.54 (1H, dd, J=2.7, 3.9 Hz), 6.64 (1H, t, J=2.3 Hz), 6.73 (1H, dd, J=2.4, 3.9 Hz), 6.97 (2H, m), 7.07 (1H, t, J=1.8 Hz), 7.16 (1H, d, J=3.5 Hz), 7.67 (1H, d, J=3.1 Hz), 8.07 (1H, dd, J=2.7, 8.6 Hz), 8.45 (1H, d, J=2.4 Hz), 9.85 (1H, brs).
MS (ESI) m/z: 491.17450 $(M+H)^+$.

(Example 60)
5-(Azetidin-1-ylcarbonyl)-3-chloro-2-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}pyridine



(60a) 5-(Azetidin-1-ylcarbonyl)-2,3-dichloropyridine

Commercially available 5,6-dichloronicotinic acid (200 mg, 1.04 mmol) was dissolved in dichloromethane (5.0 mL), and azetidine hydrochloride (125 mg, 1.34 mmol), HATU (440 mg, 1.16 mmol) and N,N-diisopropylethylamine (0.45 mL, 2.58 mmol) were added, followed by stirring at room temperature for 5 hours under nitrogen atmosphere. 0.5N hydrochloric acid (30 mL) was added, and extraction was carried out with dichloromethane (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=60%-80%) to afford the desired compound (162 mg, yield 67%) as a colorless liquid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.38-2.46 (2H, m), 4.25 (2H, t, J=7.6 Hz), 4.37 (2H, t, J=7.6 Hz), 8.10 (1H, d, J=2.3 Hz), 8.51 (1H, d, J=2.3 Hz).

(60b) 5-(Azetidin-1-ylcarbonyl)-3-chloro-2-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-

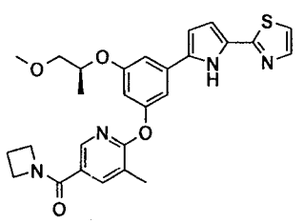
yl]phenoxy}pyridine

t-Butyl 2-{3-hydroxy-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-5-(1,3-thiazol-2-yl)-1H-pyrrole-1-carboxylate (70 mg, 0.163 mmol) synthesized in Example (38d) and 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine (75 mg, 0.325 mmol) synthesized in Example (60a) were dissolved in dimethyl sulfoxide (5.0 mL), and sodium hydride (60%, 30 mg, 0.75 mmol) was added, and stirring was carried out at 100°C for 3.5 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, a saturated aqueous ammonium chloride solution (30 mL) was added, and extraction was carried out with ethyl acetate (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=85%-100%) to afford the desired compound (58 mg, yield 68%) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.35 (3H, d, J=5.9 Hz), 2.34-2.42 (2H, m), 3.42 (3H, s), 3.51 (1H, dd, J=10.6, 4.7 Hz), 3.61 (1H, dd, J=10.4, 5.7 Hz), 4.21-4.27 (2H, m), 4.34-4.37 (2H, m), 4.56-4.59 (1H, m), 6.54 (1H, t, J=2.9 Hz), 6.66 (1H, t, J=1.8 Hz), 6.72 (1H, t, J=2.9 Hz), 6.96 (1H, s), 7.05 (1H, s), 7.16 (1H, dd, J=3.3, 0.6 Hz), 7.68 (1H, dd, J=3.3, 0.6 Hz), 8.16 (1H, dd, J=2.0, 0.8 Hz), 8.26 (1H, dd, J=1.8, 1.0 Hz), 9.57 (1H, br s).
MS (ESI) m/z: 525.13929 $(M+H)^+$.

(Example 61)

5-(Azetidin-1-ylcarbonyl)-2-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}-3-methylpyridine



(61a) 5-(Azetidin-1-ylcarbonyl)-2-chloro-3-methylpyridine

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Commercially available 6-chloro-5-methylnicotinic acid (200 mg, 1.29 mmol) was dissolved in dichloromethane (7.0 mL), and azetidine hydrochloride (160 mg, 1.71 mmol), HATU (1000 mg, 2.63 mmol) and N,N-diisopropylethylamine (0.69 mL, 3.96 mmol) were added, followed by stirring at room temperature overnight under nitrogen atmosphere. 0.5N hydrochloric acid (30 mL) was added, and extraction was carried out with dichloromethane (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=60%-75%) to afford the desired compound (160 mg, yield 64%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.32 (3H, s), 2.36-2.42 (2H, m), 4.24 (2H, t, J=7.6 Hz), 4.35 (2H, t, J=7.6 Hz), 7.95 (1H, dd, J=9.3, 1.0 Hz), 8.26 (1H, d, J=1.0 Hz).

(61b) 5-(Azetidin-1-ylcarbonyl)-2-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}-3-methylpyridine

t-Butyl 2-{3-hydroxy-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-5-(1,3-thiazol-2-yl)-1H-pyrrole-1-carboxylate (59 mg, 0.137 mmol) synthesized in Example (38d) and 5-(azetidin-1-ylcarbonyl)-2-chloro-3-methylpyridine (45 mg, 0.232 mmol) synthesized in Example (61a) were dissolved in dimethyl sulfoxide (3.0 mL), and sodium hydride (60%, 25 mg, 0.63 mmol) was added, followed by stirring at 80°C for 4.5 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, a saturated aqueous ammonium chloride solution (30 mL) was added, and extraction was carried out with ethyl acetate (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=60%-80%)

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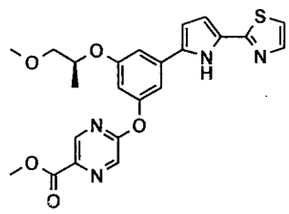
to afford the desired compound (50 mg, yield 72%) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.35 (3H, d, J=6.3 Hz), 2.32-2.38 (2H, m), 2.40 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J=10.2, 4.3 Hz), 3.60 (1H, dd, J=10.2, 5.9 Hz), 4.23 (2H, t, J=7.2 Hz), 4.34 (2H, t, J=6.6 Hz), 4.56-4.58 (1H, m), 6.55 (1H, dd, J=3.9, 2.7 Hz), 6.63 (1H, t, J=2.0 Hz), 6.72 (1H, dd, J=3.9, 2.3 Hz), 6.92 (1H, t, J=1.8 Hz), 7.00 (1H, dd, J=3.9, 1.6 Hz), 7.16 (1H, d, J=3.1 Hz), 7.67 (1H, d, J=3.1 Hz), 7.94 (1H, dd, J=2.3, 0.8 Hz), 8.22 (1H, d, J=2.3 Hz), 9.46 (1H, br s).

MS (ESI) m/z: 505.19091 $(M+H)^+$.

(Example 62)

Methyl 5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}pyrazine-2-carboxylate



(62a) Methyl 5-hydroxypyrazine-2-carboxylate

Commercially available 5-hydroxypyrazine-2-carboxylic acid (1.00 g, 7.14 mmol) was dissolved in methanol (5 mL), and a 4N hydrochloric acid/dioxane solution (25 mL) was added, followed by stirring at 60°C for 1.5 hours and heating to reflux at 80°C for 2.5 hours. The reaction solution was brought back to room temperature, the solvent was distilled off under reduced pressure, and ethyl acetate (20 mL) was added to the resulting residue to allow it to be suspended. The resulting precipitate was filtered off, and washed with ethyl acetate, followed by vacuum drying, to afford the desired compound (673 mg, yield 61%) as an orange-brown solid.

^{1}H-NMR (CD_3OD, 400 MHz): δ 3.31 (1H, s), 3.85 (3H, s), 8.00 (1H, d, J=1.2 Hz), 8.13 (1H, d, J=1.2 Hz).

(62b) Methyl 5-Chloropyrazine-2-carboxylate

Methyl 5-hydroxypyrazine-2-carboxylate (673 mg, 4.37 mmol) synthesized in Example (62a) was dissolved in phosphorous oxytrichloride (6.1 mL), and a few drops of N,N-dimethylformamide were added, followed by heating to reflux for 2 hours under nitrogen atmosphere. The reaction solution was poured into ice water, and extraction was carried out three times with chloroform (30 mL). The organic layer was washed with saturated aqueous sodium hydrogencarbonate solution and saturated brine (100 mL each), and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure to afford the desired compound (611 mg, yield 81%) as a gray solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.05 (3H, s), 8.71 (1H, d, J=1.6 Hz), 9.10 (1H, d, J=1.2 Hz).

(62c) Methyl 5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}pyrazine-2-carboxylate

t-Butyl 2-{3-hydroxy-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-5-(1,3-thiazol-2-yl)-1H-pyrrole-1-carboxylate (200 mg, 0.464 mmol) synthesized in Example (38d) and methyl 5-chloropyrazine-2-carboxylate (120 mg, 0.695 mmol) synthesized in Example (62b) were dissolved in N,N-dimethylformamide (10 mL), and potassium carbonate (257 mg, 1.86 mmol) was added, followed by stirring at 80°C for 7 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, water (40 mL) was added, and extraction was carried out with ethyl acetate (40 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-50%). The resulting yellow solid was dissolved in dichloromethane (2 mL), and trifluoroacetic acid (4 mL) was added, followed by stirring at room temperature for 1.5 hours. To the reaction solution, a saturated aqueous sodium hydrogencarbonate solution (40 mL) was added, and extraction was

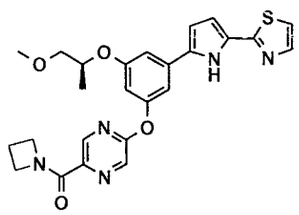
carried out twice with ethyl acetate (40 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-50%) to afford the desired compound (164 mg, yield 93%) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.35 (3H, d, J=6.3 Hz), 3.42 (3H, s), 3.52 (1H, dd, J=10.2, 4.3 Hz), 3.60 (1H, dd, J=10.2, 5.9 Hz), 4.02 (3H, s), 4.56-4.63 (1H, m), 6.55 (1H, dd, J=3.9, 2.7 Hz), 6.67 (1H, t, J=2.2 Hz), 6.75 (1H, dd, J=3.9, 2.3 Hz), 6.98 (1H, t, J=1.8 Hz), 7.10 (1H, t, J=1.8 Hz), 7.18 (1H, d, J=3.5 Hz), 7.68 (1H, d, J=3.1 Hz), 8.51 (1H, d, J=1.2 Hz), 8.87 (1H, d, J=1.2 Hz), 9.74 (1H, br s).

MS (ESI) m/z: 467 $(M+H)^+$.

(Example 63)

2-(Azetidin-1-ylcarbonyl)-5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}pyrazine



(63a) 5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}pyrazine-2-carboxylic acid

Methyl 5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}pyrazine-2-carboxylate (423 mg, 0.907 mmol) synthesized in Example (62c) was dissolved in methanol (10 mL), and water (2 mL) and lithium hydroxide monohydrate (76.2 mg, 1.82 mmol) were added, followed by stirring at 50°C for 1 hour under nitrogen atmosphere. To the reaction solution, water (30 mL) was added, and extraction was carried out twice with ethyl acetate (30 mL), followed by drying over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using

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silica gel column chromatography (elution solvent: dichloromethane/methanol=0%-10%) to afford the desired compound (269 mg, yield 66%) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.38 (3H, d, J=6.3 Hz), 3.44 (3H, s), 3.54 (1H, dd, J=10.2, 4.3 Hz), 3.63 (1H, dd, J=10.2, 5.9 Hz), 4.60-4.65 (1H, m), 6.62 (1H, dd, J=3.9, 2.3 Hz), 6.71 (1H, t, J=2.2 Hz), 6.82 (1H, dd, J=3.9, 2.3 Hz), 7.16-7.18 (2H, m), 7.37 (1H, s), 7.67 (1H, d, J=3.5 Hz), 8.54 (1H, d, J=1.2 Hz), 8.81 (1H, s), 11.30 (1H, br s).

(63b) 2-(Azetidin-1-ylcarbonyl)-5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}pyrazine

5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}pyrazine-2-carboxylic acid (28.0 mg, 0.062 mmol) synthesized in Example (63a) was dissolved in tetrahydrofuran (3 mL), and azetidine hydrochloride (17.4 mg, 0.186 mmol), HATU (35.3 mg, 0.093 mmol) and N,N-diisopropylethylamine (65 μL, 0.37 mmol) were added, followed by stirring at room temperature for 28 hours under nitrogen atmosphere. To the reaction solution, water (15 mL) was added, and extraction was carried out with ethyl acetate (15 mL), followed by drying over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using preparative TLC (developing solvent: methanol/dichloromethane=15%) to afford the desired compound (29.1 mg, yield 96%) as a white solid.

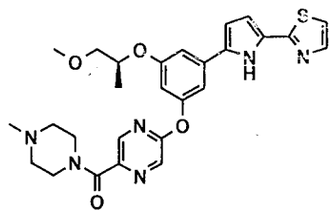
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.35 (3H, d, J=5.9 Hz), 2.35-2.41 (2H, m), 3.42 (3H, s), 3.51 (1H, dd, J=10.3, 3.9 Hz), 3.60 (1H, dd, J=10.3, 5.9 Hz), 4.26 (2H, t, J=7.8 Hz), 4.54-4.60 (1H, m), 4.69 (2H, t, J=7.8 Hz), 6.54 (1H, t, J=3.2 Hz), 6.65 (1H, s), 6.73 (1H, t, J=2.9 Hz), 6.95 (1H, s), 7.06 (1H, t, J=1.7 Hz), 7.17 (1H, d, J=2.9 Hz), 7.67 (1H, d, J=3.4 Hz), 8.31 (1H, s), 8.88 (1H, s), 9.69 (1H, br s).

MS (ESI) m/z: 492.16821 $(M+H)^+$.

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(Example 64)

2-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}-5-[(4-methylpiperazin-1-yl)carbonyl]pyrazine



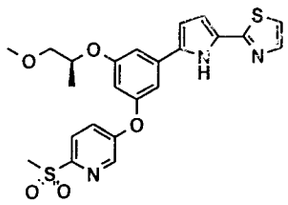
5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}pyrazine-2-carboxylic acid (40.4 mg, 0.089 mmol) synthesized in Example (63a) was dissolved in tetrahydrofuran (5 mL), and 1-methylpiperazine (30 μL, 0.27 mmol), HATU (67.9 mg, 0.18 mmol) and N,N-diisopropylethylamine (93 μL, 0.54 mmol) were added, followed by stirring at room temperature for 12 hours under nitrogen atmosphere. To the reaction solution, water (15 mL) was added, and extraction was carried out with ethyl acetate (15 mL), followed by drying over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/dichloromethane=0%-5%) to afford the desired compound (47 mg, yield 98%) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.35 (3H, d, J=6.3 Hz), 2.37 (3H, s), 2.50 (2H, br s), 2.56 (2H, br s), 3.42 (3H, s), 3.52 (1H, dd, J=10.2, 4.3 Hz), 3.61 (1H, dd, J=10.4, 6.1 Hz), 3.75 (2H, br s), 3.85 (2H, br s), 4.54-4.62 (1H, m), 6.54 (1H, t, J=3.3 Hz), 6.65 (1H, t, J=2.0 Hz), 6.73 (1H, dd, J=3.9, 2.3 Hz), 6.95 (1H, t, J=1.8 Hz), 7.06 (1H, t, J=1.8 Hz), 7.17 (1H, d, J=3.1 Hz), 7.68 (1H, d, J=3.1 Hz), 8.35 (1H, d, J=1.2 Hz), 8.56 (1H, d, J=1.2 Hz), 9.59 (1H, br s).

MS (ESI) m/z: 535.21022 $(M+H)^+$.

(Example 65)

5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}-2-(methylsulfonyl)pyridine



(65a) 5-Bromo-2-(methylthio)pyridine

Commercially available 2,5-dibromo pyridine (6.01 g, 25.4 mmol) was dissolved in N,N-dimethylformamide (50 mL), and sodium thiomethoxide (2.20 g, 31.4 mmol) was added, followed by stirring at 0°C for 3.5 hours under nitrogen atmosphere. The reaction solution was brought back to room temperature, water (250 mL) was added, and extraction was carried out with diethyl ether (250 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=3%-5%) to afford the desired compound (4.90 g, yield 94%) as a white solid. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.54 (3H, s), 7.08 (1H, d, J=8.2 Hz), 7.58 (1H, dd, J=8.6, 2.3 Hz), 8.49 (1H, d, J=2.0 Hz).

(65b) 5-Fluoro-2-(methylsulfonyl)pyridine

5-Bromo-2-(methylthio)pyridine (4.90 g, 24.0 mmol) synthesized in Example (65a) was dissolved in tetrahydrofuran (100 mL), and n-butyl lithium (1.57 mol/L hexane solution, 17.0 mL, 26.7 mmol) was added dropwise at -78°C, followed by stirring at -78°C for 1 hour under nitrogen atmosphere. N-fluorobenzenesulfonimide (11.0 g, 34.9 mmol) was dissolved in tetrahydrofuran (25 mL), followed by dropwise addition to the reaction solution at -78°C, and stirring was carried out at -78°C for 2 hours under nitrogen atmosphere. The reaction solution was brought back to room temperature, and stirring was carried out for 1.5 hours. A saturated aqueous ammonium chloride solution (200 mL) was added, and extraction was carried out with diethyl ether (300 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium

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sulfate. The solvent was distilled off under slightly reduced pressure.

The resulting residue was dissolved in methylene chloride (150 mL), and m-chloroperbenzoic acid (65%, 16.5 g, 62.1 mmol) was slowly added at 0°C, followed by stirring at 0°C for 1.5 hours under nitrogen atmosphere. After removal of white solid material by Celite filtration, a saturated aqueous sodium hydrogencarbonate solution (100 mL) was added, and extraction was carried out with methylene chloride (400 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=3%-5%) to afford the desired compound (1.95 g, yield 46%) as a yellowish white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.24 (3H, s), 7.67 (1H, ddd, J=9.9, 6.9, 1.9 Hz), 8.16 (1H, dd, J=8.6, 4.3 Hz), 8.59 (1H, d, J=2.7 Hz).

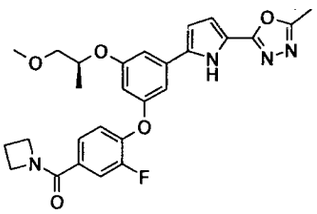
(65c) 5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[5-(1,3-thiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}-2-(methylsulfonyl)pyridine

t-Butyl 2-{3-hydroxy-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-5-(1,3-thiazol-2-yl)-1H-pyrrole-1-carboxylate (70.0 mg, 0.16 mmol) synthesized in Example (38d) and 5-fluoro-2-(methylsulfonyl)pyridine (35.0 mg, 0.20 mmol) synthesized in Example (65b) were dissolved in N,N-dimethylformamide (5 mL), and stirring was carried out at 90°C for 3 days under nitrogen atmosphere. To the reaction solution, water (15 mL) was added, followed by extraction with ethyl acetate (30 mL), and washing was carried out with saturated brine (30ml), followed by drying over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-40%) to afford the desired compound (28 mg, yield 35%) as a pale yellow solid.

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^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J=6.3 Hz), 3.24 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J=10.4, 4.1 Hz), 3.59 (1H, dd, J=10.2, 6.3 Hz), 4.58 (1H, dd, J=10.4, 6.1 Hz), 6.54-6.56 (2H, m), 6.73 (1H, dd, J=3.7, 2.5 Hz), 6.86 (1H, t, J=1.8 Hz), 7.04 (1H, t, J=2.0 Hz), 7.18 (1H, d, J=3.5 Hz), 7.43 (1H, dd, J=8.6, 2.7 Hz), 7.68 (1H, d, J=3.1 Hz), 8.05 (1H, d, J=9.0 Hz), 8.49 (1H, d, J=2.7 Hz), 9.62 (1H, br s).
MS (ESI) m/z: 486.11507 $(M+H)^+$.

(Example 66)
2-(5-{3-[4-(Azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-1,3,4-oxadiazole



(66a) t-Butyl 2,5-dibromo-1H-pyrrole-1-carboxylate

Commercially available t-butyl 1-pyrrolecarboxylate (46.68 g, 279 mmol) was dissolved in tetrahydrofuran (500 mL), and cooled to -78°C. To this, was added N-bromosuccinimide (100.48 g, 565 mmol) in small portions over 1 hour. The temperature of the reaction solution was raised naturally, and stirring was carried out at room temperature for 18 hours. The reaction solution was cooled to 0°C followed by addition of sodium sulphite (36.43 g) and stirring for 30 minutes, and subsequently hexane (200 mL) was added to give a precipitate, which was removed by Celite filtration. The solvent of the filtrate was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=1%-5%) to afford the desired compound (52.69 g, yield 58%) as a colorless oil.
^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.65 (9H, s), 6.25 (2H, s).
MS (EI) m/z: 323 (M^+).

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(66b) 2-Benzyl 1-t-butyl 5-bromo-1H-pyrrole-1,2-dicarboxylate

t-Butyl 2,5-dibromo-1H-pyrrole-1-carboxylate (10.98 g, 33.8 mmol) synthesized in Example (66a) was dissolved in diethyl ether (135 mL), and cooled to -78°C. n-Butyl lithium (2.77M hexane solution, 12.8 mL, 35.5 mmol) was added dropwise slowly, and stirring was carried out for 1 hour. To the reaction solution, benzyl chloroformate (6.25 mL, 44.0 mmol) was added dropwise slowly, and stirring was carried out for 30 minutes. With the temperature of the reaction solution being gradually raised to room temperature, stirring was carried out for 1 hour. To the reaction solution, were added a saturated aqueous ammonium chloride solution (200 mL) and diethyl ether (300 mL), and the solution was separated. The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=5%-45%) to afford the desired compound (8.80 g, yield 68%) as a reddish brown oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.56 (9H, s), 5.26 (2H, s), 6.21 (1H, d, J=3.9 Hz), 6.85 (1H, d, J=3.9 Hz), 7.28-7.39 (5H, m).

MS (FAB) m/z: 380 $(M+H)^+$.

(66c) 2-Benzyl 1-t-butyl 5-{3-hydroxy-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrole-1,2-dicarboxylate

2-Benzyl 1-t-butyl 5-bromo-1H-pyrrole-1,2-dicarboxylate (8.75 g, 23.0 mmol) synthesized in Example (66b) and 3-[(1S)-2-methoxy-1-methylethoxy]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (7.11 g, 23.1 mmol) synthesized in Example (38c) were dissolved in a mixed solvent of 1,4-dioxane (92 mL) and water (23 mL), and [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloride dichloromethane complex (570 mg, 0.698 mmol) and potassium carbonate (7.95 g, 57.5 mmol) were added, followed by stirring at 55°C for 3 hours under nitrogen atmosphere. After the reaction solution was cooled to room temperature, water (200 mL)

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was added, and extraction was carried out with ethyl acetate (200 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=15%-35%) to afford the desired compound (8.32 g, yield 75%) as a brown oil.

^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.29 (3H, d, J=6.3 Hz), 1.41 (9H, s), 3.40 (3H, s), 3.47 (1H, dd, J=10.3, 4.4 Hz), 3.57 (1H, dd, J=10.3, 5.9 Hz), 4.48-4.54 (1H, m), 5.20 (1H, s), 5.30 (2H, s), 6.17 (1H, d, J=3.4 Hz), 6.44 (1H, s), 6.48 (1H, s), 6.57 (1H, s), 6.94 (1H, d, J=3.4 Hz), 7.42-7.31 (5H, m).

MS (FAB) m/z: 481 (M^+).

(66d) Benzyl 5-{3-(2-Fluoro-4-formylphenoxy)-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrole-2-carboxylate

2-Benzyl 1-t-butyl 5-{3-hydroxy-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrole-1,2-dicarboxylate (8.30 g, 17.2 mmol) synthesized in Example (66c) was dissolved in N,N-dimethylformamide (86 mL), and 3,4-difluorobenzaldehyde (2.85 mL, 25.9 mmol) and potassium carbonate (11.96 g, 86.5 mmol) were added, followed by stirring at 90°C for 24 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, water (100 mL) was added, and extraction was carried out with diethyl ether (300 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate.

The solvent was distilled off under reduced pressure to give a residue, which was dissolved in dichloromethane (20 mL), and trifluoroacetic acid (10 mL) was added, followed by stirring at room temperature for 1 hour. The solvent was distilled off under reduced pressure to give a residue, which was dissolved in ethyl acetate (200 mL), and washed with saturated aqueous sodium hydrogencarbonate solution (200 mL). After washing further with saturated brine, drying was carried out over anhydrous magnesium

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sulfate. The solvent was distilled off under reduced pressure to give a residue, which was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=15%-35%) to afford the desired compound (6.34 g, yield 73%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J=6.3 Hz), 3.40 (3H, s), 3.50 (1H, dd, J=10.2, 3.9 Hz), 3.58 (1H, dd, J=10.4, 6.1 Hz), 4.53-4.60 (1H, m), 5.32 (2H, s), 6.50 (1H, t, J=3.3 Hz), 6.59 (1H, s), 6.83 (1H, s), 6.96-6.98 (2H, m), 7.12 (1H, t, J=8.0 Hz), 7.32-7.44(5H, m), 7.62 (1H, d, J=8.2 Hz), 7.72 (1H, dd, J=10.4, 1.8 Hz), 9.29 (1H, s), 9.92 (1H, d, J=2.0 Hz).

MS (FAB) m/z: 503 (M^+).

(66e) 4-{3-{5-[(Benzyloxy)carbonyl]-1H-pyrrol-2-yl}-5-[(1S)-2-methoxy-1-methylethoxy]phenoxy)-3-fluorobenzoic acid

Benzyl 5-{3-(2-Fluoro-4-formylphenoxy)-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrole-2-carboxylate (6.33 g, 12.6 mmol) synthesized in Example (66d) was suspended in a mixed solvent of t-butanol (120 mL) and water (40 mL), and sodium dihydrogen phosphate dihydrate (8.86 g, 56.8 mmol) and 2-methyl-2-butene (12.05 mL, 113 mmol) were added. Under ice cooling, sodium chlorite (80%, 2.93 g, 25.9 mmol) was added slowly, and stirring was carried out at room temperature for 2 hours. Saturated brine (200 mL) was added, followed by extraction with dichloromethane (200 mL), and drying was carried out over anhydrous magnesium sulfate to afford the desired compound (7.17 g, yield ~100%) as a pale yellow oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.36 (3H, d, J=6.3 Hz), 3.43 (3H, s), 3.53 (1H, dd, J=10.2, 3.9 Hz), 3.62 (1H, dd, J=10.2, 5.9 Hz), 4.58-4.65 (1H, m), 5.34 (2H, s), 6.55 (1H, dd, J=3.9, 2.7 Hz), 6.69 (1H, t, J=2.0 Hz), 7.02-7.06 (3H, m), 7.11 (1H, s), 7.34-7.44(5H, m), 7.66 (1H, d, J=8.6 Hz), 7.77 (1H, dd, J=10.9, 2.0 Hz), 10.68 (1H, br s).

MS (FAB) m/z: 519 (M^+).

(66f) Benzyl 5-{3-[4-(Azetidin-1-ylcarbonyl)-2-fluorophenoxy]-

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5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrole-2-carboxylate benzyl

4-(3-{5-[(Benzyloxy)carbonyl]-1H-pyrrol-2-yl}-5-[(1S)-2-methoxy-1-methylethoxy]phenoxy)-3-fluorobenzoic acid (7.14 g, 13.7 mmol) synthesized in Example (66e) was dissolved in dichloromethane (120 mL). Under ice cooling, azetidine hydrochloride (1.772 g, 18.9 mmol), WSCI·HCl (3.62 g, 18.9 mmol), triethylamine (2.65 mL, 19.1 mmol) and 4-dimethylaminopyridine (464 mg, 3.80 mmol) were added, and stirring was carried out at room temperature for 6 hours under nitrogen atmosphere. To the reaction solution, 0.5N hydrochloric acid (300 mL) was added, and extraction was carried out with dichloromethane (300 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=60%-85%) to afford the desired compound (4.12 g, yield 59%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J=6.3 Hz), 2.34-2.41 (2H, m), 3.40 (3H, s), 3.49 (1H, dd, J=10.4,4.1 Hz), 3.57 (1H, dd, J=10.4, 6.1 Hz), 4.21-4.27 (2H, br m), 4.33-4.39 (2H, br m), 4.51-4.57 (1H, m), 5.33 (2H, s), 6.48 (1H, dd, J=3.9, 2.7 Hz), 6.53 (1H, t, J=2.2 Hz), 6.78 (1H, t, J=1.8 Hz), 6.89 (1H, t, J=1.8 Hz), 6.97 (1H, dd, J=3.9, 2.3 Hz), 7.06 (1H, t, J=8.0 Hz), 7.34-7.44 (6H, m), 7.52 (1H, dd, J=10.9, 2.0 Hz), 9.19 (1H, br s).
MS (FAB) m/z: 558 (M^+).

(66g) 5-{3-[4-(Azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrole-2-carboxylic acid

Benzyl 5-{3-[4-(azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrole-2-carboxylate (4.25 g, 7.61 mmol) synthesized in Example (66f) was dissolved in ethanol (150 mL), and a 10% palladium carbon catalyst (804 mg) was added, followed by stirring for 2 hours under hydrogen atmosphere. The palladium carbon catalyst was removed by Celite

filtration, and the solvent was distilled off under reduced pressure to afford the desired compound (3.45 g, yield 97%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J=6.3 Hz), 2.32-2.40 (2H, m), 3.44 (3H, s), 3.52 (1H, dd, J=10.0, 4.1 Hz), 3.64 (1H, dd, J=10.0, 6.3 Hz), 4.20-4.26 (2H, br m), 4.31-4.38 (2H, br m), 4.66-4.72 (1H, m), 6.48-6.50 (2H, m), 6.86 (1H, s), 7.00 (1H, s), 7.05 (1H, t, J=7.6 Hz), 7.16 (1H, s), 7.38 (1H, d, J=7.8 Hz), 7.50 (1H, d, J=11.3 Hz), 10.17 (1H, br s).

MS (ESI) m/z: 469.17889 $(M+H)^+$.

(66h) N'-Acetyl-5-{3-[4-(azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrole-2-carbohydrazide

5-{3-[4-(Azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrole-2-carboxylic acid (126 mg, 0.27 mmol) synthesized in Example (66g) and acetohydrazide (40 mg, 0.54 mmol) were dissolved in dichloromethane (5 mL), and HATU (153 mg, 0.40 mmol) and N,N-diisopropylethylamine (70 μL, 0.40 mmol) were added at room temperature, followed by stirring under nitrogen atmosphere for 1 hour. The reaction solution was diluted with dichloromethane (60 mL), washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/dichloromethane=5%) to afford the desired product (87 mg, yield 62%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.26 (3H, d, J=6.3 Hz), 1.91 (3H, s), 2.30-3.38 (2H, m), 3.37 (3H, s), 3.46 (1H, dd, J=3.8, 10.1 Hz) 3.58 (1H, dd, J=6.2, 10.1 Hz), 4.18-4.24 (2H, brm), 4.30-4.36 (2H, brm), 4.55-4.59 (1H, m), 6.43 (1H, dd, J=2.7, 4.0 Hz), 6.46 (1H, t, J=2.1 Hz), 6.81 (1H, dd, J=2.4,4.1 Hz), 6.87 (1H, s), 7.01 (1H, t, J=8.2 Hz), 7.07 (1H, s), 7.35 (1H, d, J=8.6 Hz), 7.46 (1H, dd, J=2.0, 10.9 Hz), 9.10 (1H, brs), 9.36 (1H, brs),

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10.62 (1H, brs).

(66i) 2-(5-{3-[4-(Azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-1,3,4-oxadiazole

N'-Acetyl-5-{3-[4-(azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrole-2-carbohydrazide (86 mg, 0.16 mmol) synthesized in Example (66h) was dissolved in dichloromethane (5 mL), and triethylamine (0.1 mL, 0.72 mmol) and p-toluenesulfonic acid chloride (69 mg, 0.36 mmol) were added, followed by stirring at room temperature overnight. The reaction solution was diluted with dichloromethane (60 mL), washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=50%-100%) to afford the desired product (57 mg, yield 69%) as a white solid.

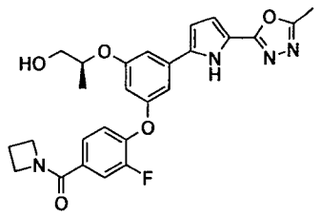
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J=6.3 Hz), 2.34-3.42 (2H, m), 2.58 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J=3.9, 10.4 Hz) 3.59 (1H, dd, J=6.1, 10.3 Hz), 4.22-4.27 (2H, brm), 4.35-4.40 (2H, brm), 4.54-4.59 (1H, m), 6.54 (1H, t, J=2.2 Hz), 6.55 (1H, dd, J=2.2, 2.7 Hz), 6.80 (1H, t, J=1.7 Hz), 6.85 (1H, dd, J=1.9, 2.4 Hz), 6.93 (1H, dd, J=1.2, 1.6 Hz), 7.08 (1H, t, J=8.2 Hz), 7.41 (1H, d, J=8.5 Hz), 7.52 (1H, dd, J=2.0, 11.1 Hz), 9.49 (1H, brs).

MS (ESI) m/z: 507.20129 $(M+H)^+$.

(Example 67)

(2S)-2-{3-[4-(Azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}propan-1-ol

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2-(5-{3-[4-(Azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-1,3,4-oxadiazole (379.2 mg, 0.748 mmol) synthesized in Example (66i) was dissolved in dichloromethane (15 mL), and a boron tribromide/dichloromethane solution (1M, 750 µL, 0.75 mmol) was added at -78°C under nitrogen atmosphere, followed by stirring at 0°C for 3 hours. To the reaction solution, a saturated aqueous sodium hydrogencarbonate solution was added, and extraction was carried out with ethyl acetate. The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/dichloromethane=2%-8%) to afford the desired compound (76.9 mg, yield 21%) as a pale yellow solid.

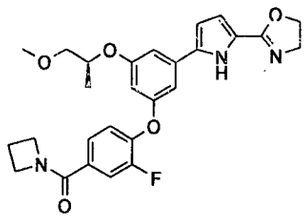
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.29 (3H, d, J=6.3 Hz), 2.34-2.42 (2H, m), 2.58 (3H, s), 2.80 (1H, t, J=6.1 Hz), 3.76-3.79 (2H, m), 4.22-4.26 (2H, br m), 4.35-4.39 (2H, br m), 4.52-4.59 (1H, m), 6.45 (1H, t, J=2.2 Hz), 6.53 (1H, dd, J=3.9, 2.7 Hz), 6.79 (1H, t, J=1.8 Hz), 6.84 (1H, dd, J=3.9, 2.3 Hz), 6.91 (1H, t, J=1.8 Hz), 7.05 (1H, t, J=8.2 Hz), 7.38-7.41 (1H, m), 7.51 (1H, dd, J=10.9, 2.0 Hz), 9.92 (1H, br s).

MS (ESI) m/z: 493.18999 $(M+H)^+$.

(Example 68)

2-(5-{3-[4-(Azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-oxazole

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(68a) 5-{3-[4-(Azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-N-(2-chloroethyl)-1H-pyrrole-2-carboxamide

5-{3-[4-(Azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrole-2-carboxylic acid (66 mg, 0.15 mmol) synthesized in Example (66g), 2-chloroethylamine hydrochloride (34 mg, 0.30 mmol) and 4-dimethylaminopyridine (18 mg, 0.15 mmol) were dissolved in dichloromethane (10 mL), and WSCI·HCl (31 mg, 0.16 mmol) was added at room temperature, followed by stirring for 1 hour under nitrogen atmosphere. The reaction solution was diluted with dichloromethane (60 mL), washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=30%-60%) to afford the desired product (56 mg, yield 79%) as a white solid.

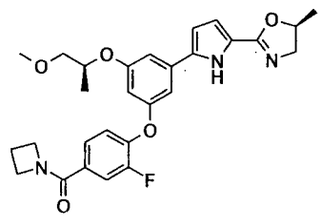
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J=6.3 Hz), 2.35-3.49 (2H, m), 3.41 (3H, s), 3.50 (1H, dd, J=4.1,10.7 Hz) 3.58 (1H, dd, J=6.1,10.3 Hz), 3.71 (2H, t, J=5.4 Hz), 3.77 (2H, t, J=5.6 Hz), 4.22-4.27 (2H, brm), 4.35-4.40 (2H, brm), 4.53-4.57 (1H, m), 6.24-6.28 (1H, m), 6.47 (1H, t, J=3.0 Hz), 6.52 (1H, t, J=2.1 Hz), 6.62 (1H, dd, J=2.5, 4.1 Hz), 6.78 (1H, t, J=1.6 Hz), 6.90 (1H, t, J=1.6 Hz), 7.06 (1H, t, J=8.0 Hz), 7.40 (1H, d, J=8.5 Hz), 7.52 (1H, dd, J=2.0, 11.0 Hz), 9.43 (1H, brs).

(68b) 2-(5-{3-[4-(Azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl)-4,5-dihydro-1,3-oxazole

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5-{3-[4-(Azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-N-(2-chloroethyl)-1H-pyrrole-2-carboxamide (85 mg, 0.16 mmol) synthesized in Example (68a) was dissolved in tetrahydrofuran (3 mL), and sodium hydride (37 mg, 0.82 mmol) was added at 0°C, followed by stirring at room temperature for 20 hours. To the reaction solution, a saturated aqueous sodium hydrogencarbonate solution was added, and extraction was carried out with ethyl acetate (50 mL). After washing with saturated brine, drying was carried out over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate100%-methanol/chloroform=2%) to afford the desired product (33 mg, yield 41%) as a pale yellow solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J=6.3 Hz), 2.34-3.41 (2H, m), 3.41 (3H, s), 3.49 (1H, dd, J=3.9, 10.5 Hz) 3.58 (1H, dd, J=5.9, 10.2 Hz), 4.00 (2H, t, J=9.3 Hz), 4.22-4.26 (2H, brm), 4.35-4.39 (2H, brm), 4.40 (2H, t, J=9.3 Hz), 4.53-4.57 (1H, m), 6.48 (1H, d, J=3.8 Hz), 6.51 (1H, t, J=2.0 Hz), 6.75 (1H, d, J=3.8 Hz), 6.78 (1H, t, J=1.6 Hz), 6.91 (1H, s), 7.06 (1H, t, J=8.1 Hz), 7.40 (1H, d, J=8.5 Hz), 7.52 (1H, dd, J=2.0, 11.0 Hz).
MS (ESI) m/z: 494.20834 (M+H)$^+$.

(Example 69)
(5S)-2-(5-{3-[4-(Azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-4,5-dihydro-1,3-oxazole



(69a) 5-{3-[4-(Azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-N-[(2R)-2-hydroxypropyl]-1H-pyrrole-2-carboxamide

5-{3-[4-(Azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[(1S)-

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2-methoxy-1-methylethoxy]phenyl}-1H-pyrrole-2-carboxylic acid (580 mg, 1.24 mmol) synthesized in Example (66g) was dissolved in dichloromethane (15 mL), and (R)-(-)-1-amino-2-propanol (196 μL, 2.48 mol), WSCI·HCl (366 mg, 1.91 mmol) and 4-dimethylaminopyridine (228 mg, 1.87 mmol) were added, followed by stirring at room temperature for 18 hours under nitrogen atmosphere. To the reaction solution, 0.25N hydrochloric acid (100 mL) was added, and extraction was carried out with ethyl acetate (100 mL). The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/dichloromethane=3%-9%) to afford the desired compound (486 mg, yield 75%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.22 (3H, d, J=6.3 Hz), 1.30 (3H, d, J=6.3 Hz), 2.33-2.41 (2H, m), 2.77 (1H, d, J=3.9 Hz), 3.22-3.29 (1H, m), 3.41 (3H, s), 3.50 (1H, dd, J=10.2, 3.9 Hz), 3.55-3.62 (2H, m), 3.94-4.01 (1H, br m), 4.20-4.26 (2H, br m), 4.33-4.39 (2H, br m), 4.51-4.59 (1H, m), 6.43-6.46 (2H, m), 6.51 (1H, t, J=2.2 Hz), 6.62 (1H, dd, J=3.9, 2.3 Hz), 6.80 (1H, t, J=1.8 Hz), 6.91 (1H, t, J=1.8 Hz), 7.04 (1H, t, J=8.2 Hz), 7.37 (1H, d, J=8.6 Hz), 7.50 (1H, dd, J=11.3,2.0 Hz), 9.80 (1H, br s).
MS (FAB) m/z: 526 $(M+H)^+$.

(69b) (5S)-2-(5-{3-[4-(Azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-4,5-dihydro-1,3-oxazole

5-{3-[4-(Azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-N-[(2R)-2-hydroxypropyl]-1H-pyrrole-2-carboxamide (464 mg, 0.883 mmol) synthesized in Example (69a) was dissolved in tetrahydrofuran (17 mL), and anhydrous methanesulfonic acid (558 mg, 3.20 mmol) and triethylamine (860 μL, 6.20 mmol) were added, followed by stirring at room temperature for 3 days under nitrogen atmosphere. To the reaction solution, saturated aqueous sodium hydrogencarbonate solution was added, and extraction was carried

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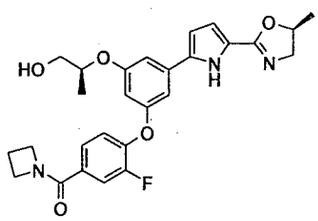
out with ethyl acetate. The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/dichloromethane=3%-9%) to afford the desired compound (228 mg, yield 51%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J=6.3 Hz), 1.43 (3H, d, J=6.3 Hz), 2.34-2.41 (2H, m), 3.41 (3H, s), 3.50 (1H, dd, J=10.2, 3.9 Hz), 3.52-3.59 (2H, m), 4.08 (1H, dd, J=13.9, 9.2 Hz), 4.22-4.26 (2H, br m), 4.35-4.38 (2H, br m), 4.53-4.60 (1H, m), 4.80-4.89 (1H, m), 6.48 (1H, d, J=3.9 Hz), 6.51 (1H, t, J=2.2 Hz), 6.77 (1H, d, J=3.9 Hz), 6.79 (1H, t, J=1.8 Hz), 6.93 (1H, s), 7.05 (1H, t, J=8.2 Hz), 7.37-7.40 (1H, m), 7.51 (1H, dd, J=10.9, 2.0 Hz).

MS (ESI) m/z: 508.22382 $(M+H)^+$.

(Example 70)

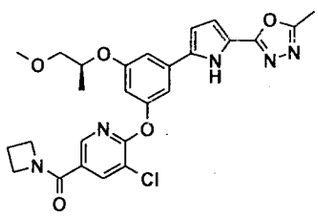
(2S)-2-(3-[4-(Azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)propan-1-ol



(5S)-2-(5-{3-[4-(Azetidin-1-ylcarbonyl)-2-fluorophenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-4,5-dihydro-1,3-oxazole (337.8 mg, 0.666 mmol) synthesized in Example (69b) was dissolved in dichloromethane (10 mL), and a boron tribromide/dichloromethane solution (1M, 1 mL, 1 mmol) was added at -78°C under nitrogen atmosphere, followed by stirring at room temperature for 1 hour. To the reaction solution, a saturated aqueous sodium hydrogencarbonate solution was added, and extraction was carried out with ethyl acetate. The organic layer was washed with saturated brine, and

subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/dichloromethane=2%-8%) to afford the desired compound (93.7 mg, yield 29%) as a pale yellow solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.26 (3H, d, J=6.3 Hz), 1.43 (3H, d, J=6.3 Hz), 2.33-2.41 (2H, m), 3.55 (1H, dd, J=13.7, 7.4 Hz), 3.73-3.81 (2H, m), 4.08 (1H, dd, J=13.7, 9.4 Hz), 4.22-4.26 (2H, br m), 4.33-4.37 (2H, br m), 4.56-4.64 (1H, m), 4.81-4.90 (1H, m), 6.30 (1H, t, J=2.2 Hz), 6.44 (1H, d, J=3.9 Hz), 6.74-6.76 (2H, m), 6.86 (1H, s), 7.00 (1H, t, J=8.2 Hz), 7.34-7.37 (1H, m), 7.49 (1H, dd, J=10.9, 2.0 Hz).
MS (ESI) m/z: 494.20864 $(M+H)^+$.

(Example 71)
5-(Azetidin-1-ylcarbonyl)-3-chloro-2-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}pyridine



(71a) 5-(3-{[5-(Azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[(1S)-2-methoxy-1-methylethoxy]phenyl)-1H-pyrrole-2-carboxylic acid

2-Benzyl 1-t-butyl 5-{3-hydroxy-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrole-1,2-dicarboxylate (5.21 g, 10.82 mmol) synthesized in Example (66c) and 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine (2.55 g, 11.04 mmol) synthesized in Example (60a) were dissolved in acetonitrile (100 mL), and potassium carbonate (4.30 g, 31.11 mmol) was added, followed by stirring for 1 day with heating to reflux under nitrogen atmosphere. The reaction solution was cooled to room temperature, water (200 mL) was added, and extraction was carried out with ethyl acetate (200 mL). The organic layer was

washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=75%-90%).

The resulting compound was dissolved in trifluoroacetic acid (15 mL), and stirring was carried out at room temperature for 1.5 hours under nitrogen atmosphere. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=75%-90%).

The resulting compound was dissolved in tetrahydrofuran (20 mL), and palladium carbon (800mg) was added, followed by stirring at room temperature for 4 hours under hydrogen atmosphere. After Celite filtration, the solvent was distilled off. To the resulting residue, a saturated aqueous sodium hydrogencarbonate solution (30 mL) was added, and extraction was carried out with diethyl ether. To the resulting aqueous layer, 2N hydrochloric acid (50 mL) was added, and extraction was carried out with ethyl acetate. The resulting organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure to afford the desired compound (3.52 g, yield 67%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.35 (3H, d, J=6.3 Hz), 2.35-2.42 (2H, m), 3.45 (3H, s), 3.54 (1H, dd, J=10.0, 4.1 Hz), 3.65 (1H, dd, J=10.4, 6.1 Hz), 4.24 (2H, t, J=7.6 Hz), 4.35 (2H, t, J=6.3 Hz), 4.65-4.71 (1H, m), 6.53 (1H, dd, J=3.5, 2.7 Hz), 6.70 (1H, t, J=2.2 Hz), 7.01-7.02 (2H, br m), 7.21 (1H, s), 8.16 (1H, d, J=2.3 Hz), 8.27 (1H, d, J=2.0 Hz), 9.97 (1H, br s).

(71b) 5-(Azetidin-1-ylcarbonyl)-3-chloro-2-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}pyridine

5-(3-{[5-(Azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[(1S)-2-methoxy-1-methylethoxy]phenyl)-1H-pyrrole-2-

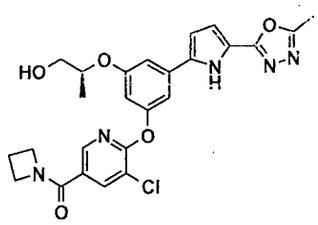
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carboxylic acid (600 mg, 1.23 mmol) synthesized in Example (71a) was dissolved in dichloromethane (15 mL), and acetohydrazide (200 mg, 2.70 mmol), WSCI·HCl (510 mg, 2.66 mmol) and 4-dimethylaminopyridine (300 mg, 2.46 mmol) were added, followed by stirring at room temperature for 1 day under nitrogen atmosphere. A saturated aqueous ammonium chloride solution (100 mL) was added, and extraction was carried out with dichloromethane (100 mL). The organic layer was washed with saturated brine, subsequently dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure.

This residue was dissolved in dichloromethane (15 mL), and p-toluenesulfonyl chloride (500 mg, 2.62 mmol) and triethylamine (1.0 mL, 7.17 mmol) were added, followed by stirring at room temperature for 5 hours under nitrogen atmosphere. To the reaction solution, a saturated aqueous ammonium chloride solution (30 mL) was added, and extraction was carried out with dichloromethane (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate) to afford the desired compound (520 mg, yield 81%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.35 (3H, d, J=6.3 Hz), 2.35-2.43 (1H, m), 2.59 (3H, s), 3.42 (3H, s), 3.52 (1H, dd, J=10.2, 4.3 Hz), 3.61 (1H, dd, J=10.2, 5.9 Hz), 4.24 (2H, t, J=7.4 Hz), 4.37 (2H, t, J=7.6 Hz), 4.56-4.62 (1H, m), 6.58 (1H, dd, J=3.9, 2.7 Hz), 6.70 (1H, t, J=2.2 Hz), 6.85 (1H, dd, J=3.9, 2.3 Hz), 6.96 (1H, t, J=1.6 Hz), 7.05 (1H, t, J=2.0 Hz), 8.17 (1H, d, J=2.0 Hz), 8.27 (1H, d, J=2.0 Hz), 9.57 (1H, br s).
MS (ESI) m/z: 524.17210 $(M+H)^+$.

(Example 72)
(2S)-2-(3-{[5-(Azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrrol-2-yl]phenoxy)propan-1-ol

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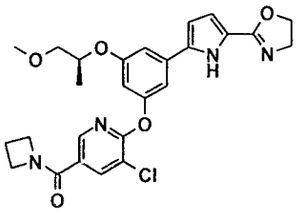
5-(Azetidin-1-ylcarbonyl)-3-chloro-2-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}pyridine (370 mg, 0.706 mmol) synthesized in Example (71b) was dissolved in dichloromethane (10 mL), and boron tribromide (1.0 mol/L dichloromethane solution, 1.10 mL, 1.10 mmol) was added dropwise at -78°C, followed by stirring at room temperature for 1 hour under nitrogen atmosphere. To this reaction solution, a saturated aqueous ammonium chloride solution (20 mL) was added, and extraction was carried out with dichloromethane (20 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/dichloromethane=1%-3%) to afford the desired compound (205 mg, yield 57%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.30 (3H, d, J=6.3 Hz), 1.78 (1H, d, J=7.8 Hz), 2.34-2.42 (2H, m), 2.57 (3H, s), 2.71-2.87 (1H, m), 3.73-3.80 (2H, m), 4.23 (2H, t, J=7.6 Hz), 4.35 (2H, t, J=7.4 Hz), 4.52-4.58 (1H, m), 6.56 (1H, t, J=2.9 Hz), 6.64 (1H, d, J=1.6 Hz), 6.84 (1H, dd, J=3.9, 2.3 Hz), 6.96 (1H, t, J=1.8 Hz), 7.01 (1H, t, J=1.8 Hz), 8.16 (1H, d, J=2.0 Hz), 8.26 (1H, d, J=2.3 Hz), 9.92 (1H, s).

MS (ESI) m/z: 510.15468 $(M+H)^+$.

(Example 73)

5-(Azetidin-1-ylcarbonyl)-3-chloro-2-{3-[5-(4,5-dihydro-1,3-oxazol-2-yl)-1H-pyrrol-2-yl]-5-[(1S)-2-methoxy-1-methylethoxy]phenoxy}pyridine



(73a) 5-(3-{[5-(Azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[(1S)-2-methoxy-1-methylethoxy]phenyl)-N-(2-chloroethyl)-1H-pyrrole-2-carboxamide

5-(3-{[5-(Azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[(1S)-2-methoxy-1-methylethoxy]phenyl)-1H-pyrrole-2-carboxylic acid (800 mg, 1.65 mmol) synthesized in Example (71a) was dissolved in dichloromethane (10.0 mL), and 2-chloroethylamine hydrochloride (300 mg, 2.59 mmol), WSCI·HCl (630 mg, 3.29 mmol) and 4-dimethylaminopyridine (400 mg, 3.27 mmol) were added, followed by stirring at room temperature under nitrogen atmosphere for 2.5 days. To the reaction solution, a saturated aqueous ammonium chloride solution (30 mL) was added, and extraction was carried out with dichloromethane (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate) to afford the desired compound (210 mg, yield 23%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J=6.3 Hz), 2.35-2.42 (2H, m), 3.42 (3H, s), 3.51 (1H, dd, J=10.6, 4.7 Hz), 3.60 (1H, dd, J=10.2, 5.9 Hz), 3.68-3.73 (2H, m), 3.75-3.80 (2H, m), 4.24 (2H, t, J=7.8 Hz), 4.36 (2H, t, J=7.0 Hz), 4.55-4.60 (1H, m), 6.27 (1H, t, J=5.7 Hz), 6.50 (1H, dd, J=3.9, 2.7 Hz), 6.63 (1H, dd, J=3.7, 2.5 Hz), 6.68 (1H, t, J=2.2 Hz), 6.95 (1H, t, J=1.8 Hz), 7.03 (1H, t, J=1.8 Hz), 8.16 (1H, d, J=2.3 Hz), 8.26 (1H, d, J=2.0 Hz), 9.55 (1H, br s).

(73b) 5-(Azetidin-1-ylcarbonyl)-3-chloro-2-{3-[5-(4,5-dihydro-1,3-oxazol-2-yl)-1H-pyrrol-2-yl]-5-[(1S)-2-methoxy-1-methylethoxy]phenoxy}pyridine

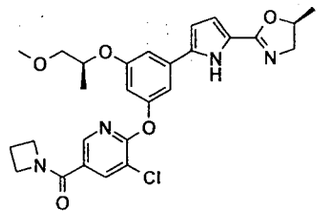
5-(3-{[5-(Azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[(1S)-2-methoxy-1-methylethoxy]phenyl)-N-(2-chloroethyl)-1H-pyrrole-2-carboxamide (210 mg, 0.384 mmol) synthesized in Example (73a) was dissolved in tetrahydrofuran (10.0 mL), and sodium hydride (60%, 80 mg, 2.00 mmol) was added, followed by stirring at room temperature for 7.5 hours under nitrogen atmosphere. To the reaction solution, a saturated aqueous ammonium chloride solution (30 mL) was added, and extraction was carried out with dichloromethane (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate) to afford the desired compound (120 mg, yield 62%) as a white solid.

^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.34 (3H, d, J=6.3 Hz), 2.35-2.42 (2H, m), 3.41 (3H, s), 3.50 (1H, dd, J=10.3, 4.4 Hz), 3.60 (1H, dd, J=10.3, 5.9 Hz), 4.00 (2H, t, J=9.3 Hz), 4.24 (2H, t, J=6.8 Hz), 4.36 (2H, t, J=6.3 Hz), 4.40 (2H, t, J=9.3 Hz), 4.55-4.61 (1H, m), 6.50 (1H, d, J=3.9 Hz), 6.66 (1H, t, J=2.0 Hz), 6.75 (1H, d, J=3.9 Hz), 6.94 (1H, s), 7.04 (1H, t, J=5.1 Hz), 8.15 (1H, d, J=2.0 Hz), 8.26 (1H, d, J=2.0 Hz).

MS (ESI) m/z: 511.17658 $(M+H)^+$.

(Example 74)

5-(Azetidin-1-ylcarbonyl)-3-chloro-2-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)pyridine



5-(3-{[5-(Azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[(1S)-2-methoxy-1-methylethoxy]phenyl)-1H-pyrrole-2-carboxylic acid (800 mg, 1.65 mmol) synthesized in Example (71a)

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was dissolved in dichloromethane (15 mL), and (R)-(-)-1-amino-2-propanol (0.35 mL, 4.45 mmol), WSCI·HCl (630 mg, 3.29 mmol) and 4-dimethylaminopyridine (800 mg, 6.55 mmol) were added, followed by stirring at room temperature for 8 hours under nitrogen atmosphere. To the reaction solution, a saturated aqueous ammonium chloride solution (30 mL) was added, and extraction was carried out with dichloromethane (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/dichloromethane=3%-8%) to afford a yellow solid.

This was dissolved in tetrahydrofuran (15 mL), and anhydrous methanesulfonic acid (500 mg, 2.87 mmol) and triethylamine (0.80 mL, 5.74 mmol) were added, followed by stirring at room temperature overnight under nitrogen atmosphere. To the reaction solution, a saturated aqueous ammonium chloride solution (30 mL) was added, and extraction was carried out with dichloromethane (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate) to afford the desired compound (520 mg, yield 60%) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J=6.3 Hz), 1.43 (3H, d, J=6.3 Hz), 2.35-2.42 (2H, m), 3.41 (3H, s), 3.45-3.64 (3H, m), 4.08-4.12 (1H, m), 4.23 (2H, t, J=7.0 Hz), 4.36 (2H, t, J=8.4 Hz), 4.54-4.62 (1H, m), 4.84-4.87 (1H, m), 6.51 (1H, d, J=3.5 Hz), 6.66 (1H, t, J=2.2 Hz), 6.75-6.78 (1H, m), 6.94 (1H, s), 7.02-7.09 (1H, m), 8.16 (1H, d, J=2.0 Hz), 8.26 (1H, d, J=2.0 Hz).

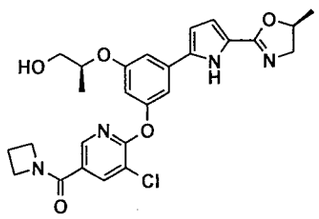
MS (ESI) m/z: 525.19126 $(M+H)^+$.

(Example 75)

(2S)-2-(3-{[5-(Azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-

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yl}phenoxy)propan-1-ol



5-(azetidin-1-ylcarbonyl)-3-chloro-2-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)pyridine (320 mg, 0.610 mmol) synthesized in Example 74 was dissolved in dichloromethane (10 mL), and boron tribromide (1.0 mol/L dichloromethane solution, 0.92 mL, 0.92 mmol) was added dropwise at -78°C, followed by stirring at room temperature for 1 hour under nitrogen atmosphere. To this reaction solution, a saturated aqueous ammonium chloride solution (20 mL) was added, and extraction was carried out with dichloromethane (20 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/dichloromethane=1%-3%) to afford the desired compound (165 mg, yield 53%) as a yellow solid.

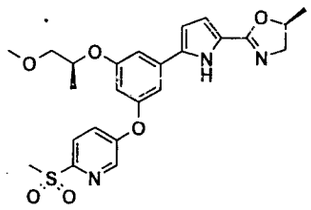
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.28 (3H, d, J=6.3 Hz), 1.40 (3H, d, J=5.9 Hz), 2.34-2.42 (2H, m), 3.52 (1H, dd, J=13.7, 7.4 Hz), 3.76 (2H, d, J=5.5 Hz), 4.06 (1H, dd, J=13.9, 9.2 Hz), 4.23 (2H, t, J=7.8 Hz), 4.34 (2H, t, J=7.4 Hz), 4.51-4.60 (1H, m), 4.76-4.86 (1H, m), 6.44 (1H, d, J=3.1 Hz), 6.53 (1H, s), 6.72 (1H, d, J=3.5 Hz), 6.87-6.92 (2H, m), 8.15 (1H, d, J=2.0 Hz), 8.23 (1H, d, J=1.2 Hz), 10.05 (1H, br s).

MS (ESI) m/z: 511.17339 $(M+H)^+$.

(Example 76)

5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-2-(methylsulfonyl)pyridine

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(76a) Benzyl 5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxylate

2-Benzyl 1-t-butyl 5-{3-hydroxy-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrole-1,2-dicarboxylate (5.05 g, 10.49 mmol) synthesized in Example (66c) and 5-fluoro-2-(methylsulfonyl)pyridine (2.05 g, 11.70 mmol) synthesized in Example (65b) were dissolved in N,N-dimethylformamide (30 mL), and potassium carbonate (4.50 g, 32.56 mmol) was added, followed by stirring at 80°C for 3 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, water (150 mL) was added, and extraction was carried out with diethyl ether (150 mL). The organic layer was washed with saturated brine, subsequently dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure.

The resulting compound was dissolved in trifluoroacetic acid (10 mL), and stirring was carried out at room temperature for 1 hour under nitrogen atmosphere. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=35%-50%) to afford the desired compound (5.08 g, yield 90%) as a white oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J=6.3 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.51 (1H, dd, J=10.3, 3.9 Hz), 3.58 (1H, dd, J=10.3, 6.3 Hz), 4.54-4.61 (1H, m), 5.33 (2H, s), 6.51 (1H, t, J=3.2 Hz), 6.59 (1H, s), 6.86 (1H, s), 6.99 (1H, t, J=2.9 Hz), 7.02 (1H, s), 7.32-7.45 (7H, m), 8.04 (1H, d, J=8.8 Hz), 8.48 (1H, s), 9.36 (1H, br s).

(76b) 5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxylic

acid

Benzyl 5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxylate (5.08 g, 9.47 mmol) synthesized in Example (76a) was dissolved in ethyl acetate (30 mL), and a 10% palladium carbon catalyst (1.10 g) was added, followed by stirring at room temperature for 3 hours under hydrogen atmosphere. After Celite filtration, the solvent was distilled off under reduced pressure to afford the desired compound as a white solid (4.30 g, yield ~100%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J=5.9 Hz), 3.23 (3H, s), 3.47 (3H, s), 3.57 (1H, dd, J=9.8, 3.9 Hz), 3.67 (1H, dd, J=10.0, 6.6 Hz), 4.72-4.80 (1H, m), 6.52 (1H, s), 6.59 (1H, s), 6.92 (1H, s), 7.03 (1H, s), 7.32 (1H, s), 7.45 (1H, dd, J=8.5, 1.7 Hz), 8.05 (1H, d, J=8.8 Hz), 8.49 (1H, d, J=2.4 Hz), 10.31 (1H, br s).

(76c) 5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-2-(methylsulfonyl)pyridine

5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxylic acid (1000 mg, 2.24 mmol) synthesized in Example (76b) was dissolved in methanol (20 mL), and (R)-(-)-1-amino-2-propanol (0.40 mL, 5.08 mmol) and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride n hydrate (1000 mg, 3.61 mmol) were added, followed by stirring at room temperature overnight under nitrogen atmosphere. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=1%-3%) to afford a yellow solid.

This was dissolved in tetrahydrofuran (20 mL), and anhydrous methanesulfonic acid (600 mg, 3.44 mmol) and triethylamine (0.70 mL, 5.02 mmol) were added, followed by stirring at room temperature overnight under nitrogen atmosphere. To the reaction solution, a saturated aqueous ammonium chloride solution (50 mL) was added, and extraction was carried out with

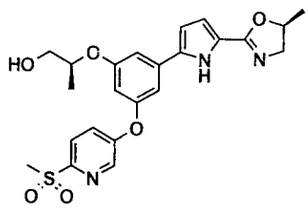
methylene chloride (50 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=1%-3%) to afford the desired compound (450 mg, yield 41%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J=6.3 Hz), 1.43 (3H, d, J=6.3 Hz), 3.23 (3H, s), 3.42 (3H, s), 3.49-3.61 (4H, m), 4.09 (1H, dd, J=13.9, 8.8 Hz), 4.53-4.63 (1H, m), 4.79-4.88 (1H, m), 6.51 (1H, d, J=3.9 Hz), 6.57 (1H, d, J=1.6 Hz), 6.76 (1H, d, J=3.9 Hz), 6.83 (1H, s), 7.02 (1H, s), 7.44 (1H, dd, J=8.6, 2.3 Hz), 8.05 (1H, d, J=8.6 Hz), 8.49 (1H, s).

MS (ESI) m/z: 486.17067 $(M+H)^+$.

(Example 77)

(2S)-2-(3-{5-[(5S)-5-Methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol



5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-2-(methylsulfonyl)pyridine (310 mg, 0.638 mmol) synthesized in Example (76c) was dissolved in methylene chloride (7.0 mL), and boron tribromide (1.0 mol/L dichloromethane solution, 1.00 mL, 1.0 mmol) was added dropwise at -78°C, followed by stirring at room temperature for 1 hour under nitrogen atmosphere. To this reaction solution, a saturated aqueous ammonium chloride solution (20 mL) was added, and extraction was carried out with methylene chloride (20 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure,

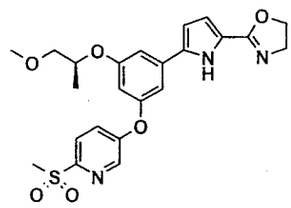
and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=1%-3%) to afford the desired compound (245 mg, yield 81%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.29 (3H, d, J=6.3 Hz), 1.43 (3H, d, J=6.3 Hz), 3.23 (3H, s), 3.55 (1H, dd, J=13.9, 7.2 Hz), 3.79 (2H, d, J=5.1 Hz), 4.09 (1H, dd, J=14.1,9.4 Hz), 4.56-4.63 (1H, m), 4.81-4.88 (1H, m), 6.38 (1H, br s), 6.48 (1H, t, J=3.3 Hz), 6.75 (1H, d, J=3.5 Hz), 6.80 (1H, br s), 6.96 (1H, br s), 7.39 (1H, br s), 8.03 (1H, d, J=8.2 Hz), 8.45 (1H, s).

MS (ESI) m/z: 472.15208 $(M+H)^+$.

(Example 78)

5-{3-[5-(4,5-Dihydro-1,3-oxazol-2-yl)-1H-pyrrol-2-yl]-5-[(1S)-2-methoxy-1-methylethoxy]phenoxy}-2-(methylsulfonyl)pyridine



(78a) 3-Bromo-5-methoxyphenol

Commercially available 1-bromo-3,5-dimethoxybenzene (18.74 g, 86.3 mmol) was dissolved in 1-methyl-2-pyrrolidone (100 mL), and sodium thiomethoxide (6.74 g, 96.2 mmol) was added, followed by stirring at 100°C for 3 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, 1N hydrochloric acid (200 mL) was added, and extraction was carried out with diethyl ether (500 mL). The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=20%-25%) to afford the desired compound (15.03 g, yield 86%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.77 (3H, s), 4.82 (1H, s), 6.33 (1H, t, J=2.4 Hz), 6.61 (1H, t, J=2.0 Hz), 6.66 (1H, t, J=2.0 Hz).

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(78b) 1-Bromo-3-methoxy-5-[(1S)-2-methoxy-1-methylethoxy]benzene

3-Bromo-5-methoxyphenol (7.60 g, 37.4 mmol) synthesized in Example (78a) was dissolved in toluene (100 mL), and R-(-)-1-methoxy-2-propanol (4.40 mL, 44.9 mmol) and triphenylphosphine (13.8 g, 52.6 mmol) were added, followed by dropwise addition of diethyl azodicarboxylate (2.2 mol/l toluene solution, 24 mL, 52.8 mmol) at 0°C and stirring at room temperature for 1.5 hours under nitrogen atmosphere. The solvent was distilled off under reduced pressure, diethyl ether (100 mL) was added, and the deposit was filtered to be removed. The mother liquor was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=10%-20%) to afford the desired compound (9.22 g, yield 89%) as a colorless liquid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.30 (3H, d, J=6.3 Hz), 3.40 (3H, s), 3.47 (1H, dd, J=10.6, 4.3 Hz), 3.55 (1H, dd, J=10.4, 6.1 Hz), 3.76 (3H, s), 4.46-4.52 (1H, m), 6.42 (1H, t, J=2.2 Hz), 6.65 (1H, dd, J=2.3, 1.6 Hz), 6.69 (1H, t, J=2.0 Hz).
MS (EI) m/z: 274 $(M)^+$.

(78c) 3-Bromo-5-[(1S)-2-methoxy-1-methylethoxy]phenol

1-Bromo-3-methoxy-5-[(1S)-2-methoxy-1-methylethoxy]benzene (9.21 g, 33.5 mmol) synthesized in Example (78b) was dissolved in 1-methyl-2-pyrrolidone (100 mL), and sodium thiomethoxide (2.75 g, 37.3 mmol) was added, followed by stirring at 130°C for 3 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, 2N hydrochloric acid (500 mL) was added, and extraction was carried out with diethyl ether (300 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=20%-25%) to afford the desired compound (8.30 g, yield 95%) as a

colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.29 (3H, d, J=6.3 Hz), 3.41 (3H, s), 3.46 (1H, dd, J=10.2, 4.3 Hz), 3.55 (1H, dd, J=10.6, 5.9 Hz), 4.45-4.51 (1H, m), 4.96 (1H, br s), 6.36 (1H, t, J= 2.0 Hz), 6.59 (1H, t, J= 2.0 Hz), 6.68 (1H, t, J= 2.0 Hz).

MS (EI) m/z: 260 $(M)^+$.

(78d) 3-[(1S)-2-Methoxy-1-methylethoxy]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol

3-Bromo-5-[(1S)-2-methoxy-1-methylethoxy]phenol (8.30 g, 31.8 mmol) synthesized in Example (78c) was dissolved in N,N-dimethylformamide (100 mL), and bis(pinacolate)diboron (10.50 g, 41.3 mmol), [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloride dichloromethane complex (810 mg, 0.992 mmol) and potassium acetate (15.50 g, 158 mmol) were added, followed by stirring at 90°C for 3 hours under nitrogen atmosphere. After the reaction solution was cooled to room temperature, water (500 mL) was added, and extraction was carried out with diethyl ether (300 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=20%-30%) to afford the desired compound (8.75 g, yield 89%) as a brown oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.26 (3H, d, J=4.1 Hz), 1.33 (12H, s), 3.41 (1H, s), 3.47 (1H, dd, J=10.2, 4.7 Hz), 3.57 (1H, dd, J=10.6, 5.9 Hz), 4.52-4.58 (1H, m), 4.80 (1H, brs), 6.55 (1H, t, J=2.4 Hz), 6.83 (1H, d, J=2.4 Hz), 6.95 (1H, d, J=2.4 Hz).

MS (FAB) m/z: 309 $(M+H)^+$.

(78e) t-Butyl 2,5-dibromo-1H-pyrrole-1-carboxylate

Commercially available t-butyl 1-pyrrolecarboxylate (46.68 g, 279 mmol) was dissolved in tetrahydrofuran (500 mL), and cooled to -78°C. To this, N-bromosuccinimide (100.48 g, 565 mmol) was added in small portions over 1 hour. The temperature

of the reaction solution was raised naturally, and stirring was carried out at room temperature for 18 hours. The reaction solution was cooled to 0°C, sodium sulphite (36.43g) was added, followed by stirring for 30 minutes, and subsequently hexane (200 mL) was added to give a precipitate, which was removed by Celite filtration. The solvent of the filtrate was distilled off uner reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=1%-5%) to afford the desired compound (52.69 g, yield 58%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.65 (9H, s), 6.25 (2H, s).

MS (EI) m/z: 323 (M^+).

(78f) 2-Benzyl 1-t-butyl 5-bromo-1H-pyrrole-1,2-dicarboxylate

t-Butyl 2,5-dibromo-1H-pyrrole-1-carboxylate (10.98 g, 33.8 mmol) synthesized in Example (78e) was dissolved in diethyl ether (135 mL), and cooled to -78°C. n-Butyl lithium (2.77 mol/L hexane solution, 12.8 mL, 35.5 mmol) was added dropwise slowly, and stirring was carried out for 1 hour. To the reaction solution, benzyl chloroformate (6.25 mL, 44.0 mmol) was added dropwise slowly, and stirring was carried out for 30 minutes. With the temperature of the reaction solution being raised gradually to room temperature, stirring was carried out for 1 hour. To the reaction solution, were added a saturated aqueous ammonium chloride solution (200 mL) and diethyl ether (300 mL), and the solution was separated. The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=5%-45%) to afford the desired compound (8.80 g, yield 68%) as a reddish brown oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.56 (9H, s), 5.26 (2H, s), 6.21 (1H, d, J=3.9 Hz), 6.85 (1H, d, J=3.9 Hz), 7.28-7.39 (5H, m).

MS (FAB) m/z: 380 $(M+H)^+$.

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(78g) 2-Benzyl 1-t-butyl 5-{3-hydroxy-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrole-1,2-dicarboxylate

2-Benzyl 1-t-butyl 5-bromo-1H-pyrrole-1,2-dicarboxylate (8.75 g, 23.0 mmol) synthesized in Example (78f) and 3-[(1S)-2-methoxy-1-methylethoxy]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (7.11 g, 23.1 mmol) synthesized in Example (78d) were dissolved in a mixed solvent of 1,4-dioxane (92 mL) and water (23 mL), and [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloride dichloromethane complex (570 mg, 0.698 mmol) and potassium carbonate (7.95 g, 57.5 mmol) were added, followed by stirring at 55°C for 3 hours under nitrogen atmosphere. After the reaction solution was cooled to room temperature, water (200 mL) was added, and extraction was carried out with ethyl acetate (200 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=15%-35%) to afford the desired compound (8.32 g, yield 75%) as a brown oil.

^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.29 (3H, d, J=6.3 Hz), 1.41 (9H, s), 3.40 (3H, s), 3.47 (1H, dd, J=10.3, 4.4 Hz), 3.57 (1H, dd, J=10.3, 5.9 Hz), 4.48-4.54 (1H, m), 5.20 (1H, s), 5.30 (2H, s), 6.17 (1H, d, J=3.4 Hz), 6.44 (1H, s), 6.48 (1H, s), 6.57 (1H, s), 6.94 (1H, d, J=3.4 Hz), 7.42-7.31 (5H, m).

MS (FAB) m/z: 481 (M^+).

(78h) 5-Bromo-2-(methylthio)pyridine

Commercially available 2,5-dibromo pyridine (6.01 g, 25.4 mmol) was dissolved in N,N-dimethylformamide (50 mL), and sodium thiomethoxide (2.20 g, 31.4 mmol) was added, followed by stirring at 0°C for 3.5 hours under nitrogen atmosphere. The reaction solution was brought back to room temperature, water (250 mL) was added, and extraction was carried out with diethyl ether (250 mL). The organic layer was washed with saturated

brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=3%-5%) to afford the desired compound (4.90 g, yield 94%) as a white solid. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.54 (3H, s), 7.08 (1H, d, J=8.2 Hz), 7.58 (1H, dd, J=8.6, 2.3 Hz), 8.49 (1H, d, J=2.0 Hz).

(78i) 5-Fluoro-2-(methylsulfonyl)pyridine

5-Bromo-2-(methylthio)pyridine (4.90 g, 24.0 mmol) synthesized in Example (78h) was dissolved in tetrahydrofuran (100 mL), and n-butyl lithium (1.57 mol/L hexane solution, 17.0 mL, 26.7 mmol) was added dropwise at -78°C, followed by stirring at -78°C for 1 hour under nitrogen atmosphere. N-Fluorobenzenesulfonimide (11.0 g, 34.9 mmol) was dissolved in tetrahydrofuran (25 mL), followed by dropwise addition to the reaction solution at -78°C, and stirring was carried out at -78°C for 2 hours under nitrogen atmosphere. The reaction solution was brought back to room temperature, and stirring was carried out for 1.5 hours. A saturated aqueous ammonium chloride solution (200 mL) was added, and extraction was carried out with diethyl ether (300 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under slightly reduced pressure.

The resulting residue was dissolved in methylene chloride (150 mL), and m-chloroperbenzoic acid (65%, 16.5 g, 62.1 mmol) was added slowly at 0°C, followed by stirring at 0°C for 1.5 hours under nitrogen atmosphere. After the white solid material was removed by Celite filtration, a saturated aqueous sodium hydrogencarbonate solution (100 mL) was added, and extraction was carried out with methylene chloride (400 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl

acetate/hexane=3%-5%) to afford the desired compound (1.95 g, yield 46%) as a yellowish white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.24 (3H, s), 7.67 (1H, ddd, J=9.9, 6.9, 1.9 Hz), 8.16 (1H, dd, J=8.6, 4.3 Hz), 8.59 (1H, d, J=2.7 Hz).

(78j) Benzyl 5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxylate

2-Benzyl 1-t-butyl 5-{3-hydroxy-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrole-1,2-dicarboxylate (5.05 g, 10.49 mmol) synthesized in Example (78g) and 5-fluoro-2-(methylsulfonyl)pyridine (2.05 g, 11.70 mmol) synthesized in Example (78i) were dissolved in N,N-dimethylformamide (30 mL), and potassium carbonate (4.50 g, 32.56 mmol) was added, followed by stirring at 80°C for 3 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, water (150 mL) was added, and extraction was carried out with diethyl ether (150 mL). The organic layer was washed with saturated brine, subsequently dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure.

The resulting compound was dissolved in trifluoroacetic acid (10 mL), and stirring was carried out at room temperature for 1 hour under nitrogen atmosphere. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=35%-50%) to afford the desired compound (5.08 g, yield 90%) as a white oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J=6.3 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.51 (1H, dd, J=10.3, 3.9 Hz), 3.58 (1H, dd, J=10.3, 6.3 Hz), 4.54-4.61 (1H, m), 5.33 (2H, s), 6.51 (1H, t, J=3.2 Hz), 6.59 (1H, s), 6.86 (1H, s), 6.99 (1H, t, J=2.9 Hz), 7.02 (1H, s), 7.32-7.45 (7H, m), 8.04 (1H, d, J=8.8 Hz), 8.48 (1H, s), 9.36 (1H, br s).

(78k) 5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[6-

(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxylic acid

Benzyl 5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxylate (5.08 g, 9.47 mmol) synthesized in Example (78j) was dissolved in ethyl acetate (30 mL), and a 10% palladium carbon catalyst (1.10 g) was added, followed by stirring at room temperature for 3 hours under hydrogen atmosphere. After Celite filtration, the solvent was distilled off under reduced pressure to afford the desired compound (4.30 g, yield ~100%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J=5.9 Hz), 3.23 (3H, s), 3.47 (3H, s), 3.57 (1H, dd, J=9.8, 3.9 Hz), 3.67 (1H, dd, J=10.0, 6.6 Hz), 4.72-4.80 (1H, m), 6.52 (1H, s), 6.59 (1H, s), 6.92 (1H, s), 7.03 (1H, s), 7.32 (1H, s), 7.45 (1H, dd, J=8.5, 1.7 Hz), 8.05 (1H, d, J=8.8 Hz), 8.49 (1H, d, J=2.4 Hz), 10.31 (1H, br s).

(78l) 5-{3-[5-(4,5-Dihydro-1,3-oxazol-2-yl)-1H-pyrrol-2-yl]-5-[(1S)-2-methoxy-1-methylethoxy]phenoxy}-2-(methylsulfonyl)pyridine

5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxylic acid (1.00 g, 2.24 mmol) synthesized in Example (78k) was dissolved in methanol (20 mL), and ethanolamine (0.30 mL, 4.97 mmol) and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride n hydrate (1.00 g, 3.61 mmol) were added, followed by stirring at room temperature for 1 day under nitrogen atmosphere. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=1%-3%) to afford a compound as a white solid.

This was dissolved in tetrahydrofuran (20 mL), and anhydrous methanesulfonic acid (700 mg, 4.02 mmol) and triethylamine (0.85 mL, 6.10 mmol) were added, followed by stirring at 50°C for 5 hours under nitrogen atmosphere. To the

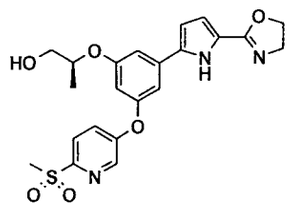
reaction solution, a saturated aqueous ammonium chloride solution (30 mL) was added, and extraction was carried out with methylene chloride (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=1%-3%) to afford the desired compound (410 mg, yield 39%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J=6.3 Hz), 3.23 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J=10.2, 3.9 Hz), 3.59 (1H, dd, J=10.6, 6.3 Hz), 4.00 (2H, t, J=9.2 Hz), 4.43 (2H, t, J=9.4 Hz), 4.55-4.61 (1H, m), 6.51 (1H, d, J=3.5 Hz), 6.57 (1H, t, J=2.2 Hz), 6.77 (1H, d, J=3.9 Hz), 6.84 (1H, t, J=1.8 Hz), 7.03 (1H, t, J=1.6 Hz), 7.44 (1H, dd, J=8.6, 2.7 Hz), 8.05 (1H, d, J=8.6 Hz), 8.49 (1H, d, J=2.7 Hz).

MS (ESI) m/z: 472.15408 $(M+H)^+$.

(Example 79)

(2S)-2-(3-[5-(4,5-Dihydro-1,3-oxazol-2-yl)-1H-pyrrol-2-yl]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol



5-{3-[5-(4,5-Dihydro-1,3-oxazol-2-yl)-1H-pyrrol-2-yl]-5-[(1S)-2-methoxy-1-methylethoxy]phenoxy}-2-(methylsulfonyl)pyridine (230 mg, 0.49 mmol) synthesized in Example (781) was dissolved in methylene chloride (10 mL), and boron tribromide (1.0 mol/L methylene chloride solution, 0.75 mL, 0.75 mmol) was added dropwise at -78°C, followed by stirring at room temperature for 1.5 hours under nitrogen atmosphere. To this reaction solution, a saturated aqueous ammonium chloride solution (20 mL) was added, and extraction was carried out with methylene chloride (20 mL). The organic layer was washed with

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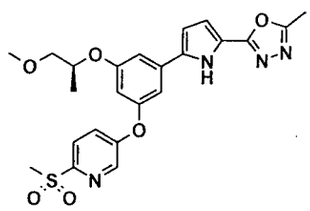
saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=2%-4%) to afford the desired compound (170 mg, yield 76%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.30 (3H, d, J=6.3 Hz), 3.23 (3H, s), 3.79 (2H, d, J=5.9 Hz), 4.01 (2H, t, J=9.4 Hz), 4.43 (2H, t, J=9.4 Hz), 4.55-4.61 (1H, m), 6.44 (1H, t, J=2.2 Hz), 6.49 (1H, d, J=3.9 Hz), 6.76 (1H, d, J=3.5 Hz), 6.81 (1H, t, J=2.0 Hz), 6.96 (1H, s), 7.40 (1H, dd, J=8.6, 2.3 Hz), 8.04 (1H, d, J=8.6 Hz), 8.46 (1H, d, J=2.3 Hz).

MS (ESI) m/z: 458.13852 $(M+H)^+$.

(Example 80)

5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}-2-(methylsulfonyl)pyridine



5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxylic acid (600 mg, 1.34 mmol) synthesized in Example (78k) was dissolved in methylene chloride (20 mL), and acetohydrazide (220 mg, 2.97 mmol), WSCI·HCl (580 mg, 3.03 mmol) and 4-dimethylaminopyridine (150 mg, 1.23 mmol) were added, followed by stirring at room temperature overnight under nitrogen atmosphere. A saturated aqueous ammonium chloride solution (100 mL) was added, and extraction was carried out with methylene chloride (100 mL). The organic layer was washed with saturated brine, subsequently dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure.

This residue was dissolved in methylene chloride (20 mL),

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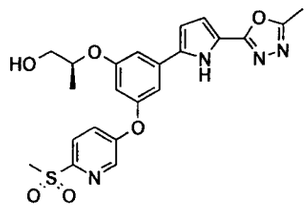
and p-toluenesulfonyl chloride (510 mg, 2.68 mmol) and triethylamine (0.75 mL, 5.38 mmol) were added, followed by stirring at room temperature for 4 hours under nitrogen atmosphere. To the reaction solution, a saturated aqueous ammonium chloride solution (50 mL) was added, and extraction was carried out with methylene chloride (50 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=60-80%) to afford the desired compound (450 mg, yield 69%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.35 (3H, d, J=6.3 Hz), 2.59 (3H, s), 3.24 (3H, s), 3.42 (3H, s), 3.52 (1H, dd, J=10.6, 3.5 Hz), 3.61 (1H, dd, J=11.3, 5.5 Hz), 4.51-4.72 (1H, m), 6.59-6.61 (2H, br m), 6.87-6.90 (2H, br m), 7.06 (1H, br s), 7.46 (1H, d, J=8.6 Hz), 8.06 (1H, d, J=8.6 Hz), 8.50 (1H, d, J=1.6 Hz), 9.66 (1H, br s).

MS (ESI) m/z: 485.14739 $(M+H)^+$.

(Example 81)

(2S)-2-(3-[5-(5-Methyl-1,3,4-oxadiazol-2-yl)-1H-pyrrol-2-yl]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol

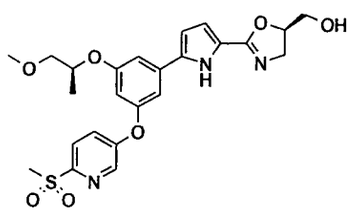


5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}-2-(methylsulfonyl)pyridine (320 mg, 0.660 mmol) synthesized in Example 80 was dissolved in methylene chloride (10 mL), and boron tribromide (1.0 mol/L methylene chloride solution, 1.00 mL, 1.00 mmol) was added dropwise at -78°C, and stirring was carried out at room temperature for 1 hour under nitrogen atmosphere. To this reaction solution, a saturated aqueous ammonium chloride

solution (20 mL) was added, and extraction was carried out with methylene chloride (20 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=1%-3%) to afford the desired compound (190 mg, yield 61%) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.29 (3H, d, J=6.3 Hz), 2.34 (1H, br s), 2.55 (3H, s), 3.21 (3H, s), 3.76 (2H, br s), 4.49-4.58 (1H, m), 6.52 (1H, s), 6.55 (1H, dd, J=3.9, 2.7 Hz), 6.81-6.84 (2H, m), 7.00 (1H, t, J=2.0 Hz), 7.42 (1H, dd, J=8.6, 2.7 Hz), 8.03 (1H, d, J=8.6 Hz), 8.45 (1H, d, J=2.7 Hz), 9.76 (1H, br s).
MS (ESI) m/z: 471.13599 $(M+H)^+$.

(Example 82)
{(5R)-2-[5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-5-yl}methanol



(82a) 5-(3-{[(2S)-1-Methoxypropan-2-yl]oxy}-5-{5-[(5R)-5-{[(tripropan-2-ylsilyl)oxy]methyl}-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-2-(methylsulfonyl)pyridine

5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxylic acid (1.70 g, 3.81 mmol) synthesized in Example (78k) was dissolved in methanol (30 mL), and (S)-(-)-3-amino-1,2-propanediol (0.80 g, 8.78 mmol) and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride n hydrate (1.70 g, 6.14 mmol) were added, followed by stirring at room temperature for 3 days under nitrogen atmosphere. The solvent was distilled off under reduced pressure, and the resulting residue was

purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=7%-10%) to afford a yellow solid.

This was dissolved in methylene chloride (40 mL), and triisopropylchlorosilane (1.32 mL, 6.17 mmol), 4-dimethylaminopyridine (0.75 g, 6.14 mmol) and triethylamine (2.87 mL, 20.59 mmol) were added, followed by stirring at room temperature for 1 day under nitrogen atmosphere. To the reaction solution, a saturated aqueous ammonium chloride solution (50 mL) was added, and extraction was carried out with methylene chloride (50 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=1%) to afford a yellow solid.

This was dissolved in tetrahydrofuran (30 mL), and anhydrous methanesulfonic acid (1.05 g, 6.03 mmol) and triethylamine (1.70 mL, 12.20 mmol) were added, followed by stirring at 50°C for 4.5 hours under nitrogen atmosphere. To the reaction solution, a saturated aqueous ammonium chloride solution (50 mL) was added, and extraction was carried out with methylene chloride (50 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=50%-70%) to afford the desired compound (1.18 g, yield 47%) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$, 500 MHz): δ 0.99-1.16 (21H, m), 1.32 (3H, d, J=6.3 Hz), 3.23 (3H, s), 3.40 (3H, s), 3.50 (1H, dd, J=10.3, 3.9 Hz), 3.58 (1H, dd, J=10.3, 5.9 Hz), 3.81-3.90 (2H, m), 3.92-4.01 (2H, m), 4.51-4.62 (1H, br s), 4.70-4.78 (1H, br s), 6.49 (1H, d, J=3.9 Hz), 6.56 (1H, s), 6.72 (1H, t, J=2.0 Hz), 6.83 (1H, s), 7.01 (1H, s), 7.43 (1H, dd, J=7.6, 1.7 Hz), 8.04 (1H, d, J=8.3 Hz), 8.48 (1H, d, J=2.4 Hz).

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(82b) {(5R)-2-[5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-5-yl}methanol

5-(3-{[(2S)-1-Methoxypropan-2-yl]oxy}-5-{5-[(5R)-5-{[(tripropan-2-ylsilyl)oxy]methyl}-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-2-(methylsulfonyl)pyridine (1.18 g, 1.79 mmol) synthesized in Example (82a) was dissolved in tetrahydrofuran (10 mL), and tetrabutylammonium fluoride (1.0 mol/L tetrahydrofuran solution, 2.00 mL, 2.00 mmol) was added at room temperature, followed by stirring at room temperature for 30 minutes under nitrogen atmosphere. To this reaction solution, a saturated aqueous ammonium chloride solution (20 mL) was added, and extraction was carried out with methylene chloride (20 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=2%-3%) to afford the desired compound (680 mg, yield 76%) as a white solid.

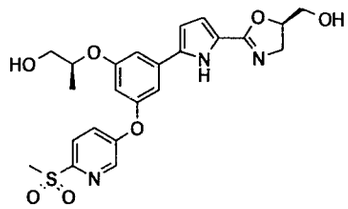
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.27 (3H, d, J=6.3 Hz), 3.21 (3H, s), 3.40 (3H, s), 3.48 (1H, dd, J=10.2, 3.9 Hz), 3.56 (1H, dd, J=10.2, 6.3 Hz), 3.68 (1H, dd, J=12.1, 5.1 Hz), 3.75 (1H, dd, J=14.5, 7.4 Hz), 3.85 (1H, d, J=9.4 Hz), 4.00 (1H, dd, J=14.1, 9.8 Hz), 4.53 (1H, br s), 4.78 (1H, br s), 6.46 (1H, d, J=3.9 Hz), 6.55 (1H, t, J=2.2 Hz), 6.72 (1H, d, J=3.9 Hz), 6.81 (1H, d, J=2.0 Hz), 6.97 (1H, s), 7.42 (1H, dd, J=8.6, 2.7 Hz), 8.03 (1H, d, J=8.6 Hz), 8.46 (1H, d, J=2.7 Hz).

MS (ESI) m/z: 502.16243 $(M+H)^+$.

(Example 83)

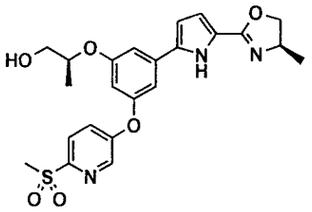
(2S)-2-(3-{5-[(5R)-5-(Hydroxymethyl)-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol

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{(5R)-2-[5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-5-yl}methanol (520 mg, 1.04 mmol) synthesized in Example (82b) was dissolved in methylene chloride (10 mL), and boron tribromide (1.0 mol/L methylene chloride solution, 2.00 mL, 2.00 mmol) was added dropwise at -78°C, followed by stirring at room temperature for 4 hours under nitrogen atmosphere. To this reaction solution, a 1N aqueous sodium hydroxide solution (20 mL) was added, and extraction was carried out with methylene chloride (20 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=3%-5%) to afford the desired compound (148 mg, yield 29%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.30 (3H, d, J=5.9 Hz), 3.23 (3H, s), 3.70-3.82 (3H, m), 3.90-3.99 (2H, m), 4.07 (1H, t, J=11.5 Hz), 4.62 (1H, br s), 4.95 (1H, br s), 6.47 (2H, d, J=3.9 Hz), 6.86 (2H, d, J=3.9 Hz), 7.15 (1H, s), 7.40 (1H, dd, J=8.8, 2.4 Hz), 8.03 (1H, d, J=8.8 Hz), 8.45 (1H, d, J=2.4 Hz), 11.26 (1H, br s).
MS (ESI) m/z: 488.14896 $(M+H)^+$.

(Example 84)
(2S)-2-(3-{5-[(4R)-4-Methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol



(84a) N-[(1R)-2-Hydroxy-1-methylethyl]-5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxamide

5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxylic acid (2.00 g, 4.48 mmol) synthesized in Example (78k), D-alaninol (0.52 mL, 6.72 mmol), HOBT·H_2O (0.73 g, 5.38 mmol) and N-methylmorpholine (0.99 mL, 8.96 mmol) were dissolved in methylene chloride (40 mL), and WSCI·HCl (0.94 g, 4.93 mmol) was added at room temperature, followed by stirring for 30 hours under nitrogen atmosphere. The reaction solution was diluted with methylene chloride (100 mL), washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=50%-90%) to afford the desired compound (1.94 g, 86%) as a white solid. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.27 (3H, d, J=6.8 Hz), 1.33 (3H, d, J=6.3 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.51 (1H, dd, J=3.9, 10.3 Hz), 3.57-3.64 (2H, m), 3.76 (1H, dd, J=3.5, 11.0 Hz), 4.21-4.27 (1H, brm), 4.55-4.60 (1H, m), 6.06 (1H, d, J=7.3 Hz), 6.48 (1H, dd, J=2.7, 4.0 Hz), 6.57 (1H, t, J=2.1 Hz), 6.60 (1H, dd, J=2.0, 2.3 Hz), 6.84 (1H, t, J=1.7 Hz), 7.01 (1H, t, J=1.7 Hz), 7.44 (1H, dd, J=2.7, 8.7 Hz), 8.04 (1H, d, J=8.7 Hz), 8.47 (1H, d, J=2.7 Hz), 9.71 (1H, brs).

(84b) 5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-2-(methylsulfonyl)pyridine

N-[(1R)-2-Hydroxy-1-methylethyl]-5-(3-[(1S)-2-methoxy-1-

methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxamide (1.94 g, 3.85 mmol) synthesized in Example (84a) was dissolved in tetrahydrofuran (35 mL), and anhydrous methanesulfonic acid (1.38 g, 7.70 mmol) and triethylamine (2.15 mL, 15.41 mmol) were added, followed by stirring at 50°C for 1.5 hours under nitrogen atmosphere. A saturated aqueous sodium hydrogencarbonate solution (30 mL) was added, and the solution was separated with ethyl acetate (50 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=30%-75%) to afford the desired compound (1.59 g, yield 85%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (6H, d, J=6.3 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J=3.9, 10.2 Hz), 3.59 (1H, dd, J=6.1,10.4 Hz), 3.93 (1H, t, J=7.8 Hz), 4.30-4.36 (1H, m), 4.50 (1H, dd, J=8.2, 9.2 Hz), 4.56-4.60 (1H, m), 6.51 (1H, d, J=3.9 Hz), 6.57 (1H, t, J=2.2 Hz), 6.75 (1H, d, J=3.8 Hz), 6.84 (1H, t, J=1.8 Hz), 7.04 (1H, t, J=1.8 Hz), 7.44 (1H, dd, J=2.8, 8.7 Hz), 8.05 (1H, d, J=8.8 Hz), 8.45 (1H, d, J=2.7 Hz).

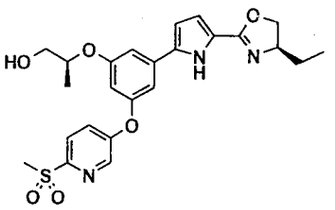
(84c) (2S)-2-(3-{5-[(4R)-4-Methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol

5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-2-(methylsulfonyl)pyridine (1.20 g, 2.47 mmol) synthesized in Example (84b) was dissolved in methylene chloride (25 mL), followed by cooling to -78°C, and boron tribromide (1.0 mol/L methylene chloride solution, 2.72 mL, 2.72 mmol) was added under nitrogen atmosphere. After the temperature was raised naturally and stirring was carried out at room temperature for 30 minutes, a saturated aqueous sodium hydrogencarbonate solution was added to neutralize the reaction solution, followed by extraction with methylene chloride (80 mL). The organic layer was washed with

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saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=70%-100%) to afford the desired compound (895 mg, 77%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.29 (3H, d, J=6.2 Hz), 1.34 (1H, d, J=6.6 Hz), 3.23 (3H, s), 3.79-3.81 (2H, m), 3.95 (1H, t, J=7.9 Hz), 4.32-4.38 (1H, m), 4.52 (1H, dd, J=8.1, 9.3 Hz), 4.61-4.65 (1H, m), 6.35 (1H, t, J=2.2 Hz), 6.47 (1H, d, J=3.9 Hz), 6.75 (1H, d, J=3.8 Hz), 6.80 (1H, dd, J=1.4, 2.4 Hz), 6.97 (1H, t, J=1.8 Hz), 7.37 (1H, dd, J=2.7, 8.8 Hz), 8.02 (1H, d, J=8.8 Hz), 8.43 (1H, d, J=2.7 Hz).
MS (ESI) m/z: 472.15382 $(M+H)^+$.

(Example 85)
(2S)-2-(3-{5-[(4R)-4-Ethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol



(85a) N-[(1R)-1-(Hydroxymethyl)propyl]-5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxamide

5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxylic acid (1.20 g, 2.69 mmol) synthesized in Example (78k), (R)-(-)-2-amino-1-butanol (0.38 mL, 4.03 mmol), HOBT·H_2O (0.44 g, 3.23 mmol) and N-methylmorpholine (0.59 mL, 5.38 mmol) were dissolved in methylene chloride (30 mL), and WSCI·HCl (0.62 g, 3.23 mmol) was added at room temperature, followed by stirring for 6 hours under nitrogen atmosphere. The reaction solution was diluted with methylene chloride (50 mL), washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and

saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=50%-90%) to afford the desired compound (1.18 g, 85%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.01 (3H, t, J=7.4 Hz), 1.33 (3H, d, J=6.3 Hz), 1.67-1.74 (2H, m), 3.23 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J=3.9, 10.4 Hz), 3.59 (1H, dd, J=6.2, 10.4 Hz), 3.69 (1H, dd, J=5.7, 10.9 Hz), 3.79 (1H, dd, 3.4, 11.0 Hz), 4.01-4.06 (1H, brm), 4.56-4.60 (1H, m), 6.02 (1H, d, J=8.3 Hz), 6.49 (1H, dd, J=2.9, 3.9 Hz), 6.58 (1H, t, J=2.3 Hz), 6.61 (1H, dd, J=2.5, 4.1 Hz), 6.84 (1H, t, J=1.8 Hz), 7.02 (1H, t, J=1.8 Hz), 7.45 (1H, dd, J=2.8, 8.7 Hz), 8.05 (1H, d, J=8.7 Hz), 8.45 (1H, dd, J=0.8, 2.8 Hz), 9.60 (1H, brs).

(85b) 5-(3-{5-[(4R)-4-Ethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-[(1S)-2-methoxy-1-methylethoxy]phenoxy)-2-(methylsulfonyl)pyridine

N-[(1R)-1-(Hydroxymethyl)propyl]-5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxamide (1.18 g, 2.28 mmol) synthesized in Example (85a) was dissolved in tetrahydrofuran (20 mL), and anhydrous methanesulfonic acid (0.82 g, 4.56 mmol) and triethylamine (1.27 mL, 9.12 mmol) were added, followed by stirring at 50°C for 1.5 hours under nitrogen atmosphere. A saturated aqueous sodium hydrogencarbonate solution (30 mL) was added, and the solution was separated with ethyl acetate (50 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=40%-70%) to afford the desired compound (1.06 g, yield 93%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.99 (3H, t, J=7.4 Hz), 1.34 (3H, d, J=6.4 Hz), 1.56-1.65 (1H, m), 1.66-1.74 (1H, m), 3.23 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J=4.0, 10.2 Hz), 3.60 (1H, dd,

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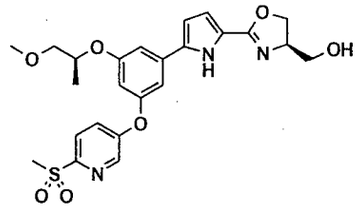
J=6.1,10.3 Hz), 4.02 (1H, t, J=7.8 Hz), 4.16-4.20 (1H, m), 4.46 (1H, t, J=8.7 Hz), 4.56-4.60 (1H, m), 6.51 (1H, d, J=3.9 Hz), 6.56 (1H, t, J=2.2 Hz), 6.74 (1H, d, J=3.8 Hz), 6.85 (1H, t, J=1.7 Hz), 7.05 (1H, t, J=1.7 Hz), 7.44 (1H, dd, J=2.7, 8.7 Hz), 8.05 (1H, dd, J=0.8, 8.5 Hz), 8.45 (1H, dd, J=0.8, 2.7 Hz).

(85c) (2S)-2-(3-{5-[(4R)-4-Ethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol

5-(3-{5-[(4R)-4-Ethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-[(1S)-2-methoxy-1-methylethoxy]phenoxy)-2-(methylsulfonyl)pyridine (1.06 g, 2.12 mmol) synthesized in Example (85b) was dissolved in methylene chloride (20 mL), followed by cooling to -78°C, and boron tribromide (1.0 mol/L methylene chloride solution, 2.33 mL, 2.33 mmol) was added under nitrogen atmosphere. After the temperature was raised naturally and stirring was carried out at room temperature for 30 minutes, a saturated aqueous sodium hydrogencarbonate solution was added to neutralize the reaction solution, followed by extraction with methylene chloride (80 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=70%-100%) to afford the desired compound (738 mg, 71%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.02 (3H, t, J=7.4 Hz), 1.28 (3H, d, J=6.2 Hz), 1.58-1.66 (1H, m), 1.67-1.74 (1H, m), 3.22 (3H, s), 3.80-3.82 (2H, m), 4.03 (1H, t, J=8.0 Hz), 4.16-4.23 (1H, m), 4.49 (1H, t, J=8.7 Hz), 4.62-4.68 (1H, m), 6.29 (1H, d, J=2.2 Hz), 6.45 (1H, t, J=3.7 Hz), 6.74 (1H, d, J=3.9 Hz), 6.79 (1H, t, J=1.8 Hz), 6.95 (1H, t, J=1.7 Hz), 7.35 (1H, dd, J=2.7, 8.7 Hz), 8.01 (1H, d, 8.7 Hz), 8.42 (1H, d, J=2.7 Hz).
MS (ESI) m/z: 486.16955 $(M+H)^+$.

(Example 86)
{(4R)-2-[5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[6-

(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}methanol



(86a) Methyl N-{[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]carbonyl}-L-serinate

5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxylic acid (1.60 g, 3.58 mmol) synthesized in Example (78k), L-serine methyl ester hydrochloride (0.61 g, 3.94 mmol), HOBT·H_2O (0.53 g, 3.94 mmol) and N-methylmorpholine (0.79 mL, 7.17 mmol) were dissolved in a mixed solvent of methylene chloride (30 mL) and N,N-dimethylformamide (7 mL), and WSCI·HCl (0.82 g, 4.30 mmol) was added at room temperature, followed by stirring for 15 hours under nitrogen atmosphere. The reaction solution was diluted with methylene chloride (100 mL), washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=50%-80%) to afford the desired compound (1.91 g, 97%) as a white solid. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.33 (3H, d, J=6.4 Hz), 3.22 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J=3.8, 10.3 Hz), 3.58 (1H, dd, J=6.3, 10.3 Hz), 3.78 (3H, s), 3.98 (1H, dd, J=3.4, 11.3 Hz), 4.04 (1H, dd, J=3.9, 11.3 Hz), 4.56-4.59 (1H, brm), 4.80-4.83 (1H, m), 6.48 (1H, dd, J=2.7, 3.8 Hz), 6.56 (1H, t, J=2.0 Hz), 6.74 (1H, dd, J=2.0, 2.4 Hz), 6.88 (1H, t, J=1.7 Hz), 6.97 (1H, d, J=7.5 Hz), 7.04 (1H, t, J=1.9 Hz), 7.43 (1H, dd, J=2.8, 8.8 Hz), 8.03 (1H, d, J=8.8 Hz), 8.46 (1H, d, J=2.8 Hz), 10.5 (1H, brs).

(86b) Methyl (4S)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-

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{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazole-4-carboxylate

Methyl N-{[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]carbonyl}-L-serinate (1.91 g, 3.57 mmol) synthesized in Example (86a) was dissolved in methylene chloride (40 mL), and bis(2-methoxyethyl)aminosulfur trifluoride (0.85 mL, 4.64 mmol) was added dropwise at -78°C. After stirring for 30 minutes under nitrogen atmosphere, potassium carbonate (0.74 g, 5.35 mmol) was added, and stirring was carried out at 0°C for 10 minutes, followed by further stirring at room temperature for 3 hours. A saturated aqueous sodium hydrogencarbonate solution (30 mL) was added, followed by extraction with methylene chloride (100 mL), and the organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=30%-70%) to afford the desired compound (1.76 g, 93%) as a white powder. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.34 (3H, d, J=6.2 Hz), 3.23 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J=4.1,10.3 Hz), 3.59 (1H, dd, J=6.3, 10.3 Hz), 3.82 (1H, s), 4.56-4.60 (2H, m), 4.67 (1H, t, J=8.2 Hz), 4.90 (1H, dd, J=5.2, 7.8 Hz), 6.50 (1H, d, J=3.8 Hz), 6.59 (1H, t, J=2.2 Hz), 6.81 (1H, d, J=3.9 Hz), 6.84 (1H, t, J=1.7 Hz), 7.03 (1H, s), 7.45 (1H, dd, J=2.7, 8.6 Hz), 8.06 (1H, d, J=8.7 Hz), 8.48 (1H, d, J=2.7 Hz).

(86c) {(4R)-2-[5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}methanol

Methyl (4S)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazole-4-carboxylate (1.76 g, 3.32 mmol) synthesized in Example (86b) was dissolved in tetrahydrofuran (30 mL), and lithium aluminum hydride (0.25 g, 6.65 mmol) was added at 0°C. After stirring for 30 minutes under nitrogen

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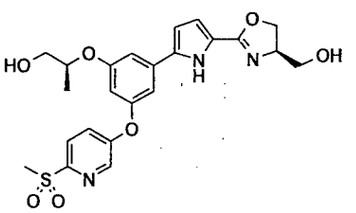
atmosphere, water (0.25 mL), a 5N aqueous sodium hydroxide solution (0.25 mL) and water (0.75 mL) were added in this order, and stirring was carried out for 10 minutes. Ethyl acetate (100 mL) was added followed by stirring for 5 minutes, and subsequently drying was carried out over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-5%) to afford the desired compound (1.15 g, 69%) as a white powder.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J=6.3 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.51 (1H, dd, J=4.1, 10.4 Hz), 3.58-3.62 (2H, m), 3.97 (1H, d, J=12.2 Hz), 4.10-4.15 (2H, m), 4.31-4.39 (2H, m), 4.56-4.60 (1H, m), 6.37 (1H, d, J=3.8 Hz), 6.47 (1H, d, J=3, 9 Hz), 6.57 (1H, t, J=2.2 Hz), 6.87 (1H, dd, J=1.2, 1.4 Hz), 7.05 (1H, t, J=1.8 Hz), 7.46 (1H, dd, J=2.8, 8.8 Hz), 8.05 (1H, dd, J=0.7, 8.8 Hz), 8.50 (1H, dd, J=0.7, 2.8 Hz).

MS (ESI) m/z: 502.16431 $(M+H)^+$.

(Example 87)

(2S)-2-(3-{5-[(4R)-4-(Hydroxymethyl)-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol



{(4R)-2-[5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}methanol (200 mg, 0.40 mmol) synthesized in Example (86c) was dissolved in methylene chloride (5 mL), followed by cooling to -78°C, and boron tribromide (1.0 mol/L methylene chloride solution, 0.80 mL, 0.80 mmol) was added under nitrogen atmosphere. After the temperature was raised naturally and stirring was carried out at room temperature for 30 minutes,

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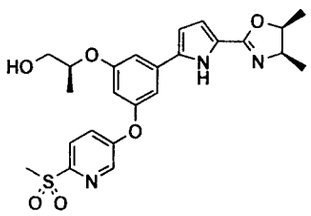
a saturated aqueous sodium hydrogencarbonate solution was added to neutralize the reaction solution, followed by extraction with methylene chloride (80 mL). The organic layer was washed with 1N aqueous sodium hydroxide solution and saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-4%) to afford the desired compound (143 mg, 74%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J=6.3 Hz), 3.23 (3H, s), 3.65 (1H, dd, J=3.5, 12.1 Hz), 3.74-3.80 (2H, m), 3.95 (1H, dd, J=2.7, 12.2 Hz), 4.20 (1H, t, J=6.8 Hz), 4.34-4.41 (1H, m), 4.41 (1H, t, J=9.8 Hz), 4.57-4.61 (1H, m), 6.37 (1H, d, J=3.9 Hz), 6.48 (1H, t, J=2.2 Hz), 6.53 (1H, d, J=3.9 Hz), 6.85 (1H, t, J=1.8 Hz), 7.01 (1H, t, J=1.8 Hz), 7.42 (1H, dd, J=2.7, 8.8 Hz), 8.04 (1H, d, J=8.8 Hz), 8.47 (1H, d, J= 2.7 Hz)

MS (ESI) m/z: 488.14910 $(M+H)^+$.

(Example 88)

(2S)-2-(3-{5-[(4R,5S)-4,5-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol



(88a) (2R,3R)-3-aminobutan-2-ol

(2R,3R)-3-(Dibenzylamino) butan-2-ol ($[\alpha]^{23}_D$ -82°, c: 1.60, chloroform solution) (2.70 g, 10.0 mmol) synthesized according to a method known to the public (J. Org. Chem., 2006, 71, 6420.) was dissolved in methanol (20 mL), and palladium hydroxide carbon (0.85 g) was added, followed by stirring at 60psi and at room temperature for 4 hours under hydrogen atmosphere. After Celite filtration, the solvent was distilled off under reduced

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pressure to afford the desired compound (0.73 g, yield 82%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.10 (3H, d, J=6.6 Hz), 1.17 (3H, d, J=6.3 Hz), 2.60-2.67 (1H, m), 3.31-3.37 (1H, m).

(88b) N-[(1R,2R)-2-Hydroxy-1-methylpropyl]-5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxamide

5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxylic acid (2.00 g, 4.48 mmol) synthesized in Example (78k) and (2R,3R)-3-aminobutan-2-ol (0.94 g, 8.96 mmol) synthesized in Example (88a) were dissolved in methanol (30 mL), and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride n hydrate (2.84 g, 8.96 mmol) was added at room temperature, followed by stirring for 3 days under nitrogen atmosphere. The solvent was distilled off under reduced pressure, water (30 mL) was added, and the solution was separated with ethyl acetate (70 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=50%-90%) to afford the desired compound (1.33 g, 57%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.23 (3H, t, J=6.3 Hz), 1.27 (3H, d, J=6.6 Hz), 1.33 (3H, d, J=6.3 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.52 (1H, dd, J=3.9, 10.3 Hz), 3.59 (1H, dd, J=6.2, 10.3 Hz), 3.82-3.86 (1H, m), 4.05-4.09 (1H, m), 4.58-4.62 (1H, m), 6.17 (1H, d, J=8.7 Hz), 6.49 (1H, dd, J=2.9, 3.9 Hz), 6.57 (1H, t, J=2.2 Hz), 6.63 (1H, dd, J=2.3, 3.9 Hz), 6.86 (1H, t, J=1.8 Hz), 7.05 (1H, t, J=1.8 Hz), 7.44 (1H, dd, J=2.8, 8.7 Hz), 8.04 (1H, d, J=8.7 Hz), 8.48 (1H, d, J=2.8 Hz), 9.83 (1H, brs).

(88c) 5-(3-{5-[(4R,5S)-4,5-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-[(1S)-2-methoxy-1-methylethoxy]phenoxy)-2-(methylsulfonyl)pyridine

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N-[(1R,2R)-2-Hydroxy-1-methylpropyl]-5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxamide (1.33 g, 2.57 mmol) synthesized in Example (88b) was dissolved in tetrahydrofuran (25 mL), and anhydrous methanesulfonic acid (0.92 g, 5.14 mmol) and triethylamine (1.43 mL, 10.28 mmol) were added, followed by stirring at 50°C for 5 hours under nitrogen atmosphere. A saturated aqueous sodium hydrogencarbonate solution (40 mL) was added, and the solution was separated with ethyl acetate (80 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=40%-70%) to afford the desired compound (0.95 g, yield 74%) as a white solid.

^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.20 (3H, t, J=6.9 Hz), 1.33 (3H, d, J=6.3 Hz), 1.33 (3H, d, J=6.6 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J=4.0, 10.4 Hz), 3.58 (1H, dd, J=6.1,10.4 Hz), 4.24-4.29 (1H, m), 4.55-4.58 (1H, m), 4.79-4.84 (1H, m), 6.50 (1H, d, J=3.8 Hz), 6.56 (1H, t, J=2.2 Hz), 6.74 (1H, d, J=3.8 Hz), 6.83 (1H, t, J=1.8 Hz), 7.01 (1H, t, J=1.8 Hz), 7.43 (1H, dd, J=2.8, 8.6 Hz), 8.05 (1H, d, J=8.6 Hz), 8.48 (1H, d, J=2.8 Hz).

(88d) (2S)-2-(3-{5-[(4R,5S)-4,5-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol

5-(3-{5-[(4R,5S)-4,5-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-[(1S)-2-methoxy-1-methylethoxy]phenoxy)-2-(methylsulfonyl)pyridine (0.95 g, 1.96 mmol) synthesized in Example (88c) was dissolved in methylene chloride (20 mL) and cooled to -78°C, and boron tribromide (1.0 mol/L methylene chloride solution, 2.15 mL, 2.15 mmol) was added under nitrogen atmosphere. After the temperature was raised naturally and the solution was stirred at room temperature for 30 minutes, a

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saturated aqueous sodium hydrogencarbonate solution was added to neutralize the reaction solution, followed by extraction with methylene chloride (80 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=70%-100%) to afford the desired compound (617 mg, 67%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.23 (3H, t, J=7.0 Hz), 1.27 (3H, d, J=6.2 Hz), 1.34 (3H, d, J=6.6 Hz), 3.23 (3H, s), 3.81-3.83 (2H, m), 4.27-4.35 (1H, m), 4.65-4.70 (1H, m), 4.81-4.89 (1H, m), 6.24 (1H, t, J=2.2 Hz), 6.44 (1H, d, J=3.8 Hz), 6.73 (1H, d, J=3.8 Hz), 6.76 (1H, dd, J=1.2, 2.2 Hz), 6.92 (1H, t, J=1.7 Hz), 7.32 (1H, dd, J=2.8, 8.8 Hz), 8.00 (1H, d, J=8.8 Hz), 8.41 (1H, d, J=2.8 Hz).
MS (ESI) m/z: 486.17002 $(M+H)^+$.

(Example 89)
{(4R,5R)-2-[5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4-methyl-4,5-dihydro-1,3-oxazol-5-yl}methanol
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(89a) (2R,3R)-3-[(Diphenylmethyl)amino]-1-[(tripropan-2-ylsilyl)oxy]butan-2-ol

Molecular sieves 4A (10g) were added into dehydrated methylene chloride (200 mL). Into this system, were added titanium tetraisopropoxide (8.8 mL, 30 mmol) and L-(+)-tartaric acid diethyl (6.2 mL, 36 mmol) at -20°C, and stirring was carried out at the same temperature for 15 minutes. (2E)-2-Buten-1-ol (25 mL, 295 mmol), which was dissolved in dehydrated methylene chloride (50 mL), was added dropwise at -20°C, and stirring was carried out at the same temperature for 15 minutes. Subsequently, into the system, t-butyl hydroperoxide (methylene chloride was added to conduct a solution-separating operation, followed by further addition of molecular sieves 4A (5g) and stirring for 20 minutes) (5-6 mol/L decane solution, 100 mL,

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0.5-0.6 mmol) was added at -20°C, and stirring was carried out at -20°C for 8.5 hours under nitrogen atmosphere, and the solution was left still overnight at -30°C.

Into this system, were added n-tributylphosphine (75 mL, 300 mmol), titanium tetraisopropoxide (135 mL, 460 mmol) and 1,1-diphenylmethanamine (75 mL, 440 mmol) at room temperature, and stirring was carried out at the same temperature for 1 week. To the reaction solution, water (30 mL) was added, and the deposit was filtered off. To the mother liquor, water (400 mL) was added, and extraction was carried out with methylene chloride (1L). The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=15%-40%) to afford a dark brown liquid.

This liquid was dissolved in methylene chloride (300 mL), and triethylamine (85 mL, 610 mmol) and triisopropylsilyl chloride (50 mL, 234 mmol) were added at room temperature, followed by stirring at room temperature for 1.5 days. A saturated aqueous ammonium chloride solution (500 mL) was added, and extraction was carried out with methylene chloride (500 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-5%) to afford the desired compound (80.5 g, yield 64%) as a white solid. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.96-1.07 (21H, m), 1.10 (3H, d, J=6.3 Hz), 2.72-2.81 (1H, m), 3.28 (1H, br s), 3.56-3.63 (1H, m), 3.72 (1H, dd, J=10.2, 5.9 Hz), 3.80 (1H, dd, J=10.2, 3.9 Hz), 4.98 (1H, s), 7.15-7.20 (2H, m), 7.23-7.29 (4H, m), 7.34-7.40 (4H, m).

(89b) Benzyl{(2R,3R)-3-hydroxy-4-[(tripropan-2-ylsilyl)oxy]butan-2-yl}carbamate

(2R,3R)-3-[(Diphenylmethyl)amino]-1-[(triisopropan-2-ylsilyl)oxy]butan-2-ol (10.3 g, 24.1 mmol) synthesized in Example (89a) was dissolved in ethanol (40 mL), and palladium

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carbon (3.20g) was added, followed by stirring at room temperature for 6 hours under hydrogen atmosphere. After Celite filtration, the solvent was distilled off under reduced pressure to afford a compound as a colorless liquid.

This was dissolved in water (40 mL) heated to 50°C, and sodium hydrogencarbonate (4.50 g, 53.6 mmol) and benzyl chloroformate (3.50 mL, 24.5 mmol) were added at room temperature, followed by d stirring at room temperature for 5 hours. Methylene chloride (100 mL) was added, and extraction was carried out. The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=10%-15%) to afford the desired compound (7.00 g, yield 73%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.04-1.09 (21H, m), 1.18 (3H, d, J=6.8 Hz), 2.67 (1H, br s), 3.65-3.73 (2H, m), 3.77 (1H, dd, J=10.0, 3.7 Hz), 3.86 (1H, br s), 5.10 (2H, s), 5.27 (1H, br s), 7.30-7.38 (5H, m).

(89c) (5R,6S)-5,10-Dimethyl-3-oxo-1-phenyl-9,9-di(propan-2-yl)-2,8-dioxa-4-aza-9-silaundecan-6-yl 4-nitrobenzoate

Benzyl{(2R,3R)-3-hydroxy-4-[(tripropan-2-ylsilyl)oxy]butan-2-yl}carbamate (7.00 g, 17.7 mmol) synthesized in Example (89b) was dissolved in toluene (80 mL), and 4-nitro benzoic acid (6.10 g, 36.5 mmol) and triphenylphosphine (11.85g, 45.2 mmol) were added, followed by cooling to 0°C. Under nitrogen atmosphere, diethyl azodicarboxylate (40% toluene solution, 20.3 mL, 44.7 mmol) was added dropwise over 10 minutes, and stirring was carried out at room temperature for 4 hours. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=10%-15%) to afford the desired compound (7.90 g, yield 82%) as a yellow liquid.

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^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.96-1.09 (21H, m), 1.29 (3H, d, J=7.0 Hz), 3.90-4.01 (1H, m), 4.25-4.32 (1H, m), 4.95-5.10 (3H, m), 5.13-5.20 (1H, m), 7.24-7.39 (5H, m), 8.14-8.21 (2H, m), 8.23-8.30 (2H, m).

(89d) Benzyl{(2R,3S)-3-hydroxy-4-[(tripropan-2-ylsilyl)oxy]butan-2-yl}carbamate

(5R,6S)-5,10-Dimethyl-3-oxo-1-phenyl-9,9-di(propan-2-yl)-2,8-dioxa-4-aza-9-silaundecan-6-yl 4-nitrobenzoate (7.90 g, 14.5 mmol) synthesized in Example (89c) was dissolved in methylene chloride (150 mL), and diisobutylaluminum hydride (1.0 mol/L hexane solution, 30.0 mL, 30.0 mmol) was added, followed by stirring at -40°C for 8 hours under nitrogen atmosphere. The reaction solution was brought back to 0°C, and methanol (5.0 mL) was added, followed by addition of a 5N aqueous sodium hydroxide solution (150 mL), and extraction was carried out with methylene chloride (200 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=10%-15%) to afford the desired compound (3.70 g, yield 65%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.01-1.13 (21H, m), 1.26 (3H, d, J=6.6 Hz), 2.72 (1H, br s), 3.55-3.67 (2H, m), 3.73 (2H, br s), 5.10 (2H, s), 5.13 (1H, br s), 7.31-7.36 (5H, m).

(89e) (2S,3R)-3-amino-1-[(tripropan-2-ylsilyl)oxy]butan-2-ol

Benzyl{(2R,3S)-3-hydroxy-4-[(tripropan-2-ylsilyl)oxy]butan-2-yl}carbamate (3.70 g, 9.35 mmol) synthesized in Example (89d) was dissolved in ethanol (30 mL), and palladium carbon (1.00g) was added, followed by stirring at room temperature for 8 hours under hydrogen atmosphere. After Celite filtration, the solvent was distilled off under reduced pressure to afford the desired compound (2.65 g, yield ~100%) as a pale yellow liquid.

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^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.04-1.14 (24H, m), 2.95-3.02 (1H, m), 3.30-3.35 (1H, m), 3.66 (1H, dd, J=9.8, 6.3 Hz), 3.76 (1H, dd, J=9.8, 4.3 Hz).

(89f) N-{(1R,2S)-2-Hydroxy-1-methyl-3-[(triisopropylsilyl)oxy]propyl}-5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxamide

5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxylic acid (1.20 g, 2.69 mmol) synthesized in Example (78k), (2S,3R)-3-amino-1-[(tripropan-2-ylsilyl)oxy]butan-2-ol (1.08 g, 4.11 mmol) synthesized in Example (89e), HOBT·H_2O (0.44 g, 3.23 mmol) and N-methylmorpholine (0.59 mL, 5.38 mmol) were dissolved in N,N-dimethylformamide (20 mL), and WSCI·HCl (0.62 g, 3.23 mmol) was added at room temperature, followed by stirring for 18 hours under nitrogen atmosphere. To the reaction solution, saturated brine (30 mL) was added, and extraction was carried out with ethyl acetate (60 mL). After washing with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, drying was carried out over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=20%-50%) to afford the desired compound (1.69 g, 91%) as a white powder. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.03-1.13 (21H, m), 1.34 (3H, d, J=6.3 Hz), 1.35 (3H, d, J=6.8 Hz), 3.23 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J=4.0, 10.3 Hz), 3.54-3.61 (2H, m), 3.73-3.78 (2H, m), 4.14-4.18 (1H, m), 4.56-4.60 (1H, m), 6.31 (1H, brm), 6.49 (1H, dd, J=2.9, 3.9 Hz), 6.57-6.60 (2H, m), 6.84 (1H, dd, J=1.5, 2.3 Hz), 7.02 (1H, t, J=1.8 Hz), 7.45 (1H, dd, J=2.8, 8.8 Hz), 8.09 (1H, d, J=8.7 Hz), 8.49 (1H, d, J=2.7 Hz), 9.52 (1H, brs).

(89g) 5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(4R,5R)-4-methyl-5-{[(triisopropylsilyl)oxy]methyl}-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-2-(methylsulfonyl)pyridine

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N-[(1R,2S)-2-Hydroxy-1-methyl-3-[(triisopropylsilyl)oxy]propyl]-5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxamide (1.69 g, 2.45 mmol) synthesized in Example (89f) was dissolved in tetrahydrofuran (25 mL), and anhydrous methanesulfonic acid (0.88 g, 4.90 mmol) and triethylamine (1.37 mL, 9.80 mmol) were added, followed by stirring at 50°C for 5 hours under nitrogen atmosphere. A saturated aqueous sodium hydrogencarbonate solution (40 mL) was added, and the solution was separated with ethyl acetate (60 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=10%-50%) to afford the desired compound (1.23 g, yield 75%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.04-1.14 (21H, m), 1.34 (6H, d, J=6.3 Hz), 3.23 (3H, s), 3.42 (3H, s), 3.50 (1H, dd, J=4.0, 10.3 Hz), 3.59 (1H, dd, J=6.1,10.3 Hz), 3.94 (2H, d, J=5.3 Hz), 4.37-4.41 (1H, m), 4.56-4.60 (1H, m), 4.65-4.69 (1H, m), 6.49 (1H, d, J=3.9 Hz), 6.56 (1H, t, J=2.1 Hz), 6.74 (1H, d, J=3.8 Hz), 6.85 (1H, s), 7.04 (1H, s), 7.44 (1H, dd, J=2.8, 8.6 Hz), 8.05 (1H, d, J=8.6 Hz), 8.48 (1H, d, J=2.8 Hz).

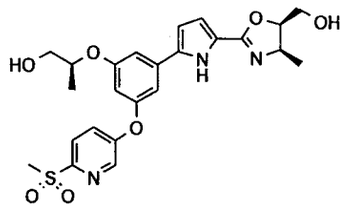
(89h) {(4R,5R)-2-[5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4-methyl-4,5-dihydro-1,3-oxazol-5-yl}methanol

5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(4R,5R)-4-methyl-5-{[(triisopropylsilyl)oxy]methyl}-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-2-(methylsulfonyl)pyridine (1.23 g, 1.83 mmol) synthesized in Example (89g) was dissolved in tetrahydrofuran (20 mL), and tetrabutylammonium fluoride (1.0 mol/L tetrahydrofuran solution, 2.11 mL, 2.11 mmol) is added at room temperature, followed by stirring at room temperature for 1 hour under nitrogen atmosphere. Water (20 mL) was added, and extraction was carried out with ethyl acetate (50 mL). The

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organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=90%-100%) to afford the desired compound (715 mg, yield 76%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.26 (3H, d, J=7.1 Hz), 1.31 (3H, d, J=6.3 Hz), 3.23 (3H, s), 3.42 (3H, s), 3.50 (1H, dd, J=3.9, 10.3 Hz), 3.59 (1H, dd, J=6.3, 10.3 Hz), 3.85 (2H, d, J=5.4 Hz), 4.36-4.42 (1H, m), 4.53-4.48 (1H, m), 4.70-4.76 (1H, m), 6.50 (1H, d, J=3.8 Hz), 6.57 (1H, t, J=2.1 Hz), 6.77 (1H, d, J=3.8 Hz), 6.84 (1H, t, 1.8 Hz), 7.00 (1H, t, 1.8 Hz), 7.43 (1H, dd, J=2.8, 8.8 Hz), 8.04 (1H, d, J=8.8 Hz), 8.48 (1H, d, J=2.8 Hz).
MS (ESI) m/z: 516.17829 $(M+H)^+$.

(Example 90)
(2S)-2-(3-{5-[(4R,5R)-5-(Hydroxymethyl)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol



{(4R,5R)-2-[5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4-methyl-4,5-dihydro-1,3-oxazol-2-yl}methanol (200 mg, 0.39 mmol) synthesized in Example (89h) was dissolved in methylene chloride (5 mL), and boron tribromide (1.0 mol/L methylene chloride solution, 0.78 mL, 0.78 mmol) was added at -78°C under nitrogen atmosphere, and subsequently the temperature was brought back to room temperature and stirring was carried out for 45 minutes. To the reaction solution, a saturated aqueous sodium hydrogencarbonate solution was added, and extraction was carried out with methylene chloride. The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate.

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The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-4%) to afford the desired compound (87 mg, yield 45%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.29 (6H, t, J=5.9 Hz), 3.23 (3H, s), 3.79 (2H, d, J=4.9 Hz), 3.85 (2H, d, J=6.3 Hz), 4.41 (1H, dt, J=16.3, 7.1 Hz), 4.59 (1H, dd, J=11.5, 5.6 Hz), 4.73-4.77 (1H, m), 6.38 (1H, s), 6.46 (1H, d, J=3.4 Hz), 6.77 (1H, d, J=3.9 Hz), 6.81 (1H, s), 6.98 (1H, s), 7.35 (1H, d, J=8.8 Hz), 8.01 (1H, d, J=8.8 Hz), 8.44 (1H, s).

MS (ESI) m/z: 502.16510 $(M+H)^+$.

(Example 91)

{(4R,5S)-2-[5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazol-4-yl}methanol

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(91a) N-[(1R,2R)-2-Hydroxy-1-(hydroxymethyl)propyl]-5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxamide

5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxylic acid (1.20 g, 2.69 mmol) synthesized in Example (78k) and commercially available L-threoninol (0.57 g, 5.38 mmol) were dissolved in methanol (25 mL), and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride n hydrate (1.70 g, 5.38 mmol) was added at room temperature, followed by stirring for 3.5 hours under nitrogen atmosphere. The solvent was distilled off under reduced pressure, and the resulting residue was diluted with ethyl acetate (100 mL). After washing with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, drying was carried out over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent:

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methanol/methylene chloride=0%-6%) to afford the desired compound (883 mg, 62%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.23 (3H, d, J=6.4 Hz), 1.30 (3H, d, J=6.3 Hz), 3.23 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J=3.9, 10.2 Hz), 3.58 (1H, dd, J=6.4, 10.4 Hz), 3.87 (2H, d, J=4.0 Hz), 3.97-4.03 (1H, brm), 4.22-4.26 (1H, m), 4.55-4.58 (1H, m), 6.49 (1H, dd, J=2.8, 3.9 Hz), 6.57 (1H, t, J=2.2 Hz), 6.68-6.71 (2H, m), 6.86 (1H, t, J=1.7 Hz), 7.02 (1H, t, J=1.8 Hz), 7.44 (1H, dd, J=2.7, 8.7 Hz), 8.04 (1H, d, J=8.8 Hz), 8.47 (1H, d, J=2.7 Hz), 10.05 (1H, brs).

(91b) N-[(1R,2R)-2-Hydroxy-1-{[(triisopropylsilyl)oxy]methyl}propyl]-5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxamide

N-[(1R,2R)-2-Hydroxy-1-(hydroxymethyl)propyl]-5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxamide (883 mg, 1.65 mmol) synthesized in Example (91a), triethylamine (1.15 mL, 8.27 mmol) and 4-dimethylaminopyridine (404 mg, 3.31 mmol) were dissolved in methylene chloride (20 mL), and triisopropylsilyl chloride (0.60 mL, 2.81 mmol) was added at room temperature, followed by stirring for 20 hours under nitrogen atmosphere. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=30%-60%) to afford the desired compound (1.03 g, 90%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.05-1.08 (18H, m), 1.09-1.16 (3H, m), 1.23 (3H, d, J=6.4 Hz), 1.34 (3H, d, J=6.3 Hz), 3.24 (3H, s), 3.42 (3H, s), 3.52 (1H, dd, J=4.0, 10.2 Hz), 3.60 (1H, dd, J=6.2, 10.4 Hz), 3.99-4.04 (1H, m), 4.03-4.06 (2H, m), 4.30-4.35 (1H, m), 4.56-4.61 (1H, m), 6.51 (1H, t, J=3.4 Hz), 6.59 (1H, t, J=2.2 Hz), 6.62-6.66 (2H, m), 6.85 (1H, t, J=1.8 Hz), 7.03 (1H, t, J=1.7 Hz), 7.46 (1H, dd, J=2.7, 8.8 Hz), 8.06 (1H, d, J=8.8 Hz), 8.49 (1H, d, J=2.7 Hz), 9.49 (1H, brs).

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(91c) 5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(4R,5S)-5-methyl-4-{[(triisopropylsilyl)oxy]methyl}-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-2-(methylsulfonyl)pyridine

N-[(1R,2R)-2-Hydroxy-1-{[(triisopropylsilyl)oxy]methyl}propyl]-5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxamide (1.03 g, 1.49 mmol) synthesized in Example (91b) was dissolved in tetrahydrofuran (20 mL), and anhydrous methanesulfonic acid (0.54 g, 2.99 mmol) and triethylamine (0.83 mL, 5.97 mmol) were added, followed by stirring at 50°C for 4.5 hours under nitrogen atmosphere. A saturated aqueous sodium hydrogencarbonate solution (30 mL) was added, and the solution was separated with ethyl acetate (50 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=20%-50%) to afford the desired compound (901 mg, yield 90%) as a white solid.

^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.03-1.13 (21H, m), 1.33 (3H, d, J=6.3 Hz), 1.52 (3H, d, J=6.6 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J=3.9, 10.4 Hz), 3.58 (1H, dd, J=6.2, 10.5 Hz), 3.81 (1H, t, J=9.5 Hz), 3.95 (1H, dd, J=3.9, 10.4 Hz), 4.21-4.25 (2H, m), 4.56-4.59 (1H, m), 4.89-4.93 (1H, m), 6.50 (1H, d, J=3.9 Hz), 6.56 (1H, t, J=2.2 Hz), 6.76 (1H, d, J=3.9 Hz), 6.84 (1H, s), 7.02 (1H, s), 7.44 (1H, dd, J=2.7, 8.8 Hz), 8.05 (1H, d, J=8.8 Hz), 8.48 (1H, d, J=2.7 Hz).

(91d) {(4R,5S)-2-[5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazol-4-yl}methanol

5-(3-{(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(4R,5S)-5-methyl-4-{[(triisopropylsilyl)oxy]methyl}-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-2-(methylsulfonyl)pyridine (901 mg, 1.34 mmol) synthesized in Example (91c) was dissolved in tetrahydrofuran (15 mL), and tetrabutylammonium fluoride (1

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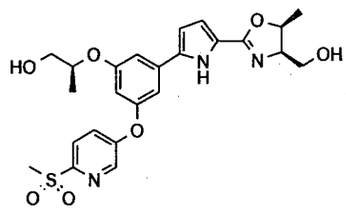
mol/L tetrahydrofuran solution, 1.54 mL, 1.54 mmol) was added at 0°C, followed by stirring at room temperature for 1 hour under nitrogen atmosphere. Water (20 mL) was added, and extraction was carried out with ethyl acetate (40 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=80%-100%) to afford the desired compound (578 mg, yield 84%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J=6.3 Hz), 1.39 (3H, d, J=6.8 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J=4.1, 10.4 Hz), 3.59 (1H, dd, J=6.1, 10.4 Hz), 3.77 (1H, dd, J=6.2, 11.2 Hz), 3.84 (1H, dd, J=3.7, 11.8 Hz), 4.22-4.27 (1H, m), 4.54-4.61 (1H, m), 4.83-4.90 (1H, m), 6.45 (1H, d, J=3.8 Hz), 6.55 (1H, t, J=2.2 Hz), 6.68 (1H, d, J=3.9 Hz), 6.90 (1H, t, 1.8 Hz), 7.07 (1H, t, 1.8 Hz), 7.43 (1H, dd, J=2.8, 8.7 Hz), 8.04 (1H, d, J=8.7 Hz), 8.49 (1H, d, J=2.8 Hz).

MS (ESI) m/z: 516.17933 $(M+H)^+$.

(Example 92)

(2S)-2-(3-{5-[(4R,5S)-4-(Hydroxymethyl)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol



{{(4R,5S)-2-[5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazol-4-yl}methanol (178 mg, 0.35 mmol) synthesized in Example (91d) was dissolved in methylene chloride (5 mL), and boron tribromide (1.0 mol/L methylene chloride solution, 0.70 mL, 0.70 mmol) was added at -78°C, and subsequently the temperature was brought back to room

temperature and stirring was carried out for 45 minutes. To the reaction solution, a saturated aqueous sodium hydrogencarbonate solution was added, and extraction was carried out with methylene chloride. The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-4%) to afford the desired compound (142 mg, yield 82%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.30 (3H, d, J=6.3 Hz), 1.43 (3H, d, J=6.6 Hz), 3.23 (3H, s), 3.76-3.87 (4H, m), 4.22-4.27 (1H, m), 4.53-4.60 (1H, m), 4.92-4.84 (1H, m), 6.45 (1H, d, J=3.9 Hz), 6.48 (1H, s), 6.69 (1H, d, J=3.9 Hz), 6.87 (1H, t, J=1.8 Hz), 7.02 (1H, s), 7.41 (1H, dd, J=8.6, 2.7 Hz), 8.03 (1H, d, J=8.6 Hz), 8.47 (1H, d, J=2.7 Hz).
MS (ESI) m/z: 502.16583 $(M+H)^+$.

(Example 93)
(1S)-1-{(4S)-2-[5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol
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(93a) N-[(1S,2S)-2-Hydroxy-1-(hydroxymethyl)propyl]-5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxamide

5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxylic acid (1.20 g, 2.69 mmol) synthesized in Example (78k), commercially available D-threoninol (0.34 g, 3.23 mmol), HOBT·H_2O (0.40 g, 3.23 mmol) and N-methylmorpholine (0.59 mL, 5.38 mmol) were dissolved in N,N-dimethylformamide (20 mL), and WSCI·HCl (0.62 g, 3.23 mmol) was added at room temperature, followed by stirring for 20 hours under nitrogen atmosphere. To the reaction solution, saturated brine (30 mL) was added, and extraction was carried out with ethyl acetate (60 mL). After washing with 1N hydrochloric acid, a saturated aqueous sodium

hydrogencarbonate solution and saturated brine, drying was carried out over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-7%) to afford the desired compound (1.24 g, 86%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.25 (3H, d, J=6.3 Hz), 1.33 (3H, d, J=6.3 Hz), 3.23 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J=3.9, 10.3 Hz), 3.59 (1H, dd, J=6.3, 10.4 Hz), 3.90-3.91 (2H, m), 3.98-4.03 (1H, brm), 4.23-4.29 (1H, m), 4.56-4.60 (1H, m), 6.50 (1H, t, J=3.2 Hz), 6.58 (1H, t, J=2.2 Hz), 6.66 (1H, brm), 6.69-6.70 (1H, m), 6.85 (1H, t, J=1.7 Hz), 7.03 (1H, t, J=1.7 Hz), 7.44 (1H, dd, J=2.7, 8.7 Hz), 8.04 (1H, d, J=8.7 Hz), 8.48 (1H, d, J=2.7 Hz), 9.77 (1H, brs).

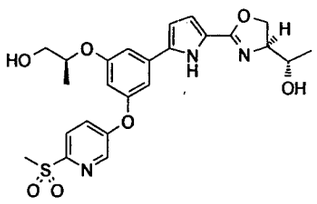
(93b) (1S)-1-{(4S)-2-[5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol

N-[(1S,2S)-2-Hydroxy-1-(hydroxymethyl)propyl]-5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxamide (1.24 g, 2.32 mmol) synthesized in Example (93a) was dissolved in tetrahydrofuran (20 mL), and anhydrous methanesulfonic acid (0.63 g, 3.49 mmol) and triethylamine (0.97 mL, 6.97 mmol) were added at 0°C, followed by stirring for 1 hour under nitrogen atmosphere. The temperature was raised naturally, and stirring was carried out at room temperature for 2 hours, followed by stirring at 50°C for 2 hours. A saturated aqueous sodium hydrogencarbonate solution (30 mL) was added, and the solution was separated with ethyl acetate (50 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=60%-100%) to afford the desired compound (800 mg, yield 67%) as a white solid.

^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.24 (3H, d, J=6.3 Hz), 1.33 (3H, d, J=6.3 Hz), 3.23 (3H, s), 3.40 (3H, s), 3.50 (1H, dd, J=4.0, 10.3 Hz), 3.58 (1H, dd, J=6.3, 10.3 Hz), 3.71 (1H, t, J=6.2 Hz), 4.08-4.14 (2H, m), 4.41-4.44 (1H, m), 4.54-4.59 (1H, m), 6.50 (1H, d, J=3.9 Hz), 6.56 (1H, t, J=2.1 Hz), 6.74 (1H, d, J=3.9 Hz), 6.86 (1H, t, 2.0 Hz), 7.05 (1H, t, 1.9 Hz), 7.42 (1H, dd, J=2.7, 8.8 Hz), 8.03 (1H, d, J=8.8 Hz), 8.47 (1H, d, J=2.8 Hz). MS (ESI) m/z: 516.17981 $(M+H)^+$.

(Example 94)

(2S)-2-[3-(5-{(4S)-4-[(1S)-1-Hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl}-1H-pyrrol-2-yl)-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy]propan-1-ol



(1S)-1-{(4S)-2-[5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol (187 mg, 0.36 mmol) synthesized in Example (93b) was dissolved in methylene chloride (5 mL) and subsequently cooled to -78°C, and boron tribromide (1.0 mol/L methylene chloride solution, 0.73 mL, 0.73 mmol) was added under nitrogen atmosphere. The temperature was raised naturally, followed by stirring at room temperature for 30 minutes, and subsequently a saturated aqueous sodium hydrogencarbonate solution was added to neutralize the reaction solution, followed by extraction with methylene chloride (70 mL). The organic layer was washed with a 1N aqueous sodium hydroxide solution and saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-4%) to afford the desired compound (134 mg, 74%) as a white solid.

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^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.28 (6H, d, J=6.6 Hz), 3.22 (3H, s), 3.72-3.81 (3H, m), 4.13-4.19 (2H, m), 4.42-4.45 (1H, m), 4.59-4.65 (1H, m), 6.41 (1H, t, J=2.2 Hz), 6.45 (1H, d, J=3.9 Hz), 6.72 (1H, d, J=3.9 Hz), 6.83 (1H, s), 6.99 (1H, s), 7.37 (1H, dd, J=2.7, 8.8 Hz), 8.02 (1H, d, J=8.8 Hz), 8.44 (1H, d, J=2.7 Hz).
MS (ESI) m/z: 502.16521 $(M+H)^+$.

(Example 95)
(1R)-1-{(4S)-2-[5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol

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(95a) N-[(1S,2R)-2-Hydroxy-1-(hydroxymethyl)propyl]-5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxamide

5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxylic acid (1.47 g, 3.29 mmol) synthesized in Example (78k), commercially available D-allo-threoninol (0.52 g, 4.94 mmol), HOBT·H_2O (0.49 g, 3.62 mmol) and N-methylmorpholine (0.72 mL, 6.58 mmol) were dissolved in N,N-dimethylformamide (10 mL), and WSCI·HCl (0.76 g, 3.95 mmol) was added at room temperature, followed by stirring for 5.5 hours under nitrogen atmosphere. To the reaction solution, saturated brine (40 mL) was added, and extraction was carried out with ethyl acetate (70 mL). After washed with saturated brine, drying was carried out over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-6%) to afford the desired compound (1.42 g, 81%) as a white solid.
^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.31 (3H, d, J=6.2 Hz), 1.32 (3H, d, J=6.6 Hz), 2.84-2.86 (1H, m), 2.89 (1H, d, J=6.2 Hz), 3.23 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J=3.9, 10.3 Hz), 3.59 (1H, dd, J=6.3, 10.3 Hz), 3.80-3.84 (1H, brm), 3.92-3.96 (1H, m), 4.07-4.11 (2H, brm), 4.54-4.59 (1H, m), 6.49 (1H, dd, J=2.9, 3.9 Hz),

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6.57 (1H, t, J=2.2 Hz), 6.67 (1H, dd, J=2.3, 3.9 Hz), 6.80 (1H, d, J=8.0 Hz), 6.86 (1H, t, J=1.8 Hz), 7.01 (1H, t, J=1.8 Hz), 7.43 (1H, dd, J=2.8, 8.7 Hz), 8.03 (1H, d, J=8.7 Hz), 8.47 (1H, d, J=2.8 Hz), 9.94 (1H, brs).

(95b) (1R)-1-{(4S)-2-[5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol

N-[(1S,2R)-2-Hydroxy-1-(hydroxymethyl)propyl]-5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrole-2-carboxamide (1.42 g, 2.66 mmol) synthesized in Example (95a) was dissolved in tetrahydrofuran (25 mL), and anhydrous methanesulfonic acid (0.72 g, 3.99 mmol) and triethylamine (1.11 mL, 7.98 mmol) were added at 0°C, followed by stirring for 1 hour under nitrogen atmosphere. The temperature was raised naturally, and stirring was carried out at room temperature for 1 hour, followed by stirring at 50°C for 2 hours. A saturated aqueous sodium hydrogencarbonate solution (30 mL) was added, and the solution was separated with ethyl acetate (50 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=50%-100%) to afford the desired compound (758 mg, yield 55%) as a white solid.

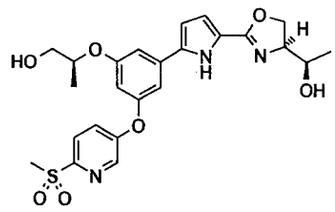
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.15 (3H, d, J=6.3 Hz), 1.35 (3H, d, J=6.3 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.51 (1H, dd, J=4.0, 10.4 Hz), 3.59 (1H, dd, J=6.2, 10.4 Hz), 4.20-4.27 (4H, m), 4.56-4.62 (1H, m), 6.36 (1H, d, J=3.8 Hz), 6.41 (1H, d, J=3.8 Hz), 6.57 (1H, t, J=2.1 Hz), 6.90 (1H, t, 1.8 Hz), 7.07 (1H, t, 1.8 Hz), 7.45 (1H, dd, J=2.8, 8.7 Hz), 8.05 (1H, d, J=8.7 Hz), 8.50 (1H, d, J=2.8 Hz).

MS (ESI) m/z: 516.17893 $(M+H)^+$.

(Example 96)

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(2S)-2-[3-(5-{(4S)-4-[(1R)-1-Hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl}-1H-pyrrol-2-yl)-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy]propan-1-ol



(1R)-1-{(4S)-2-[5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol (178 mg, 0.35 mmol) synthesized in Example (95b) was dissolved in methylene chloride (5 mL) and subsequently cooled to -78°C, and boron tribromide (1.0 mol/L methylene chloride solution, 0.69 mL, 0.69 mmol) was added under nitrogen atmosphere. The temperature was raised naturally, followed by stirring at room temperature for 30 minutes, and subsequently a saturated aqueous sodium hydrogencarbonate solution was added to neutralize the reaction solution, followed by extraction with methylene chloride (70 mL). The organic layer was washed with a 1N aqueous sodium hydroxide solution and saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-4%) to afford the desired compound (132 mg, 76%) as a white solid.

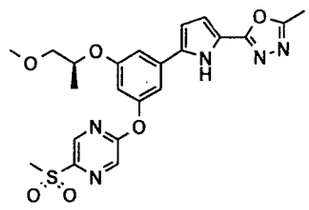
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.19 (3H, d, 6.3 Hz), 1.31 (3H, d, J=6.3 Hz), 3.23 (3H, s), 3.73-3.81 (2H, m), 4.17-4.25 (2H, m), 4.32 (1H, s), 4.34 (1H, d, J=1.5 Hz), 4.57-4.61 (1H, m), 6.39 (1H, d, J=3.9 Hz), 6.49 (1H, d, J=2.1 Hz), 6.54 (1H, d, J=3.9 Hz), 6.87 (1H, t, J=1.8 Hz), 7.02 (1H, t, J=1.8 Hz), 7.42 (1H, dd, J=2.8, 8.6 Hz), 8.04 (1H, d, J= 8.6 Hz), 8.47 (1H, d, J=2.8 Hz).

MS (ESI) m/z: 502.16427 $(M+H)^+$.

(Example 97)

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2-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}-5-(methylsulfonyl)pyrazine



(97a) 5-(Methylsulfanyl)pyrazine-2-amine

2-Aminopyrazine (50.8 g, 0.53 mol) was dissolved in methylene chloride (1.0 L), and N-bromosuccinimide (97.9 g, 0.55 mol) was added at 0°C over 30 minutes, followed by stirring at 0°C for 2.5 hours under nitrogen atmosphere. The reaction solution was brought back to room temperature, and the deposit was filtered off. The deposit which was filtered off was washed with ethyl acetate. The mother liquor was collected, and the solvent was distilled off under reduced pressure. This operation was repeated twice to give a mother liquor, of which the solvent was distilled off under reduced pressure to afford a compound as a yellow solid.

This was dissolved in N,N-dimethylformamide (300 mL), and sodium thiomethoxide (75.0 g, 1.07 mol) was added, followed by stirring at 100°C for 3 hours under nitrogen atmosphere. The reaction solution was brought back to room temperature, and water (1.5L) was added, followed by extraction with ethyl acetate (1.0 L). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=20%-30%) to afford the desired compound (42.5 g, yield 56%) as an orange solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.52 (3H, s), 4.41 (2H, br s), 7.92 (1H, d, J=1.6 Hz), 7.98 (1H, d, J=1.6 Hz).

(97b) 2-Chloro-5-(methylsulfanyl)pyrazine

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Sodium nitrite (50.9 g, 0.74 mol) was dissolved in water (150 mL), followed by dropwise addition into a 5N aqueous hydrochloric acid solution (1.0 L) at 0°C over 1 hour. Subsequently, 5-(methylsulfanyl)pyrazine-2-amine (40.4 g, 0.28 mol) synthesized in Example (97a) was added at 0°C over 40 minutes, and stirring was carried out at 0°C for 1 hour. The reaction solution was brought back to room temperature, and water (500 mL) was added, followed by extraction with ethyl acetate (1.0 L). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=10%-20%) to afford the desired compound (11.9 g, yield 26%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.57 (3H, s), 8.24 (1H, d, J=1.2 Hz), 8.39 (1H, d, J=1.2 Hz).

(97c) 2-Chloro-5-(methylsulfonyl)pyrazine

2-Chloro-5-(methylsulfanyl)pyrazine (10.82 g, 67.4 mmol) synthesized in Example (97b) was dissolved in methylene chloride (200 mL), and m-chloroperbenzoic acid (approximately 65%, 37.4 g, approximately 140 mmol) was added slowly at 0°C, followed by stirring at 0°C for 1.5 hours under nitrogen atmosphere. A saturated aqueous sodium hydrogencarbonate solution (300 mL) was added, and extraction was carried out with methylene chloride (400 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=30%-50%) to afford the desired compound (10.1 g, yield 78%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.27 (3H, s), 8.70 (1H, d, J=1.2 Hz), 9.09 (1H, d, J=1.2 Hz).

(97d) Benzyl 5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrole-2-carboxylate

2-Benzyl 1-t-butyl 5-{3-hydroxy-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrole-1,2-dicarboxylate (3.40 g, 7.06 mmol) synthesized in Example (78g) and 2-chloro-5-(methylsulfonyl)pyrazine (1.92 g, 7.06 mmol) synthesized in Example (97c) were dissolved in acetonitrile (35 mL), and potassium carbonate (2.93 g, 21.2 mmol) was added, followed by heating to reflux for 11 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, and water (100 mL) was added, followed by extraction twice with ethyl acetate (50 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-50%).

The resulting brown solid (3.85g) was dissolved in methylene chloride (5 mL), and trifluoroacetic acid (5 mL) was added, followed by stirring at room temperature for 1 hour. To the reaction solution, a saturated aqueous sodium hydrogencarbonate solution (50 mL) was added, and extraction was carried out twice with ethyl acetate (50 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-60%) to afford the desired compound (3.58 g, yield 88%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.35 (3H, d, J=6.3 Hz), 3.24 (3H, s), 3.42 (3H, s), 3.52 (1H, dd, J=10.3, 3.9 Hz), 3.60 (1H, dd, J=10.3, 5.9 Hz), 4.57-4.61 (1H, m), 5.34 (2H, s), 6.53 (1H, dd, J=3.9, 2.9 Hz), 6.70 (1H, t, J=2.2 Hz), 6.93 (1H, t, J=1.5 Hz), 6.99 (1H, dd, J=3.9, 2.4 Hz), 7.06 (1H, t, J=1.7 Hz), 7.34-7.45 (5H, m), 8.50 (1H, d, J=1.5 Hz), 8.81 (1H, d, J=1.5 Hz), 9.18 (1H, s).

(97e) 5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrole-2-carboxylic acid

Benzyl 5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrole-2-carboxylate (3.58 g, 6.66 mmol) synthesized in Example (97d) was dissolved in methanol (100 mL), and a 10% palladium carbon catalyst (2.00 g) was added, followed by stirring at room temperature for 3 hours under hydrogen atmosphere. The palladium carbon catalyst was removed by Celite filtration, followed by washing with tetrahydrofuran. The solvent was distilled off under reduced pressure to afford the desired compound (2.56 g, 86%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J=6.3 Hz), 3.22 (3H, s), 3.45 (3H, s), 3.55 (1H, dd, J=10.2, 3.9 Hz), 3.66 (1H, dd, J=9.4, 5.9 Hz), 4.72 (1H, s), 6.49 (1H, s), 6.66 (1H, s), 6.99 (2H, s), 7.29 (1H, s), 8.47 (1H, s), 8.79 (1H, s), 10.23 (1H, br s).

(97f) 2-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}-5-(methylsulfonyl)pyrazine

5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrole-2-carboxylic acid (700 mg, 1.56 mmol) synthesized in Example (97e) and 4-dimethylaminopyridine (172 mg, 1.41 mmol) were dissolved in methylene chloride (15 mL), and WSCI·HCl (689 mg, 3.60 mmol) and acetohydrazide (255 mg, 3.44 mmol) were added at room temperature, followed by stirring for 14 hours under nitrogen atmosphere. The reaction solution was diluted with methylene chloride (50 mL), and washed with a saturated aqueous sodium hydrogencarbonate solution and saturated brine, followed by drying over anhydrous magnesium sulfate, and subsequently the solvent was distilled off under reduced pressure.

The resulting yellow solid (788mg) was dissolved in methylene chloride (10 mL), and p-toluenesulfonyl chloride (597

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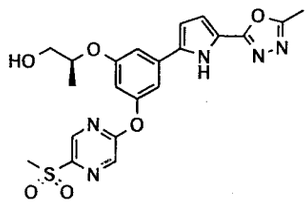
mg, 3.13 mmol) and triethylamine (0.87 mL, 6.26 mmol) were added, followed by stirring at room temperature for 6 hours under nitrogen atmosphere. To the reaction solution, a saturated aqueous sodium hydrogencarbonate solution (30 mL) was added, and extraction was carried out twice with methylene chloride (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-5%) to afford the desired compound (456 mg, yield 60%) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.36 (3H, d, J=6.3 Hz), 2.59 (3H, s), 3.24 (3H, s), 3.42 (3H, s), 3.53 (1H, dd, J=10.4, 4.1 Hz), 3.61 (1H, dd, J=10.2, 5.9 Hz), 4.56-4.63 (1H, m), 6.59 (1H, t, J=3.1 Hz), 6.69 (1H, t, J=2.0 Hz), 6.86 (1H, dd, J=3.7, 2.5 Hz), 6.95 (1H, t, J=1.6 Hz), 7.08 (1H, t, J=1.8 Hz), 8.51 (1H, d, J=1.2 Hz), 8.81 (1H, d, J=1.2 Hz), 9.43 (1H, s).

MS (ESI) m/z: 486.14274 $(M+H)^+$.

(Example 98)

(2S)-2-(3-[5-(5-Methyl-1,3,4-oxadiazol-2-yl)-1H-pyrrol-2-yl]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol



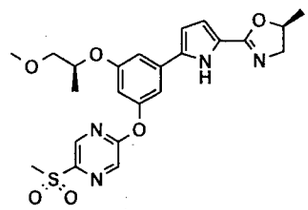
2-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrrol-2-yl]phenoxy}-5-(methylsulfonyl)pyrazine (382 mg, 0.79 mmol) synthesized in Example (97f) was dissolved in methylene chloride (10 mL), and boron tribromide (1.0 mol/L methylene chloride solution, 1.58 mL, 1.58 mmol) was added at -78°C under nitrogen atmosphere. Subsequently the temperature was brought back to room temperature, followed by stirring for 1.5 hours under nitrogen

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atmosphere. To the reaction solution, a saturated aqueous sodium hydrogencarbonate solution was added, and extraction was carried out with ethyl acetate. The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-5%) to afford the desired compound (219 mg, yield 59%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J=6.3 Hz), 2.59 (3H, s), 2.70 (1H, br s), 3.25 (3H, s), 3.79-3.82 (2H, m), 4.54-4.61 (1H, m), 6.57 (1H, t, J=3.1 Hz), 6.63 (1H, t, J=2.0 Hz), 6.86 (1H, dd, J=3.7, 2.5 Hz), 6.96 (1H, t, J=1.8 Hz), 7.07 (1H, t, J=1.8 Hz), 8.50 (1H, d, J=1.6 Hz), 8.80 (1H, d, J=1.2 Hz), 9.84 (1H, br s).
MS (ESI) m/z: 472.12965 $(M+H)^+$.

(Example 99)
2-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-5-(methylsulfonyl)pyrazine



5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrole-2-carboxylic acid (700 mg, 1.56 mmol) synthesized in Example (97e) and 4-dimethylaminopyridine (96 mg, 0.78 mmol) were dissolved in methylene chloride (20 mL), and WSCI·HCl (480 mg, 2.50 mmol) and (R)-1-amino-2-propanol (283 μL, 3.60 mmol) were added at room temperature, followed by stirring for 14 hours under nitrogen atmosphere. The reaction solution was diluted with methylene chloride (60 mL), washed with saturated aqueous sodium hydrogencarbonate solution and saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was

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distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-8%).

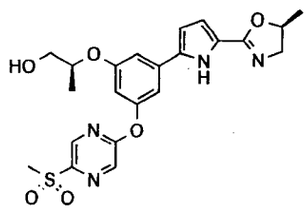
The resulting white solid (546mg) was dissolved in tetrahydrofuran (15 mL), and anhydrous methanesulfonic acid (377 mg, 2.16 mmol) and triethylamine (0.45 mL, 3.25 mmol) were added, followed by stirring at 50°C for 4 hours under nitrogen atmosphere. To the reaction solution, a saturated aqueous sodium hydrogencarbonate solution (30 mL) was added, and extraction was carried out twice with ethyl acetate (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-5%) to afford the desired compound (509 mg, yield 67%) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J=6.3 Hz), 1.42 (3H, d, J=6.3 Hz), 3.24 (3H, s), 3.42 (3H, s), 3.49-3.62 (3H, m), 4.07 (1H, dd, J=13.5, 8.8 Hz), 4.53-4.61 (1H, m), 4.79-4.87 (1H, m), 6.51 (1H, d, J=3.9 Hz), 6.65 (1H, t, J=2.0 Hz), 6.75 (1H, d, J=3.9 Hz), 6.91 (1H, t, J=1.6 Hz), 7.06 (1H, t, J=1.8 Hz), 8.49 (1H, s), 8.81 (1H, s).

MS (ESI) m/z: 487.16506 $(M+H)^+$.

(Example 100)

(2S)-2-(3-{5-[(5S)-5-Methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol



2-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-5-

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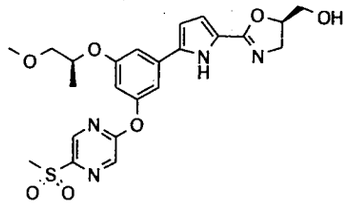
acid (1.07 g, 2.39 mmol) synthesized in Example (97e) was dissolved in methylene chloride (20 mL), and WSCI·HCl (732 mg, 3.82 mmol), (S)-(-)-3-amino-1,2-propanediol (500 mg, 5.49 mmol) and 4-dimethylaminopyridine (146 mg, 1.19m mmol) were added at room temperature, followed by stirring for 25 hours under nitrogen atmosphere. The reaction solution was diluted with ethyl acetate (50 mL), washed with a saturated aqueous sodium hydrogencarbonate solution and saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-5%) to afford the desired product (666 mg, 54%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.35 (4H, d, J=6.1 Hz), 3.24 (4H, s), 3.42 (3H, s), 3.53 (1H, dd, J=10.3, 3.9 Hz), 3.59-3.63 (5H, m), 3.84-3.87 (1H, m), 4.58 (1H, dt, J=11.7, 5.2 Hz), 6.41 (1H, s), 6.50 (1H, t, J=3.2 Hz), 6.64 (1H, dd, J=3.7, 2.7 Hz), 6.68 (1H, d, J=2.0 Hz), 6.95 (1H, s), 7.08 (1H, s), 8.50 (1H, s), 8.81 (1H, s), 9.79 (1H, s).

(101b) N-{(2S)-2-Hydroxy-3-[(triisopropylsilyl)oxy]propyl}-5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrole-2-carboxamide

N-[(2S)-2,3-Dihydroxypropyl]-5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrole-2-carboxamide (666 mg, 1.28 mmol) synthesized in Example (101a) was dissolved in methylene chloride (20 mL), and triethylamine (0.89 mL, 6.40 mmol), triisopropylsilyl chloride (410 μL, 1.92 mmol) and 4-dimethylaminopyridine (234 mg, 1.92m mmol) were added, followed by stirring for 14 hours under nitrogen atmosphere. The reaction solution was diluted with methylene chloride (50 mL), washed with water and saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column

(methylsulfonyl)pyrazine (426 mg, 0.88 mmol) synthesized in Example 99 was dissolved in methylene chloride (10 mL), and boron tribromide (1.0 mol/L methylene chloride solution, 1.76 mL, 1.76 mmol) was added at -78°C under nitrogen atmosphere. Subsequently, the temperature was brought back to room temperature, fcllowed by stirring for 1.5 hours. To the reaction solution, a saturated aqueous sodium hydrogencarbonate solution was added, and extraction was carried out with methylene chloride. The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-5%) to afford the desired compound (243 mg, yield 59%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J=6.3 Hz), 1.44 (3H, d, J=6.3 Hz), 3.25 (3H, s), 3.56 (1H, dd, J=13.9, 7.2 Hz), 3.80 (2H, d, J=5.5 Hz), 4.10 (1H, dd, J=14.1, 9.4 Hz), 4.61 (1H, q, J=5.6 Hz), 4.86 (1H, dt, J=11.6, 4.5 Hz), 6.47 (1H, d, J=3.5 Hz), 6.50 (1H, s), 6.75 (1H, d, J=3.5 Hz), 6.89 (1H, s), 6.99 (1H, s), 8.47 (1H, d, J=1.2 Hz), 8.80 (1H, d, J=1.2 Hz).
MS (ESI) m/z: 473.14774 $(M+H)^+$.

(Example 101)
{(5R)-2-[5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-5-yl}methanol



(101a) N-[(2S)-2,3-dihydroxypropyl]-5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrole-2-carboxamide

5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrole-2-carboxylic

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chromatography (elution solvent: ethyl acetate/hexane=10%-60%) to afford the desired product (558 mg, 64%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ1.06-1.15 (21H, m), 1.35 (3H, d, J=6.3 Hz), 3.13 (1H, d, J=3.9 Hz), 3.24 (3H, s), 3.42 (3H, s), 3.52 (1H, dd, J=10.3, 3.9 Hz), 3.60 (1H, dd, J=10.3, 6.8 Hz), 3.68 (1H, dd, J=10.0, 6.1 Hz), 3.73 (1H, td, J=7.0, 3.1 Hz), 3.77 (1H, dd, J=10.0, 4.6 Hz), 3.87 (1H, s), 4.58 (1H, dd, J=10.3, 6.3 Hz), 6.33 (1H, t, J=5.6 Hz), 6.50 (1H, t, J=3.2 Hz), 6.60 (1H, t, J=3.2 Hz), 6.67 (1H, s), 6.92 (1H, s), 7.06 (1H, s), 8.50 (1H, d, J=1.0 Hz), 8.81 (1H, d, J=1.0 Hz), 9.44 (1H, s).

(101c) 2-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(5R)-5-{[(triisopropylsilyl)oxy]methyl}-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-5-(methylsulfonyl)pyrazine

N-{(2S)-2-hydroxy-3-[(triisopropylsilyl)oxy]propyl}-5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrole-2-carboxamide (558 mg, 0.82 mmol) synthesized in Example (101b) was dissolved in tetrahydrofuran (20 mL), and anhydrous methanesulfonic acid (287 mg, 1.65 mmol) and triethylamine (0.34 mL, 2.47 mmol) were added, followed by stirring at 50°C for 6 hours under nitrogen atmosphere. To the reaction solution, water (40 mL) was added, and extraction was carried out twice with methylene chloride (40 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-5%) to afford the desired compound (496 mg, yield 94%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.00-1.13 (21H, m), 1.34 (3H, d, J=6.3 Hz), 3.24 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J=10.6, 3.9 Hz), 3.60 (1H, dd, J=10.4, 6.1 Hz), 3.83-4.04 (4H, m), 4.57 (1H, td, J=6.3, 4.3 Hz), 4.72-4.79 (1H, m), 6.50 (1H, d, J=3.9 Hz), 6.65 (1H, t, J=2.0 Hz), 6.73 (1H, d, J=3.9 Hz), 6.90 (1H, t, J=1.8 Hz), 7.05 (1H, t, J=1.8 Hz), 8.49 (1H, d, J=1.2 Hz), 8.81 (1H, d, J=1.2 Hz).

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(101d) {(5R)-2-[5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[5-(methylsulfonyl}pyrazin-2-yl]oxy}phenyl}-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-5-yl}methanol

2-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(5R)-5-{[(triisopropylsilyl)oxy]methyl}-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-5-(methylsulfonyl)pyrazine (496 mg, 0.82 mmol) synthesized in Example (101c) was dissolved in tetrahydrofuran (20 mL), and tetrabutylammonium fluoride (1.0 mol/L tetrahydrofuran solution, 0.82 mL, 0.82 mmol) was added, followed by stirring for 2 hours under nitrogen atmosphere. To the reaction solution, water (40 mL) was added, and extraction was carried out twice with ethyl acetate (40 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-5%) to afford the desired compound (133 mg, yield 35%) as a white solid.

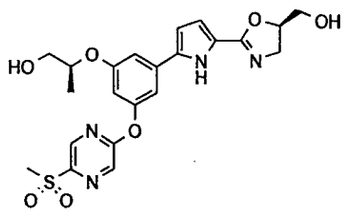
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J=6.3 Hz), 3.24 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J=10.4, 4.1 Hz), 3.60 (1H, dd, J=10.2, 5.9 Hz), 3.71 (1H, dd, J=12.5, 5.5 Hz), 3.79 (1H, dd, J=14.3, 7.6 Hz), 3.88 (1H, dd, J=12.5, 3.1 Hz), 4.04 (1H, dd, J=14.3, 10.0 Hz), 4.57 (1H, dd, J=10.0, 5.7 Hz), 4.85-4.78 (1H, m), 6.50 (1H, d, J=3.9 Hz), 6.66 (1H, t, J=2.2 Hz), 6.77 (1H, d, J=3.9 Hz), 6.93 (1H, s), 7.06 (1H, s), 8.49 (1H, d, J=1.2 Hz), 8.81 (1H, d, J=1.6 Hz).

MS (ESI) m/z: 503.15918 $(M+H)^+$.

(Example 102)

(2S)-2-(3-{5-[(5R)-5-(Hydroxymethyl)-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol

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{{(5R)-2-[5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-5-yl}methanol (105 mg, 0.21 mmol) synthesized in Example (101d) was dissolved in methylene chloride (10 mL), and boron tribromide (1.0 mol/L methylene chloride solution, 315 µL, 0.315 mmol) was added at -78°C under nitrogen atmosphere, and subsequently the temperature was brought back to room temperature, followed by stirring for 1 hour. To the reaction solution, a saturated aqueous sodium hydrogencarbonate solution was added, and extraction was carried out with methylene chloride. The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-7.5%) to afford the desired compound (67 mg, yield 66%) as a white solid.

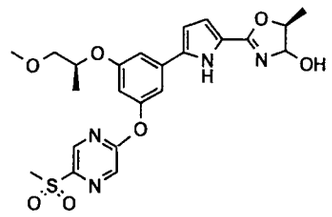
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.29 (3H, d, J=6.3 Hz), 3.24 (3H, s), 3.70-3.91 (5H, m), 4.03 (1H, dd, J=14.1, 9.8 Hz), 4.55 (1H, dd, J=10.6, 5.9 Hz), 4.85-4.78 (1H, m), 6.47 (1H, d, J=3.9 Hz), 6.58 (1H, t, J=2.0 Hz), 6.75 (1H, d, J=3.5 Hz), 6.92 (1H, t, J=1.8 Hz), 7.01 (1H, t, J=1.6 Hz), 8.48 (1H, d, J=1.2 Hz), 8.80 (1H, d, J=1.2 Hz).

MS (ESI) m/z: 489.14448 $(M+H)^+$.

(Example 103)

(5S)-2-[5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazol-4-ol

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(103a) Benzyl L-threoninate

L-threonine 21.2g (178 mmol) was dissolved in toluene (100 mL), and benzyl alcohol (100 mL, 966 mmol) and p-toluenesulfonic acid monohydrate (35.0 g, 194 mmol) were added, followed by heating to reflux for 17 hours under nitrogen atmosphere. After cooling to room temperature, water (200 mL) was added, followed by washing three times with ethyl acetate (100 mL). To the aqueous layer, a saturated aqueous sodium hydrogencarbonate solution was added, and extraction was carried out three times with ethyl acetate (100 mL). After the organic layer was washed with saturated brine, drying was carried out over anhydrous magnesium sulfate, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-15%) to afford the desired product (10.6 g, yield 28%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.22 (3H, d, J=6.3 Hz), 3.30 (1H, d, J= 6.3 Hz), 3.49 (1H, brs), 5.19 (2H, s), 7.34-7.39 (5H, m).

(103b) Benzyl N-{[5-(3-[(1S)-2-methoxy-1-methoxyethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]carbonyl}-L-threoninate

5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[5-[5-(methylsulfonyl)pyrazin-2-yl]oxy)phenyl}-1H-pyrrole-2-carboxylic acid (9.49 g, 21.2 mmol) synthesized in Example (97e) was dissolved in N,N-dimethylformamide (200 mL), and benzyl L-threoninate (4.44 g, 21.2 mmol) synthesized in Example (103a), WSCI·HCl (4.88 g, 25.5 mmol), HOBT·H_2O (3.15 g, 23.3 mmol) and N-methylmorpholine (4.66 mL, 42.4 mmol) were added, followed by stirring at room temperature for 1.5 hours under nitrogen atmosphere. Water (200 mL) was added, and extraction was carried out twice with ethyl acetate (200ml). The organic layer

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was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=70%-100%) to afford the desired product (13.5 g, yield ~100%) as a pale yellow oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.27 (3H, d, J=6.3 Hz), 1.35 (3H, d, J=6.3 Hz), 3.24 (3H, s), 3.42 (3H, s), 3.52 (1H, dd, J= 4.3, 10.2 Hz), 3.61 (1H, dd, J= 5.9, 10.2 Hz), 4.44 (1H, m), 4.59 (1H, m), 4.81 (1H, dd, J=2.7, 8.6 Hz), 5.21 (1H, d, J=12.5 Hz), 5.25 (1H, d, J=12.5 Hz), 6.52 (1H, t, J=3.9 Hz), 6.67 (1H, t, J=2.0 Hz), 6.71 (1H, brd, J=8.6 Hz), 6.75 (1H, dd, J=2.4, 3.9 Hz), 6.94 (1H, t, J=1.9 Hz), 7.08 (1H, t, J=1.9 Hz), 7.33-7.38 (5H, m), 8.49 (2H, m), 8.81 (2H, m), 9.63 (1H, brs).

(103c) Benzyl (4S,5S)-2-[5-(3-[(1S)-2-methoxy-1-methoxyethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazole-4-carboxylate

Benzyl N-{[5-(3-[(1S)-2-methoxy-1-methoxyethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]carbonyl}-L-threoninate (13.5 g, 21.2 mmol) synthesized in Example (103b) was dissolved in methylene chloride (150 mL), and cooled to -78°C. Bis(2-methoxyethyl)amino sulfur trifluoride (5.47 mL, 29.7 mmol) was added dropwise, and stirring was carried out at -78°C for 40 minutes. Potassium carbonate (5.86 g, 42.4 mmol) was added, and stirring was carried out for 1.5 hours with the temperature being raised gradually to room temperature. A saturated aqueous sodium hydrogencarbonate solution (100 mL) was added at 0°C, and extraction was carried out twice with methylene chloride (100 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=40%-70%) to afford the desired product (9.68 g, yield 74%) as a white solid.

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^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.29 (3H, d, J=6.3 Hz), 1.35 (3H, d, J=6.3 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.51 (1H, dd, J= 3.9, 10.2 Hz), 3.60 (1H, dd, J= 5.9, 10.2 Hz), 4.58 (1H, m), 4.94 (1H, d, J=9.8 Hz), 5.02 (1H, m), 5.19 (1H, d, J=12.1 Hz), 5.24 (1H, d, J=12.1 Hz), 6.51 (1H, t, J=3.9 Hz), 6.66 (1H, t, J=2.4 Hz), 6.78 (1H, t, J=3.9 Hz), 6.94 (1H, t, J=2.0 Hz), 7.08 (1H, t, J=2.4 Hz), 7.35-7.39 (5H, m), 8.48 (2H, d, J=1.2 Hz), 8.81 (2H, d, J=1.2 Hz).

(103d) (5S)-2-[5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazol-4-ol

Benzyl (4S,5S)-2-[5-(3-[(1S)-2-methoxy-1-methoxyethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazole-4-carboxylate (1.53 g, 2.47 mmol) synthesized in Example (103c) was dissolved in tetrahydrofuran (50 mL), and a 10% palladium carbon catalyst (600 mg) was added, followed by stirring at room temperature for 2.5 hours under hydrogen atmosphere. The palladium carbon catalyst was removed by Celite filtration, followed by washing with ethyl acetate. The solvent was distilled off under reduced pressure.

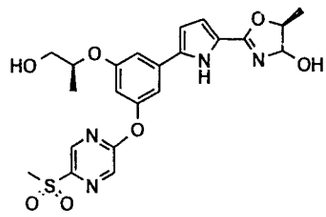
The resulting residue was dissolved in acetonitrile (60 mL), and a solution of cerium (IV) diammonium nitrate (2.03 g, 3.70 mmol) in water (30 mL) was added dropwise at 0°C. After stirring at room temperature for 17 hours under nitrogen atmosphere, a saturated aqueous sodium hydrogencarbonate solution (30 mL) was added, and extraction was carried out twice with ethyl acetate (50 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=70%-100%) to afford the desired product (645 mg, yield 52%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J=6.3 Hz), 1.37 (6/3H, d, J=6.7 Hz), 1.47 (3/3H, d, J=6.7 Hz), 3.23 (3H, s), 3.41 (3H, s),

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3.50 (1H, dd, J= 4.3, 10.2 Hz), 3.60 (1H, dd, J=5.9, 10.2 Hz), 4.50-4.66 (2H, m), 5.39 (2/3H, d, J=3.1 Hz), 5.66 (1/3H, d, J=6.7 Hz), 6.50 (1H, brd, J=3.9 Hz), 6.65 (1H, t, J=2.4 Hz), 6.82 (1H, brd, J=3.9 Hz), 6.94 (1H, t, J=2.0 Hz), 7.08 (1H, t, J=2.0 Hz), 8.48 (2H, d, J=1.2 Hz), 8.80 (2H, d, J=1.2 Hz).
MS (ESI) m/z: 503.16004 $(M+H)^+$.

(Example 104)
(5S)-2-[5-(3-[(1S)-2-Hydroxy-1-methylethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazol-4-ol

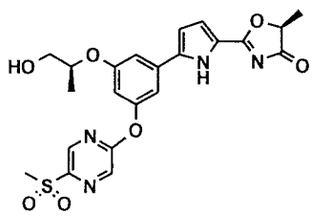


(5S)-2-[5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazol-4-ol (410 mg, 0.816 mmol) synthesized in Example (103d) was dissolved in methylene chloride (20 mL), and cooled to -78°C. Boron tribromide (1.0 mol/L methylene chloride solution, 2.04 mL, 2.04 mmol) was added, and stirring was carried out for 2 hours with the temperature being raised gradually to room temperature. A saturated aqueous sodium hydrogencarbonate solution (20 mL) was added, and extraction was carried out twice with methylene chloride (20 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=2%-10%) to afford the desired product (362 mg, yield 91%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.30 (3H, d, J=6.3 Hz), 1.38 (6/3H, d, J=6.7 Hz), 1.49 (3/3H, d, J=6.7 Hz), 3.23 (3H, s), 3.76 (2H, brd, J= 5.5 Hz), 4.51-4.57 (2H, m), 5.39 (2/3H, d, J=3.5 Hz), 5.66

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(1/3H, d, J=6.7 Hz), 6.49 (1H, d, J=3.9 Hz), 6.61 (1H, t, J=2.4 Hz), 6.81 (1H, d, J=3.9 Hz), 6.94 (1H, t, J=2.0 Hz), 7.06 (1H, t, J=2.0 Hz), 8.47 (2H, d, J=1.2 Hz), 8.78 (2H, d, J=1.2 Hz).
MS (ESI) m/z: 489.14439 $(M+H)^+$.

(Example 105)
(5S)-2-[5-(3-[(1S)-2-Hydroxy-1-methylethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazol-4(5H)-one



(105a) (5S)-2-[5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazol-4(5H)-one

(5S)-2-[5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazol-4-ol (80.0 mg, 0.159 mmol) synthesized in Example (103d) was dissolved in methylene chloride (10 mL), and pyridinium dichromate (240 mg, 0.638 mmol) and molecular sieves 4A (200mg) were added, followed by stirring at room temperature for 2 hours under nitrogen atmosphere. After Celite filtration, the solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=50%-70%) to afford the desired product (44.1 mg, yield 55%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.36 (3H, d, J=6.3 Hz), 1.62 (3H, d, J=7.0 Hz), 3.25 (3H, s), 3.42 (3H, s), 3.52 (1H, dd, J=3.9, 10.2 Hz), 3.62 (1H, dd, J=5.9, 10.2 Hz), 4.62 (1H, m), 4.81 (1H, q, J=7.0 Hz), 6.68 (1H, d, J=3.9 Hz), 6.76 (1H, t, J=2.4 Hz), 7.03 (1H, t, J=2.0 Hz), 7.17 (1H, t, J=2.0 Hz), 7.26 (1H, d, J=3.9 Hz), 8.52 (2H, d, J=1.2 Hz), 8.82 (2H, d, J=1.2 Hz).

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(105b) (5S)-2-[5-(3-[(1S)-2-Hydroxy-1-methylethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazol-4(5H)-one

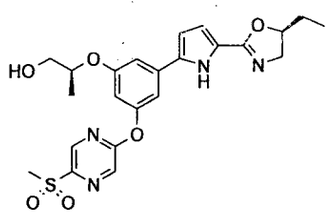
(5S)-2-[5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazol-4(5H)-one (100 mg, 0.200 mmol) synthesized in Example (105a) was dissolved in methylene chloride (10 mL), and cooled to -78°C. Boron tribromide (1.0 mol/L methylene chloride solution, 0.260 mL, 0.260 mmol) was added, and stirring was carried out for 2 hours with the temperature being raised gradually to room temperature. A saturated aqueous sodium hydrogencarbonate solution (10 mL) was added, and extraction was carried out twice with methylene chloride (10 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-10%) to afford the desired product (98.0 mg, yield ~100%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J=6.3 Hz), 1.63 (3H, dd, J=2.7, 7.0 Hz), 3.26 (3H, s), 3.80-3.84 (2H, m), 4.62 (1H, m), 4.84 (1H, q, J=7.0 Hz), 6.66 (1H, d, J=3.9 Hz), 6.69 (1H, m), 7.03 (1H, m), 7.20 (1H, m), 7.26 (1H, brd, J=3.9 Hz), 8.51 (2H, d, J=1.2 Hz), 8.81 (2H, d, J=1.2 Hz).

MS (ESI) m/z: 487.12874 $(M+H)^+$.

(Example 106)

(2S)-2-(3-{5-[(5S)-5-Ethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol



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(106a) Benzyl 5-{3-hydroxy-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrole-2-carboxylate

3-[(1S)-2-Methoxy-1-methylethoxy]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (26.79 g, 86.9 mmol) synthesized in Example (78d) and 2-benzyl 1-t-butyl 5-bromo-1H-pyrrole-1,2-dicarboxylate (32.32 g, 85.0 mmol) synthesized in Example (78f) were dissolved in 1,4-dioxane (360 mL)+water (90 mL), and [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloride dichloromethane complex (2.34 g, 2.87 mmol) and potassium carbonate (30.40 g, 220 mmol) were added, followed by stirring at 60°C for 3 hours under nitrogen atmosphere. After the reaction solution was cooled to room temperature, water (1000 mL) was added, and extraction was carried out with ethyl acetate (700 mL). The organic layer was washed with saturated brine, subsequently dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure.

The resulting residue was dissolved in methylene chloride (100 mL), and trifluoroacetic acid (120 mL) was added, followed by stirring at room temperature for 1 hour. After the reaction solution was concentrated under reduced pressure, it was diluted with ethyl acetate (500 mL), washed with saturated aqueous sodium hydrogencarbonate solution and saturated brine, subsequently dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=30%-50%) to afford the desired compound (17.40 g, yield 54%) as a brown oil.

^{1}H -NMR ($CDCl_3$, 400 Hz): δ 1.31 (3H, d, J=6.3 Hz), 3.42 (3H, s), 3.49 (1H, dd, J=9.8, 4.3 Hz), 3.59 (1H, dd, J=10.2, 6.3 Hz), 4.52-4.59 (1H, m), 5.35 (2H, s), 6.42 (1H, t, J=2.0 Hz), 6.47 (1H, dd, J=3.9, 2.7 Hz), 6.72 (1H, s), 6.77 (1H, br s), 6.80 (1H, s), 6.98 (1H, dd, J=3.9, 2.7 Hz), 7.45-7.33 (5H, m), 9.94 (1H, br s).

MS (FAB) m/z: 382 $(M+H)^+$.

(106b) Benzyl 5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-

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[(triisopropylsilyl)oxy]phenyl}-1H-pyrrole-2-carboxylate

Benzyl 5-{3-hydroxy-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrole-2-carboxylate (27.35 g, 71.7 mmol) synthesized in Example (106a) was dissolved in methylene chloride (350 mL), and triisopropylsilyl chloride (18.4 mL, 86.0 mmol), triethylamine (30.0 mL, 215 mmol) and 4-dimethylaminopyridine (10.53 g, 86.2 mmol) were added, followed by stirring at room temperature for 4 hours under nitrogen atmosphere. Water (400 mL) was added to separate the solution, and the organic layer was washed with saturated brine, followed by drying over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=3%-20%) to afford the desired product (34.41 g, yield 89%) as a pale yellow oil.

^{1}H-NMR ($CDCl_3$, 400 Hz): δ 1.11 (18H, d, J=7.0 Hz), 1.22-1.30 (3H, m), 1.32 (3H, d, J=6.3 Hz), 3.41 (3H, s), 3.49 (1H, dd, J=10.2, 4.3 Hz), 3.58 (1H, dd, J=10.2, 5.9 Hz), 4.49-4.56 (1H, m), 5.33 (2H, s), 6.43 (1H, t, J=2.3 Hz), 6.47 (1H, dd, J=3.9, 2.7 Hz), 6.66 (1H, t, J=2.0 Hz), 6.71 (1H, t, J=1.8 Hz), 6.98 (1H, dd, J=3.9, 2.7 Hz), 7.32-7.45 (5H, m), 9.19 (1H, br s).

MS (FAB) m/z: 538 $(M+H)^+$.

(106c) 5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[(triisopropylsilyl)oxy]phenyl}-1H-pyrrole-2-carboxylic acid

Benzyl 5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[(triisopropylsilyl)oxy]phenyl}-1H-pyrrole-2-carboxylate (34.40 g, 64.0 mmol) synthesized in Example (106b) was dissolved in ethanol (320 mL), and a 10% palladium carbon catalyst (3.54 g) was added, followed by stirring for 2 hours under hydrogen atmosphere. The palladium carbon catalyst was removed by Celite filtration, and the solvent was distilled off under reduced pressure to afford the desired compound (27.31 g, yield 95%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 Hz): δ 1.11 (18H, d, J=7.4 Hz), 1.22-1.30 (3H, m), 1.33 (3H, d, J=6.3 Hz), 3.46 (1H, s), 3.51 (1H, dd, J=10.2,

4.7 Hz), 3.66 (1H, dd, J=10.2, 5.9 Hz), 4.61-4.69 (1H, m), 6.43 (1H, t, J=2.0 Hz), 6.51 (1H, dd, J=3.7, 2.2 Hz), 6.74 (1H, t, J=1.6 Hz), 6.98 (1H, t, J=1.6 Hz), 7.05 (1H, dd, J=3.9, 2.3 Hz), 10.02 (1H, br s).
MS (FAB) m/z: 448 $(M+H)^+$.

(106d) N-[(2R)-2-Hydroxybutyl]-5-{3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-[(tripropan-2-ylsilyl)oxy]phenyl}-1H-pyrrole-2-carboxamide

5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[(triisopropylsilyl)oxy]phenyl}-1H-pyrrole-2-carboxylic acid (1.03 g, 2.30 mmol) synthesized in Example (106c) was dissolved in methylene chloride (20 mL), and (2R)-1-aminobutan-2-ol (0.40 g, 4.49 mmol) synthesized according to a method known to the public (Angew. Chem. Int. Ed. 2007, 46, 2245.), WSC·HCl (1.15 g, 6.00 mmol) and 4-dimethylaminopyridine (280 mg, 2.29 mmol) were added, followed by stirring at room temperature overnight under nitrogen atmosphere. To the reaction solution, a saturated aqueous ammonium chloride solution (30 mL) was added, and extraction was carried out with methylene chloride (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=60%-80%) to afford the desired compound (1.01 g, yield 85%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.99 (3H, t, J=7.4 Hz), 1.11 (18H, d, J=7.0 Hz), 1.23-1.30 (3H, m), 1.31 (3H, d, J=6.3 Hz), 1.49-1.60 (2H, m), 3.27-3.35 (1H, m), 3.42 (3H, s), 3.49 (1H, dd, J=10.2, 4.3 Hz), 3.59 (1H, dd, J=10.2, 5.9 Hz), 3.62-3.69 (1H, m), 3.70-3.76 (1H, m), 4.49-4.56 (1H, m), 6.33 (1H, t, J=5.7 Hz), 6.41 (1H, t, J=2.2 Hz), 6.45 (1H, dd, J=3.5, 3.1 Hz), 6.61 (1H, dd, J=3.7, 2.5 Hz), 6.67 (1H, t, J=1.8 Hz), 6.73 (1H, t, J=1.8 Hz), 9.58 (1H, s).

(106e) (5S)-5-Ethyl-2-[5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-

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[(tripropan-2-ylsilyl)oxy]phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazole

N-[(2R)-2-Hydroxybutyl]-5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-[(tripropan-2-ylsilyl)oxy]phenyl)-1H-pyrrole-2-carboxamide (1.01 g, 1.95 mmol) synthesized in Example (106d) was dissolved in tetrahydrofuran (40 mL), and anhydrous methanesulfonic acid (600 mg, 3.44 mmol) and triethylamine (1.60 mL, 11.48 mmol) were added, followed by stirring at 50°C for 8 hours under nitrogen atmosphere. To the reaction solution, a saturated aqueous ammonium chloride solution (50 mL) was added, and extraction was carried out with methylene chloride (80 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=50%-70%) to afford the desired compound (980 mg, yield 100%) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.01 (3H, t, J=7.4 Hz), 1.09-1.14 (18H, m), 1.24-1.30 (3H, m), 1.32 (3H, d, J=6.3 Hz), 1.71-1.82 (2H, m), 3.42 (3H, s), 3.49 (1H, dd, J=10.2, 4.3 Hz), 3.57-3.63 (2H, m), 4.04 (2H, dd, J=14.1,9.4 Hz), 4.51-4.56 (1H, m), 4.62-4.68 (1H, m), 6.39 (1H, t, J=2.2 Hz), 6.46 (1H, d, J=3.9 Hz), 6.71 (1H, s), 6.75 (1H, s), 6.76 (1H, s).

(106f) 2-(3-{5-[(5S)-5-Ethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[(2S)-1-methoxypropan-2-yl]oxy}phenoxy)-5-(methylsulfonyl)pyrazine

(5S)-5-Ethyl-2-[5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-[(tripropan-2-ylsilyl)oxy]phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazole (980 mg, 1.95 mmol) synthesized in Example (106e) was dissolved in tetrahydrofuran (20 mL), and tetrabutylammonium fluoride (1.0 mol/L tetrahydrofuran solution, 4.00 mL, 4.00 mmol) was added at room temperature, followed by stirring at room temperature for 1.5 hours under nitrogen atmosphere. To this reaction solution, a saturated aqueous ammonium chloride

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solution (30 mL) was added, and extraction was carried out with methylene chloride (40 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure to afford a yellow solid.

This was dissolved in acetonitrile (20 mL), and 2-chloro-5-(methylsulfonyl)pyrazine (420 mg, 2.18 mmol) synthesized in Example (97c) and cesium carbonate (1.42 g, 4.36 mmol) were added at room temperature, followed by stirring at room temperature for 2 hours under nitrogen atmosphere. To this reaction solution, water (30 mL) was added, and extraction was carried out with methylene chloride (40 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate=100%) to afford the desired compound (860 mg, yield 88%) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.08 (3H, t, J=7.4 Hz), 1.38 (3H, d, J=6.3 Hz), 1.81-1.94 (2H, m), 3.24 (3H, s), 3.42 (3H, s), 3.56 (1H, dd, J=10.6, 3.9 Hz), 3.62 (1H, dd, J=10.6, 5.9 Hz), 3.74 (1H, dd, J=12.7, 7.6 Hz), 4.17 (1H, dd, J=12.1,9.8 Hz), 4.74 (1H, br s), 4.99 (1H, br s), 6.61 (1H, d, J=4.3 Hz), 6.74 (1H, s), 7.06 (1H, s), 7.20 (1H, s), 7.40 (1H, s), 8.50 (1H, d, J=1.2 Hz), 8.82 (1H, d, J=1.2 Hz).

(106g) (2S)-2-(3-{5-[(5S)-5-Ethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol

2-(3-{5-[(5S)-5-Ethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[(2S)-1-methoxypropan-2-yl]oxy}phenoxy)-5-(methylsulfonyl)pyrazine (860 mg, 1.72 mmol) synthesized in Example (106f) was dissolved in methylene chloride (20 mL), and boron tribromide (1.0 mol/L methylene chloride solution, 2.50 mL, 2.50 mmol) was added dropwise at -78°C, followed by stirring at room temperature for 2 hours under nitrogen atmosphere. To this

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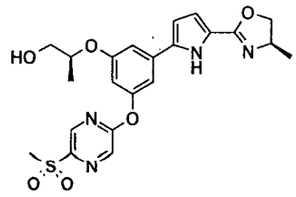
reaction solution, a saturated aqueous sodium hydrogencarbonate solution (20 mL) was added, and extraction was carried out with methylene chloride (20 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=2%-4%) to afford the desired compound (764 mg, yield 91%) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.02 (3H, t, J=7.4 Hz), 1.33 (3H, d, J=6.3 Hz), 1.67-1.85 (2H, m), 3.23 (3H, s), 3.63 (1H, dd, J=13.7, 7.8 Hz), 3.73-3.83 (2H, m), 4.07 (1H, dd, J=13.7, 9.4 Hz), 4.60 (1H, br s), 4.72 (1H, br s), 6.51 (1H, d, J=3.9 Hz), 6.60 (1H, s), 6.81 (1H, d, J=3.5 Hz), 6.96 (1H, s), 7.12 (1H, s), 8.48 (1H, d, J=1.2 Hz), 8.80 (1H, d, J=1.2 Hz).

MS (ESI) m/z: 487.16397 $(M+H)^+$.

(Example 107)

(2S)-2-{3-{5-[(4R)-4-Methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol



(107a) N-[(2R)-1-Hydroxypropan-2-yl]-5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-[(tripropan-2-ylsilyl)oxy]phenyl)-1H-pyrrole-2-carboxamide

5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[(triisopropylsilyl)oxy]phenyl}-1H-pyrrole-2-carboxylic acid (2.25 g, 5.03 mmol) synthesized in Example (106c) was dissolved in methanol (50 mL), and D-alaninol (0.70 mL, 8.97 mmol) and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride n hydrate (3.05 g, 11.02 mmol) were added, followed by stirring at room temperature for 1 day under nitrogen atmosphere. After

the solvent was distilled off under reduced pressure, a saturated aqueous ammonium chloride solution (50 mL) was added, and extraction was carried out with ethyl acetate (80 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=80%-100%) to afford the desired compound (1.95 g, yield 75%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.11 (18H, d, J=7.4 Hz), 1.23-1.28 (3H, m), 1.28 (3H, d, J=7.0 Hz), 1.32 (3H, d, J=5.9 Hz), 3.42 (3H, s), 3.49 (1H, dd, J=10.2, 4.3 Hz), 3.59 (1H, dd, J=10.2, 5.9 Hz), 3.64 (1H, dd, J=11.1, 6.1 Hz), 3.77 (1H, dd, J=10.9, 3.5 Hz), 4.24 (1H, br s), 4.53 (1H, br s), 6.05 (1H, s), 6.41 (1H, t, J=2.0 Hz), 6.45 (1H, t, J=3.3 Hz), 6.60 (1H, dd, J=3.7, 2.5 Hz), 6.67 (1H, t, J=1.8 Hz), 6.74 (1H, t, J=1.8 Hz), 9.60 (1H, s).

(107b) (4R)-2-[5-(3-{[(2S)-1-Methoxypropan-2-yl]oxy}-5-[(tripropan-2-ylsilyl)oxy]phenyl)-1H-pyrrol-2-yl]-4-methyl-4,5-dihydro-1,3-oxazole

N-[(2R)-1-Hydroxypropan-2-yl]-5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-[(tripropan-2-ylsilyl)oxy]phenyl)-1H-pyrrole-2-carboxamide (1.95 g, 3.76 mmol) synthesized in Example (107a) was dissolved in tetrahydrofuran (30 mL), and anhydrous methanesulfonic acid (1.25 g, 7.18 mmol) and triethylamine (2.80 mL, 20.09 mmol) were added, followed by stirring at 50°C for 1 day under nitrogen atmosphere. To the reaction solution, a saturated aqueous ammonium chloride solution (80 mL) was added, and extraction was carried out with methylene chloride (120 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=50%-80%) to afford the desired compound (1.18 g, yield 64%) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.12 (18H, d, J=7.4 Hz), 1.23-1.31 (3H,

m), 1.31-1.35 (6H, m), 3.42 (3H, s), 3.49 (1H, dd, J=10.2, 4.7 Hz), 3.59 (1H, dd, J=10.2, 5.9 Hz), 3.93 (1H, t, J=7.8 Hz), 4.33 (1H, br s), 4.49 (1H, dd, J=9.0, 8.2 Hz), 4.54 (1H, br s), 6.40 (1H, t, J=2.2 Hz), 6.46 (1H, d, J=3.5 Hz), 6.72 (1H, t, J=1.8 Hz), 6.74 (1H, d, J=3.9 Hz), 6.77 (1H, t, J=1.8 Hz).

(107c) 3-{[(2S)-1-Methoxypropan-2-yl]oxy}-5-{5-[(4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenol

(4R)-2-[5-(3-{[(2S)-1-Methoxypropan-2-yl]oxy}-5-[(tripropan-2-ylsilyl)oxy]phenyl)-1H-pyrrol-2-yl]-4-methyl-4,5-dihydro-1,3-oxazole (1.18 g, 2.42 mmol) synthesized in Example (107b) was dissolved in tetrahydrofuran (10 mL), and tetrabutylammonium fluoride (1.0 mol/L tetrahydrofuran solution, 3.00 mL, 3.00 mmol) was added at room temperature, followed by stirring at room temperature for 30 minutes under nitrogen atmosphere. To this reaction solution, a saturated aqueous ammonium chloride solution (30 mL) was added, and extraction was carried out with methylene chloride (40 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=1%-3%) to afford the desired compound (720 mg, yield 90%) as a yellow solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J=6.3 Hz), 1.49 (3H, d, J=6.3 Hz), 3.42 (3H, s), 3.48 (1H, dd, J=10.2, 4.7 Hz), 3.59 (1H, dd, J=10.2, 5.9 Hz), 4.02 (1H, t, J=7.6 Hz), 4.47-4.61 (3H, m), 6.38 (1H, t, J=2.2 Hz), 6.48 (1H, d, J=3.9 Hz), 6.73 (1H, t, J=1.8 Hz), 6.76 (1H, d, J=3.9 Hz), 7.09 (1H, s), 11.09 (1H, s).

(107d) 2-Bromo-5-(methylsulfonyl)pyrazine

2,5-Dibromopyrazine (270 mg, 1.14 mmol) was dissolved in tetrahydrofuran (10 mL), and sodium thiomethoxide (320 mg, 4.57 mmol) was added at room temperature, followed by stirring at room temperature for 2.5 hours under nitrogen atmosphere. To this reaction solution, water (10 mL) was added, and extraction

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was carried out with diethyl ether (10 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=5%-10%) to afford a yellow solid.

This was dissolved in methylene chloride (10 mL), and m-chloroperbenzoic acid (approximately 65%, 580 mg, approximately 2.2 mmol) was added at room temperature, followed by stirring at room temperature for 1 hour under nitrogen atmosphere. To this reaction solution, a saturated aqueous sodium hydrogencarbonate solution (10 mL) was added, and extraction was carried out with methylene chloride (10 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=15%-25%) to afford the desired compound (190 mg, yield 70%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.26 (3H, s), 8.80 (1H, d, J=1.2 Hz), 9.06 (1H, d, J=1.2 Hz).

(107e) 2-(3-{[(2S)-1-Methoxypropan-2-yl]oxy}-5-{5-[(4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-5-(methylsulfonyl)pyrazine

3-{[(2S)-1-Methoxypropan-2-yl]oxy}-5-{5-[(4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenol (340 mg, 1.03 mmol) synthesized in Example (107c) was dissolved in acetonitrile (10 mL), and 2-bromo-5-(methylsulfonyl)pyrazine (300 mg, 1.27 mmol) synthesized in Example (107d) and cesium carbonate (850 mg, 2.61 mmol) were added at room temperature, followed by stirring at room temperature for 4.5 hours under nitrogen atmosphere. To this reaction solution, water (20 mL) was added, and extraction was carried out with methylene chloride (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate.

The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate=100%) to afford the desired compound (456 mg, yield 91%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J=4.3 Hz), 1.35 (3H, d, J=3.9 Hz), 3.24 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J=10.2, 3.9 Hz), 3.60 (1H, dd, J=10.4, 6.1 Hz), 3.93 (1H, t, J=7.8 Hz), 4.33 (1H, br s), 4.51 (1H, t, J=8.6 Hz), 4.58 (1H, br s), 6.52 (1H, d, J=3.9 Hz), 6.66 (1H, t, J=2.2 Hz), 6.76 (1H, d, J=3.9 Hz), 6.92 (1H, t, J=1.8 Hz), 7.07 (1H, d, J=1.6 Hz), 8.49 (1H, d, J=1.2 Hz), 8.81 (1H, d, J=1.6 Hz).

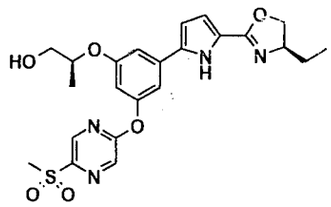
(107f) (2S)-2-(3-{5-[(4R)-4-Methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol

2-(3-{[(2S)-1-Methoxypropan-2-yl]oxy}-5-{5-[(4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-5-(methylsulfonyl)pyrazine (456 mg, 0.94 mmol) synthesized in Example (107e) was dissolved in methylene chloride (5.0 mL), and boron tribromide (1.0 mol/L methylene chloride solution, 1.50 mL, 1.50 mmol) was added dropwise at -78°C, followed by stirring at room temperature for 3 hours under nitrogen atmosphere. To this reaction solution, a saturated aqueous sodium hydrogencarbonate solution (10 mL) was added, and extraction was carried out with methylene chloride (20 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=4%-6%) to afford the desired compound (330 mg, yield 74%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J=6.3 Hz), 1.40 (3H, d, J=6.6 Hz), 3.22 (3H, s), 3.71 (1H, dd, J=11.7, 4.3 Hz), 3.81 (1H, dd, J=11.7, 6.6 Hz), 4.05-4.14 (1H, m), 4.38-4.45 (1H, m), 4.59-4.67 (2H, m), 6.53 (1H, d, J=3.9 Hz), 6.62 (1H, t, J=2.2 Hz), 6.87 (1H, d, J=3.9 Hz), 6.98 (1H, s), 7.27 (1H, s), 8.47 (1H, d,

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J=1.2 Hz), 8.79 (1H, d, J=1.2 Hz).
MS (ESI) m/z: 473.14930 $(M+H)^+$.

(Example 108)
(2S)-2-(3-{5-[(4R)-4-Ethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol



(108a) (4R)-4-Ethyl-2-[5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-[(tripropan-2-ylsilyl)oxy]phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazole

5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[(triisopropylsilyl)oxy]phenyl}-1H-pyrrole-2-carboxylic acid (1.40 g, 3.13 mmol) synthesized in Example (106c) was dissolved in methanol (20 mL), and (R)-(-)-2-amino-1-butanol (0.65 g, 7.29 mmol) and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride n hydrate (1.75 g, 6.32 mmol) was added, followed by stirring at room temperature for 2 days under nitrogen atmosphere. After the solvent was distilled off under reduced pressure, a saturated aqueous ammonium chloride solution (50 mL) was added, and extraction was carried out with methylene chloride (100 mL). The organic layer was washed with saturated aqueous sodium hydrogencarbonate solution and saturated brine, and subsequently dried over anhydrous magnesium sulfate. The resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=50%-80%) to afford a compound as a white foam.

This was dissolved in tetrahydrofuran (20 mL), and anhydrous methanesulfonic acid (0.80 g, 4.59 mmol) and triethylamine (1.20 mL, 8.61 mmol) were added, followed by stirring at 50°C overnight under nitrogen atmosphere. To the reaction solution, a saturated aqueous ammonium chloride

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solution (60 mL) was added, and extraction was carried out with methylene chloride (100 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=70%-90%) to afford the desired compound (965 mg, yield 62%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.00 (3H, t, J=7.6 Hz), 1.07-1.14 (18H, m), 1.23-1.31 (3H, m), 1.32 (3H, d, J=6.3 Hz), 1.56-1.65 (1H, m), 1.68-1.77 (1H, m), 3.41 (3H, s), 3.48 (1H, dd, J=10.0, 4.6 Hz), 3.59 (1H, dd, J=10.0, 5.6 Hz), 4.01 (1H, t, J=7.8 Hz), 4.15-4.21 (1H, m), 4.44 (1H, t, J=8.8 Hz), 4.49-4.54 (1H, m), 6.39 (1H, t, J=2.0 Hz), 6.46 (1H, d, J=3.9 Hz), 6.71 (1H, t, J=1.7 Hz), 6.74 (1H, d, J=3.4 Hz), 6.76 (1H, t, J=1.7 Hz).

(108b) 3-{5-[(4R)-4-Ethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[(2S)-1-methoxypropan-2-yl]oxy}phenol

(4R)-4-Ethyl-2-[5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-[(tripropan-2-ylsilyl)oxy]phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazole (965 mg, 1.93 mmol) synthesized in Example (108a) was dissolved in tetrahydrofuran (10 mL), and tetrabutylammonium fluoride (1.0 mol/L tetrahydrofuran solution, 2.50 mL, 2.50 mmol) was added at room temperature, followed by stirring at room temperature for 1 hour under nitrogen atmosphere. To this reaction solution, a saturated aqueous ammonium chloride solution (30 mL) was added, and extraction was carried out with methylene chloride (40 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=2%-4%) to afford the desired compound (550 mg, yield 83%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.10 (3H, t, J=7.4 Hz), 1.32 (3H, d, J=6.3 Hz), 1.73 (1H, td, J=14.1,7.0 Hz), 1.85 (1H, td, J=14.0,

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7.0 Hz), 3.41 (3H, s), 3.48 (1H, dd, J=10.2, 4.7 Hz), 3.59 (1H, dd, J=10.2, 5.9 Hz), 4.09-4.15 (1H, m), 4.32-4.40 (1H, m), 4.48-4.57 (2H, m), 6.36 (1H, t, J=2.2 Hz), 6.47 (1H, d, J=3.5 Hz), 6.72 (1H, t, J=1.8 Hz), 6.76 (1H, d, J=3.9 Hz), 7.10 (1H, t, J=1.8 Hz), 11.12 (1H, br s).

(108c) 2-(3-{5-[(4R)-4-Ethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[(2S)-1-methoxypropan-2-yl]oxy}phenoxy)-5-(methylsulfonyl)pyrazine

3-{5-[(4R)-4-Ethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[(2S)-1-methoxypropan-2-yl]oxy}phenol (272 mg, 0.79 mmol) synthesized in Example (108b) was dissolved in acetonitrile (5.0 mL), and 2-chloro-5-(methylsulfonyl)pyrazine (220 mg, 1.14 mmol) synthesized in Example (97c) and cesium carbonate (640 mg, 1.96 mmol) were added at room temperature, followed by stirring at room temperature for 3.5 hours under nitrogen atmosphere. To this reaction solution, water (20 mL) was added, and extraction was carried out with methylene chloride (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=2%-3%) to afford the desired compound (417 mg, yield ~100%) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.96 (3H, t, J=7.4 Hz), 1.34 (3H, d, J=6.3 Hz), 1.53-1.60 (1H, m), 1.65-1.72 (1H, m), 3.23 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J=10.2, 4.3 Hz), 3.59 (1H, dd, J=10.6, 5.9 Hz), 4.01 (1H, t, J=7.8 Hz), 4.11-4.19 (1H, m), 4.41-4.46 (1H, m), 4.57 (1H, br s), 6.50 (1H, d, J=3.9 Hz), 6.64 (1H, t, J=2.2 Hz), 6.73 (1H, d, J=3.5 Hz), 6.94 (1H, d, J=1.6 Hz), 7.09 (1H, d, J=1.6 Hz), 8.47 (1H, d, J=0.8 Hz), 8.80 (1H, d, J=0.8 Hz).

(108d) (2S)-2-(3-{5-[(4R)-4-Ethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-

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yl]oxy}phenoxy)propan-1-ol

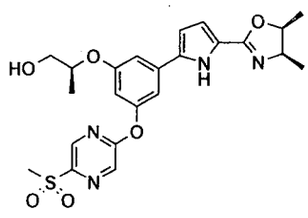
2-(3-{5-[(4R)-4-Ethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[(2S)-1-methoxypropan-2-yl]oxy}phenoxy)-5-(methylsulfonyl)pyrazine (417 mg, 0.83 mmol) synthesized in Example (108c) was dissolved in methylene chloride (10 mL), and boron tribromide (1.0 mol/L methylene chloride solution, 1.00 mL, 1.00 mmol) was added dropwise at -78°C, followed by stirring at room temperature for 1 hour under nitrogen atmosphere. To this reaction solution, a 1N aqueous sodium hydroxide solution (20 mL) was added, and extraction was carried out with methylene chloride (20 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=3%-4%) to afford the desired compound (325 mg, yield 80%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.01 (3H, t, J=7.4 Hz), 1.30 (3H, d, J=6.3 Hz), 1.57-1.64 (1H, m), 1.68-1.75 (1H, m), 3.23 (3H, s), 3.78-3.80 (2H, m), 4.02 (1H, t, J=8.0 Hz), 4.16-4.22 (1H, m), 4.47 (1H, t, J=8.8 Hz), 4.57-4.63 (1H, m), 6.45 (1H, d, J=3.5 Hz), 6.49 (1H, s), 6.73 (1H, d, J=3.9 Hz), 6.90 (1H, s), 7.01 (1H, s), 8.44 (1H, s), 8.79 (1H, s).

MS (ESI) m/z: 487.16468 $(M+H)^+$.

(Example 109)

(2S)-2-(3-{5-[(4R,5S)-4,5-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol



(109a) N-[(2R,3R)-3-Hydroxybutan-2-yl]-5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-[(tripropan-2-ylsilyl)oxy]phenyl)-1H-

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pyrrole-2-carboxamide

5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[(triisopropylsilyl)oxy]phenyl}-1H-pyrrole-2-carboxylic acid (0.89 g, 1.99 mmol) synthesized in Example (106c) was dissolved in methanol (20 mL), and (2R,3R)-3-aminobutan-2-ol (0.41 g, 4.60 mmol) synthesized in Example (88a) and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride n hydrate (1.20 g, 4.34 mmol) were added, followed by stirring at room temperature for 3 days under nitrogen atmosphere. After the solvent was distilled off under reduced pressure, a saturated aqueous ammonium chloride solution (50 mL) was added, and extraction was carried out with methylene chloride (80 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=60%-80%) to afford the desired compound (722 mg, yield 70%) as a white foam.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.11 (18H, d, J=7.0 Hz), 1.22-1.29 (3H, m), 1.24 (3H, d, J=6.3 Hz), 1.28 (3H, d, J=7.0 Hz), 1.32 (3H, d, J=6.3 Hz), 2.34 (1H, br s), 3.42 (3H, s), 3.49 (1H, dd, J=10.2, 4.3 Hz), 3.59 (1H, dd, J=10.2, 5.5 Hz), 3.84 (1H, br s), 4.03-4.13 (1H, m), 4.49-4.56 (1H, m), 6.06 (1H, d, J=8.6 Hz), 6.41 (1H, t, J=2.2 Hz), 6.45 (1H, dd, J=3.7, 2.9 Hz), 6.61 (1H, dd, J=3.9, 2.3 Hz), 6.67 (1H, t, J=1.8 Hz), 6.73 (1H, t, J=2.0 Hz), 9.49 (1H, br s).

(109b) (4R,5S)-2-[5-(3-{[(2S)-1-Methoxypropan-2-yl]oxy}-5-[(tripropan-2-ylsilyl)oxy]phenyl)-1H-pyrrol-2-yl]-4,5-dimethyl-4,5-dihydro-1,3-oxazole

N-[(2R,3R)-3-Hydroxybutan-2-yl]-5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-[(tripropan-2-ylsilyl)oxy]phenyl)-1H-pyrrole-2-carboxamide (722 mg, 1.39 mmol) synthesized in Example (109a) was dissolved in tetrahydrofuran (30 mL), and anhydrous methanesulfonic acid (430 mg, 2.47 mmol) and triethylamine (1.20 mL, 8.61 mmol) were added, and stirring was carried out at 50°C overnight under nitrogen atmosphere. The reaction solution was

brought back to room temperature, and a saturated aqueous ammonium chloride solution (50 mL) was added, followed by extraction with methylene chloride (50 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=40%-70%) to afford the desired compound (700 mg, yield 100%) as a yellow liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.11 (18H, d, J=7.0 Hz), 1.21 (3H, d, J=7.0 Hz), 1.23-1.30 (3H, m), 1.31 (3H, d, J=6.3 Hz), 1.33 (3H, d, J=6.6 Hz), 3.42 (3H, s), 3.48 (1H, dd, J=10.2, 4.3 Hz), 3.58 (1H, dd, J=10.2, 5.9 Hz), 4.24-4.32 (1H, m), 4.48-4.56 (1H, m), 4.78-4.85 (1H, m), 6.39 (1H, t, J=2.2 Hz), 6.46 (1H, d, J=3.5 Hz), 6.70 (1H, s), 6.73-6.75 (2H, m).

(109c) 3-{5-[(4R,5S)-4,5-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[(2S)-1-methoxypropan-2-yl]oxy}phenol

(4R,5S)-2-[5-(3-{[(2S)-1-Methoxypropan-2-yl]oxy}-5-[(tripropan-2-ylsilyl)oxy]phenyl)-1H-pyrrol-2-yl]-4,5-dimethyl-4,5-dihydro-1,3-oxazole (700 mg, 1.39 mmol) synthesized in Example (109b) was dissolved in tetrahydrofuran (10 mL), and tetrabutylammonium fluoride (1.0 mol/L tetrahydrofuran solution, 2.00 mL, 2.00 mmol) was added at room temperature, followed by stirring at room temperature for 30 minutes under nitrogen atmosphere. To this reaction solution, a saturated aqueous ammonium chloride solution (30 mL) was added, and extraction was carried out with methylene chloride (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=2%-3%) to afford the desired compound (420 mg, yield 88%) as a yellow liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J=6.3 Hz), 1.35-1.40 (6H, m), 3.41 (3H, s), 3.48 (1H, dd, J=10.0, 4.5 Hz), 3.59 (1H, dd,

J=10.2, 5.5 Hz), 4.40-4.48 (1H, m), 4.48-4.56 (1H, m), 4.86-4.94 (1H, m), 6.38 (1H, t, J=2.0 Hz), 6.47 (1H, d, J=3.9 Hz), 6.72 (1H, s), 6.75 (1H, d, J=3.9 Hz), 7.09 (1H, s).

(109d) 2-(3-{5-[(4R,5S)-4,5-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[(2S)-1-methoxypropan-2-yl]oxy}phenoxy)-5-(methylsulfonyl)pyrazine

3-{5-[(4R,5S)-4,5-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[(2S)-1-methoxypropan-2-yl]oxy}phenol (420 mg, 1.22 mmol) synthesized in Example (109c) was dissolved in acetonitrile (20 mL), and 2-chloro-5-(methylsulfonyl)pyrazine (345 mg, 1.46 mmol) synthesized in Example (97c) and cesium carbonate (1.02 g, 3.13 mmol) were added at room temperature, followed by stirring at room temperature overnight under nitrogen atmosphere. To this reaction solution, water (30 mL) was added, and extraction was carried out with methylene chloride (40 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=2%-3%) to afford the desired compound (513 mg, yield 84%) as a white solid.

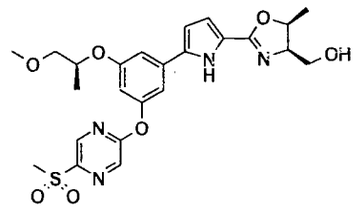
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.19-1.28 (6H, m), 1.35 (3H, d, J=6.6 Hz), 3.24 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J=10.2, 4.3 Hz), 3.61 (1H, dd, J=10.4,5.7 Hz), 4.25-4.35 (1H, m), 4.57-4.63 (1H, m), 4.81-4.91 (1H, m), 6.52 (1H, d, J=3.9 Hz), 6.76 (1H, s), 6.96 (1H, s), 7.12 (1H, s), 8.49 (1H, d, J=1.2 Hz), 8.81 (1H, d, J=1.6 Hz).

(109e) ((2S)-2-(3-{5-[(4R,5S)-4,5-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol

2-(3-{5-[(4R,5S)-4,5-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[(2S)-1-methoxypropan-2-yl]oxy}phenoxy)-5-(methylsulfonyl)pyrazine (513 mg, 1.02 mmol) synthesized in

Example (109d) was dissolved in methylene chloride (10 mL), and boron tribromide (1.0 mol/L methylene chloride solution, 1.50 mL, 1.50 mmol) was added dropwise at -78°C, followed by stirring at room temperature for 2 hours under nitrogen atmosphere. To this reaction solution, a saturated aqueous sodium hydrogencarbonate solution (20 mL) was added, and extraction was carried out with methylene chloride (20 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=4%-5%) to afford the desired compound (390 mg, yield 79%) as a pale yellow solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.22 (3H, d, J=7.0 Hz), 1.32 (3H, d, J=6.3 Hz), 1.34 (3H, d, J=6.6 Hz), 3.23 (3H, s), 3.76-3.79 (2H, m), 4.25-4.33 (1H, m), 4.54-4.60 (1H, m), 4.81-4.88 (1H, m), 6.49 (1H, d, J=3.9 Hz), 6.59 (1H, s), 6.75 (1H, d, J=3.9 Hz), 6.95 (1H, s), 7.09 (1H, s), 8.47 (1H, s), 8.80 (1H, d, J=1.2 Hz).
MS (ESI) m/z: 487.16580 $(M+H)^+$.

(Example 110)
{(4R,5S)-2-[5-(3-{[(2S)-1-Methoxypropan-2-yl]oxy}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazol-4-yl}methanol



(110a) N-[(2R,3R)-1,3-Dihydroxybutan-2-yl]-5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-[(tripropan-2-ylsilyl)oxy]phenyl)-1H-pyrrole-2-carboxamide

5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[(triisopropylsilyl)oxy]phenyl}-1H-pyrrole-2-carboxylic acid (2.05 g, 4.58 mmol) synthesized in Example (106c) was dissolved in methanol (20 mL), and commercially available L-threoninol

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(1.50 g, 14.27 mmol) and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride n hydrate (2.85 g, 10.30 mmol) were added, followed by stirring at room temperature for 3 days under nitrogen atmosphere. After the solvent was distilled off under reduced pressure, a saturated aqueous ammonium chloride solution (50 mL) was added, and extraction was carried out with methylene chloride (80 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=3%-7%) to afford the desired compound (2.10 g, yield 86%) as a white foam.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.11 (18H, d, J=7.4 Hz), 1.21-1.33 (6H, m), 1.22 (3H, d, J=6.3 Hz), 3.44 (3H, s), 3.49 (1H, dd, J=10.2, 3.9 Hz), 3.57 (1H, dd, J=10.2, 6.3 Hz), 3.83 (2H, br s), 3.96 (1H, br s), 4.26 (1H, ddd, J=12.5,6.3,2.0 Hz), 4.45-4.53 (1H, m), 6.41 (1H, t, J=2.2 Hz), 6.44 (1H, dd, J=3.5, 2.7 Hz), 6.68-6.72 (3H, m), 6.72-6.77 (1H, m), 10.36 (1H, s).

(110b) N-{(2R,3R)-3-Hydroxy-1-[(tripropan-2-ylsilyl)oxy]butan-2-yl}-5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-[(tripropan-2-ylsilyl)oxy]phenyl)-1H-pyrrole-2-carboxamide

N-[(2R,3R)-1,3-Dihydroxybutan-2-yl]-5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-[(tripropan-2-ylsilyl)oxy]phenyl)-1H-pyrrole-2-carboxamide (2.10 g, 3.93 mmol) synthesized in Example (110a) was dissolved in methylene chloride (50 mL), and triisopropylchlorosilane (1.50 mL, 7.01 mmol), 4-dimethylaminopyridine (1.50 g, 12.27 mmol) and triethylamine (5.00 mL, 35.87 mmol) were added, followed by stirring at room temperature for 1 day under nitrogen atmosphere. To the reaction solution, a saturated aqueous ammonium chloride solution (50 mL) was added, and extraction was carried out with methylene chloride (50 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column

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chromatography (elution solvent: ethyl acetate/hexane=25-40%) to afford the desired compound (2.52 g, yield 93%) as a white solid.
^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.07 (18H, d, J=6.8 Hz), 1.12 (18H, d, J=7.3 Hz), 1.21-1.31 (9H, m), 1.32 (3H, d, J=6.3 Hz), 3.42 (3H, s), 3.49 (1H, dd, J=10.3, 4.4 Hz), 3.55 (1H, br s), 3.59 (1H, dd, J=10.3, 5.9 Hz), 4.00-4.04 (1H, m), 4.04-4.06 (2H, m), 4.29-4.34 (1H, m), 4.49-4.55 (1H, m), 6.41 (1H, t, J=2.2 Hz), 6.46 (1H, dd, J=3.9, 2.9 Hz), 6.60 (1H, s), 6.61 (1H, dd, J=3.4, 2.4 Hz), 6.67 (1H, t, J=2.0 Hz), 6.72 (1H, t, J=2.0 Hz), 9.34 (1H, s).

(110c) {(4R,5S)-2-[5-(3-{[(2S)-1-Methoxypropan-2-yl]oxy}-5-[(tripropan-2-ylsilyl)oxy]phenyl)-1H-pyrrol-2-yl]-5-methyl-4-{[(tripropan-2-ylsilyl)oxy]methyl}-4,5-dihydro-1,3-oxazole

N-{(2R,3R)-3-Hydroxy-1-[(tripropan-2-ylsilyl)oxy]butan-2-yl}-5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-[(tripropan-2-ylsilyl)oxy]phenyl)-1H-pyrrole-2-carboxamide (2.52 g, 3.65 mmol) synthesized in Example (110b) was dissolved in tetrahydrofuran (20 mL), and anhydrous methanesulfonic acid (1.05 g, 6.03 mmol) and triethylamine (2.00 mL, 14.35 mmol) were added, followed by stirring at 50°C for 1 day under nitrogen atmosphere. To the reaction solution, a saturated aqueous ammonium chloride solution (50 mL) was added, and extraction was carried out with methylene chloride (50 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=10%-30%) to afford the desired compound (2.30 g, yield 94%) as a pale yellow liquid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.06 (18H, d, J=5.1 Hz), 1.11 (18H, d, J=7.4 Hz), 1.22-1.30 (6H, m), 1.31 (3H, d, J=6.3 Hz), 1.52 (3H, d, J=6.3 Hz), 3.42 (3H, s), 3.48 (1H, dd, J=10.2, 4.7 Hz), 3.59 (1H, dd, J=10.4,5.7 Hz), 3.82 (1H, dd, J=10.2, 9.0 Hz), 3.98 (1H, dd, J=10.2, 3.9 Hz), 4.24 (1H, td, J=8.7, 3.9 Hz), 4.48-4.55 (1H, m), 4.86-4.96 (1H, m), 6.39 (1H, t, J=2.2 Hz), 6.45 (1H, d, J=3.9 Hz), 6.67 (1H, s), 6.71 (1H, s), 6.75 (1H, d, J=3.9 Hz).

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(110d) {(4R,5S)-2-[5-(3-{[(2S)-1-Methoxypropan-2-yl]oxy}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazol-4-yl}methanol

{(4R,5S)-2-[5-(3-{[(2S)-1-Methoxypropan-2-yl]oxy}-5-[(tripropan-2-ylsilyl)oxy]phenyl)-1H-pyrrol-2-yl]-5-methyl-4-{[(tripropan-2-ylsilyl)oxy]methyl}-4,5-dihydro-1,3-oxazole (2.30 g, 3.42 mmol) synthesized in Example (110c) was dissolved in tetrahydrofuran (20 mL), and tetrabutylammonium fluoride (1.0 mol/L tetrahydrofuran solution, 8.00 mL, 8.00 mmol) was added at room temperature, followed by stirring at room temperature for 30 minutes under nitrogen atmosphere. To this reaction solution, a saturated aqueous ammonium chloride solution (60 mL) was added, and extraction was carried out with methylene chloride (80 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/ethyl acetate=5%-10%) to afford a white solid (2.10g).

1.20 g of the resulting compound was dissolved in acetonitrile (15 mL), and 2-chloro-5-(methylsulfonyl)pyrazine (410 mg, 2.13 mmol) synthesized in Example (97c) and potassium carbonate (0.85 g, 6.15 mmol) were added at 0°C, followed by stirring under nitrogen atmosphere at 0°C for 5 hours, and further at room temperature for 3 hours. To this reaction solution, water (30 mL) was added, and extraction was carried out with methylene chloride (40 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/ethyl acetate=4%-6%) to afford the desired compound (964 mg, yield 95%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.35 (3H, d, J=6.3 Hz), 1.40 (3H, d, J=6.3 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J=10.2, 4.3

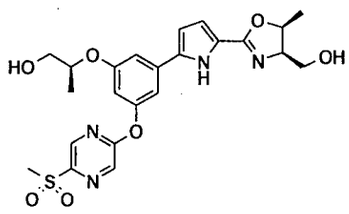
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Hz), 3.60 (1H, dd, J=10.2, 5.9 Hz), 3.77 (1H, dd, J=11.5, 6.1 Hz), 3.85 (1H, dd, J=11.7, 3.5 Hz), 4.22-4.28 (1H, m), 4.54-4.60 (1H, m), 4.82-4.88 (1H, m), 6.45 (1H, d, J=3.5 Hz), 6.65 (1H, t, J=2.2 Hz), 6.67 (1H, d, J=2.3 Hz), 6.94 (1H, t, J=1.8 Hz), 7.10 (1H, t, J=1.8 Hz), 8.48 (1H, d, J=1.2 Hz), 8.80 (1H, d, J=1.2 Hz).

MS (ESI) m/z: 517.17452 $(M+H)^+$.

(Example 111)

(2S)-2-(3-{5-[(4R,5S)-4-(Hydroxymethyl)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol



{(4R,5S)-2-[5-(3-{[(2S)-1-Methoxypropan-2-yl]oxy}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazol-4-yl}methanol (209 mg, 0.40 mmol) synthesized in Example (110d) was dissolved in methylene chloride (5.0 mL), and boron tribromide (1.0 mol/L methylene chloride solution, 0.80 mL, 0.80 mmol) was added dropwise at -78°C, followed by stirring at room temperature for 40 minutes under nitrogen atmosphere. To this reaction solution, a 1N aqueous sodium hydroxide solution (10 mL) was added, and extraction was carried out with methylene chloride (20 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=4%-6%) to afford the desired compound (169 mg, yield 83%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J=6.3 Hz), 1.41 (3H, d, J=6.6 Hz), 3.23 (3H, s), 3.76 (2H, d, J=4.7 Hz), 3.70-3.80 (1H, m), 3.85 (1H, dd, J=11.7, 3.9 Hz), 4.21-4.25 (1H, m), 4.49-4.60

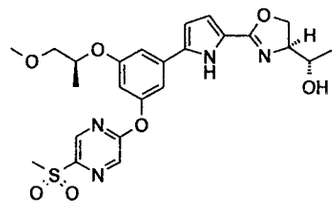
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(1H, m), 4.82-4.89 (1H, m), 6.43 (1H, d, J=2.7 Hz), 6.59 (1H, s), 6.67 (1H, d, J=2.7 Hz), 6.95 (1H, s), 7.07 (1H, s), 8.47 (1H, s), 8.78 (1H, s).

MS (ESI) m/z: 503.15957 $(M+H)^+$.

(Example 112)

(1S)-1-{(4S)-2-[5-(3-{[(2S)-1-Methoxypropan-2-yl]oxy}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol



(112a) N-[(2S,3S)-1,3-Dihydroxybutan-2-yl]-5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-[(tripropan-2-ylsilyl)oxy]phenyl)-1H-pyrrole-2-carboxamide

5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[(triisopropylsilyl)oxy]phenyl}-1H-pyrrole-2-carboxylic acid (1.75 g, 3.91 mmol) synthesized in Example (106c) was dissolved in methanol (30 mL), and D-threoninol (1.00 g, 9.51 mmol) and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride n hydrate (2.85 g, 10.30 mmol) were added, followed by stirring at room temperature for 5 days under nitrogen atmosphere. After the solvent was distilled off under reduced pressure, a saturated aqueous ammonium chloride solution (50 mL) was added, and extraction was carried out with methylene chloride (80 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=3%-7%) to afford the desired compound (1.76 g, yield 84%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.08 (18H, d, J=7.4 Hz), 1.18-1.25 (6H, m), 1.27 (3H, d, J=6.3 Hz), 2.83 (2H, br s), 3.38 (3H, s), 3.45 (1H, dd, J=10.2, 4.3 Hz), 3.55 (1H, dd, J=10.2, 5.9 Hz), 3.87

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(2H, s), 3.94-4.01 (2H, m), 4.22 (1H, br s), 4.46-4.52 (1H, m), 6.37 (1H, br s), 6.40-6.43 (1H, m), 6.59-6.66 (3H, m), 6.70 (1H, s), 9.78 (1H, br s).

(112b) (1S)-1-{(4S)-2-[5-(3-{[(2S)-1-Methoxypropan-2-yl]oxy}-5-[(tripropan-2-ylsilyl)oxy]phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol

N-[(2S,3S)-1,3-Dihydroxybutan-2-yl]-5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-[(tripropan-2-ylsilyl)oxy]phenyl)-1H-pyrrole-2-carboxamide (1.76 g, 3.29 mmol) synthesized in Example (112a) was dissolved in tetrahydrofuran (20 mL), and anhydrous methanesulfonic acid (0.54 g, 3.10 mmol) and triethylamine (1.00 mL, 7.17 mmol) were added at -40°C, followed by stirring at the same temperature for 4 hours under nitrogen atmosphere, and then at 50°C overnight. To the reaction solution, a saturated aqueous ammonium chloride solution (50 mL) was added, and extraction was carried out with methylene chloride (50 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=2%-5%) to afford the desired compound (880 mg, yield 52%) as a white foam.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.12 (18H, d, J=7.0 Hz), 1.22-1.30 (6H, m), 1.32 (3H, d, J=6.3 Hz), 3.42 (3H, s), 3.48 (1H, dd, J=10.2, 4.3 Hz), 3.59 (1H, dd, J=10.2, 5.9 Hz), 3.69-3.75 (1H, m), 4.10-4.20 (2H, m), 4.45 (1H, br s), 4.53 (1H, br s), 6.40 (1H, t, J=1.6 Hz), 6.47 (1H, d, J=3.9 Hz), 6.70 (1H, s), 6.75 (1H, s), 6.77 (1H, d, J=3.9 Hz).

(112c) 3-(5-{(4S)-4-[(1S)-1-Hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl}-1H-pyrrol-2-yl)-5-{[(2S)-1-methoxypropan-2-yl]oxy}phenol

(1S)-1-{(4S)-2-[5-(3-{[(2S)-1-Methoxypropan-2-yl]oxy}-5-[(tripropan-2-ylsilyl)oxy]phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol (1.48 g, 2.88 mmol) synthesized in

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Example (112b) was dissolved in tetrahydrofuran (20 mL), and tetrabutylammonium fluoride (1.0 mol/L tetrahydrofuran solution, 3.50 mL, 3.50 mmol) was added at room temperature, followed by stirring at room temperature for 1.5 hours under nitrogen atmosphere. To this reaction solution, a saturated aqueous ammonium chloride solution (50 mL) was added, and extraction was carried out with methylene chloride (50 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=3%-6%) to afford the desired compound (880 mg, yield 85%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J=6.3 Hz), 1.37 (3H, d, J=6.3 Hz), 3.42 (3H, s), 3.46 (1H, dd, J=10.2, 4.7 Hz), 3.61 (1H, dd, J=10.0, 5.7 Hz), 3.85-3.92 (1H, m), 4.25-4.36 (2H, m), 4.49-4.56 (2H, m), 6.48 (1H, d, J=3.9 Hz), 6.54 (1H, t, J=2.0 Hz), 6.73 (1H, t, J=1.8 Hz), 6.79 (1H, d, J=3.5 Hz), 7.06 (1H, s).

(112d) (1S)-1-{(4S)-2-[5-(3-{[(2S)-1-Methoxypropan-2-yl]oxy}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol

3-(5-{(4S)-4-[(1S)-1-Hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl}-1H-pyrrol-2-yl)-5-{[(2S)-1-methoxypropan-2-yl]oxy}phenol (880 mg, 2.44 mmol) synthesized in Example (112c) was dissolved in acetonitrile (20 mL), and 2-chloro-5-(methylsulfonyl)pyrazine (630 mg, 3.27 mmol) synthesized in Example (97c) and potassium carbonate (1.20 g, 8.68 mmol) were added, followed by stirring at room temperature for 4 hours under nitrogen atmosphere. Water (50 mL) was added, and extraction was carried out with methylene chloride (50 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=1%-3%) to afford the desired compound (1.00 g, yield 79%) as a

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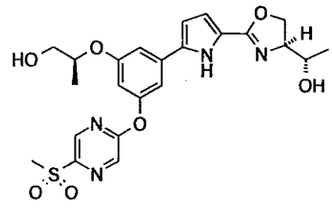
white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.28 (3H, d, J=6.3 Hz), 1.35 (3H, d, J=6.3 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.51 (1H, dd, J=10.2, 4.3 Hz), 3.60 (1H, dd, J=10.2, 6.3 Hz), 3.73 (1H, br s), 4.11-4.22 (2H, m), 4.46 (1H, br s), 4.60 (1H, br s), 6.52 (1H, d, J=3.9 Hz), 6.67 (1H, t, J=2.0 Hz), 6.78 (1H, d, J=3.9 Hz), 6.96 (1H, s), 7.12 (1H, s), 8.49 (1H, s), 8.81 (1H, s).

MS (ESI) m/z: 517.17608 $(M+H)^+$.

(Example 113)

(2S)-2-[3-(5-{(4S)-4-[(1S)-1-Hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl}-1H-pyrrol-2-yl)-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy]propan-1-ol



(1S)-1-{(4S)-2-[5-(3-{[(2S)-1-Methoxypropan-2-yl]oxy}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol (204 mg, 0.395 mmol) synthesized in Example (112d) was dissolved in methylene chloride (5.0 mL), and boron tribromide (1.0 mol/L methylene chloride solution, 0.80 mL, 0.80 mmol) was added dropwise at -78°C, followed by stirring at room temperature for 1.5 hours under nitrogen atmosphere. To this reaction solution, a 1N aqueous sodium hydroxide solution (10 mL) was added, and extraction was carried out with methylene chloride (20 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=3%-5%) to afford the desired compound (159 mg, yield 80%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.28 (3H, d, J=6.3 Hz), 1.32 (3H, d, J=6.3 Hz), 3.24 (3H, s), 3.73-3.78 (3H, m), 4.12-4.23 (2H, m),

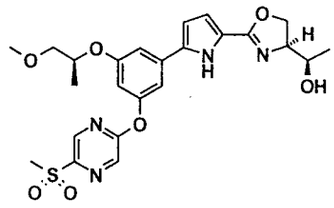
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4.46 (1H, br s), 4.52-4.59 (1H, m), 6.50 (1H, d, J=3.9 Hz), 6.62 (1H, t, J=2.0 Hz), 6.76 (1H, d, J=3.9 Hz), 6.94 (1H, t, J=1.8 Hz), 7.08 (1H, s), 8.49 (1H, d, J=1.2 Hz), 8.80 (1H, d, J=1.2 Hz).

MS (ESI) m/z: 503.15930 $(M+H)^+$.

(Example 114)

(1R)-1-{(4S)-2-[5-(3-{[(2S)-1-Methoxypropan-2-yl]oxy}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol



(114a) N-[(2S,3R)-1,3-Dihydroxybutan-2-yl]-5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-[(tripropan-2-ylsilyl)oxy]phenyl)-1H-pyrrole-2-carboxamide

5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[(triisopropylsilyl)oxy]phenyl}-1H-pyrrole-2-carboxylic acid (1.63 g, 3.64 mmol) synthesized in Example (106c) was dissolved in methanol (20 mL), and D-allo-threoninol (1.05 g, 9.99 mmol) and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride n hydrate (2.00 g, 7.23 mmol) were added, followed by stirring at room temperature for 1 day under nitrogen atmosphere. After the solvent was distilled off under reduced pressure, a saturated aqueous ammonium chloride solution (50 mL) was added, and extraction was carried out with methylene chloride (80 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=3%-7%) to afford the desired compound (1.70 g, yield 87%) as a white foam.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.07 (18H, d, J=7.0 Hz), 1.17-1.27 (9H, m), 2.01 (1H, br s), 3.37 (3H, s), 3.44 (1H, dd, J=10.0, 4.1 Hz),

3.44 (1H, s), 3.53 (1H, dd, J=10.4, 6.1 Hz), 3.72-3.78 (1H, m), 3.88-3.93 (1H, m), 3.93-3.95 (1H, m), 3.96-4.04 (2H, m), 4.44-4.52 (1H, m), 6.35 (1H, t, J=2.0 Hz), 6.39 (1H, t, J=3.1 Hz), 6.67 (1H, t, J=1.8 Hz), 6.70 (1H, s), 6.72 (1H, s), 6.99 (1H, d, J=7.8 Hz), 10.34 (1H, br s).

(114b) (1R)-1-{(4S)-2-[5-(3-{[(2S)-1-Methoxypropan-2-yl]oxy}-5-[(tripropan-2-ylsilyl)oxy]phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol

N-[(2S,3R)-1,3-Dihydroxybutan-2-yl]-5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-[(tripropan-2-ylsilyl)oxy]phenyl)-1H-pyrrole-2-carboxamide (1.70 g, 3.18 mmol) synthesized in Example (114a) was dissolved in tetrahydrofuran (20 mL), and anhydrous methanesulfonic acid (0.78 g, 4.48 mmol) and triethylamine (1.50 mL, 10.76 mmol) were added at 0°C, followed by stirring at the same temperature for 1.5 hours under nitrogen atmosphere, followed by stirring at 50°C overnight. To the reaction solution, a saturated aqueous ammonium chloride solution (50 mL) was added, and extraction was carried out with methylene chloride (50 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=2%-4%) to afford the desired compound (1.30 g, yield 79%) as a white foam.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.10-1.14 (18H, m), 1.20 (3H, d, J=6.6 Hz), 1.23-1.32 (3H, m), 1.34 (3H, d, J=6.3 Hz), 3.41 (3H, s), 3.48 (1H, dd, J=10.2, 4.3 Hz), 3.59 (1H, dd, J=10.2, 5.9 Hz), 4.20-4.34 (4H, m), 4.53 (1H, br s), 6.33 (1H, d, J=3.9 Hz), 6.40 (1H, t, J=2.0 Hz), 6.44 (1H, br s), 6.74 (1H, t, J=1.8 Hz), 6.78 (1H, t, J=1.8 Hz).

(114c) 3-(5-{(4S)-4-[(1R)-1-Hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl}-1H-pyrrol-2-yl)-5-{[(2S)-1-methoxypropan-2-yl]oxy}phenol

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(1R)-1-{(4S)-2-[5-(3-{[(2S)-1-Methoxypropan-2-yl]oxy}-5-[(tripropan-2-ylsilyl)oxy]phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol (1.30 g, 2.52 mmol) synthesized in Example (114b) was dissolved in tetrahydrofuran (15 mL), and tetrabutylammonium fluoride (1.0 mol/L tetrahydrofuran solution, 4.00 mL, 4.00 mmol) was added at room temperature, followed by stirring at room temperature for 1 hour under nitrogen atmosphere. To this reaction solution, a saturated aqueous ammonium chloride solution (50 mL) was added, and extraction was carried out with methylene chloride (50 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/ethyl acetate=8%-12%) to afford the desired compound (766 mg, yield 85%) as a white foam.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.31 (6H, d, J=6.3 Hz), 3.28 (1H, br s), 3.42 (3H, s), 3.47 (1H, dd, J=10.2, 4.3 Hz), 3.61 (1H, dd, J=10.2, 5.9 Hz), 4.23 (1H, br s), 4.35-4.43 (1H, m), 4.47-4.56 (3H, m), 6.46-6.49 (2H, m), 6.72 (1H, s), 6.78 (1H, d, J=3.5 Hz), 7.04 (1H, t, J=1.8 Hz), 11.07 (1H, s).

(114d) (1R)-1-{(4S)-2-[5-(3-{[(2S)-1-Methoxypropan-2-yl]oxy}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol

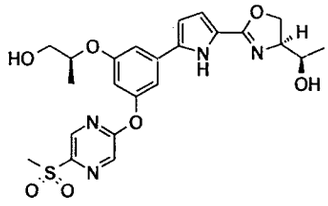
3-(5-{(4S)-4-[(1R)-1-Hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl}-1H-pyrrol-2-yl)-5-{[(2S)-1-methoxypropan-2-yl]oxy}phenol (766 mg, 2.13 mmol) synthesized in Example (114c) was dissolved in acetonitrile (15 mL), and 2-chloro-5-(methylsulfonyl)pyrazine (590 mg, 3.06 mmol) synthesized in Example (97c) and potassium carbonate (870 mg, 6.29 mmol) were added, followed by stirring at room temperature for 4 hours under nitrogen atmosphere. Water (50 mL) was added, and extraction was carried out with methylene chloride (50 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure,

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and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/ethyl acetate=5%-8%) to afford the desired compound (890 mg, yield 81%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.17 (3H, d, J=6.6 Hz), 1.36 (3H, d, J=6.3 Hz), 3.23 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J=10.4, 4.1 Hz), 3.60 (1H, dd, J=10.2, 5.9 Hz), 4.10-4.26 (2H, m), 4.28-4.35 (2H, m), 4.58 (1H, br s), 6.42 (1H, d, J=3.9 Hz), 6.56 (1H, d, J=3.5 Hz), 6.66 (1H, t, J=2.2 Hz), 6.96 (1H, d, J=1.6 Hz), 7.11 (1H, s), 8.49 (1H, d, J=1.2 Hz), 8.81 (1H, d, J=1.2 Hz).
MS (ESI) m/z: 517.17565 $(M+H)^+$.

(Example 115)
(2S)-2-[3-(5-{(4S)-4-[(1R)-1-Hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl}-1H-pyrrol-2-yl)-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy]propan-1-ol



(1R)-1-{(4S)-2-[5-(3-{[(2S)-1-Methoxypropan-2-yl]oxy}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol (213 mg, 0.412 mmol) synthesized in Example (114d) was dissolved in methylene chloride (5.0 mL), and boron tribromide (1.0 mol/L methylene chloride solution, 0.80 mL, 0.80 mmol) was added dropwise at -78°C, followed by stirring at room temperature for 1.5 hours under nitrogen atmosphere. To this reaction solution, a saturated aqueous sodium hydrogencarbonate solution (10 mL) was added, and extraction was carried out with methylene chloride (20 mL). The organic layer was washed with 1N aqueous sodium hydroxide solution (10 mL), and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent:

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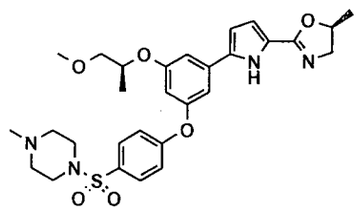
methanol/methylene chloride=4%-5%) to afford the desired compound (147 mg, yield 71%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.18 (3H, d, J=6.3 Hz), 1.33 (3H, d, J=6.3 Hz), 1.61 (2H, br s), 3.23 (3H, s), 3.73-3.82 (2H, m), 4.16-4.26 (2H, m), 4.30-4.36 (2H, m), 4.54-4.61 (1H, m), 6.39 (1H, d, J=3.9 Hz), 6.53 (1H, d, J=3.5 Hz), 6.61 (1H, s), 6.95 (1H, s), 7.07 (1H, s), 8.48 (1H, d, J=1.2 Hz), 8.80 (1H, d, J=1.6 Hz).

MS (ESI) m/z: 503.15973 $(M+H)^+$.

(Example 116)

1-{[4-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)phenyl]sulfonyl}-4-methylpiperazine



(116a) 1-[(4-Fluorophenyl)sulfonyl]-4-methylpiperazine

Commercially available 4-fluorobenzenesulfonyl chloride (1.00 g, 5.14 mmol) was suspended in water (15 mL), and N-methylpiperazine (0.68 mL, 6.17 mmol) and potassium carbonate (1.56 g, 11.3 mmol) were added, followed by stirring at room temperature for 14 hours under nitrogen atmosphere. To the reaction solution, water (50 mL) was added, followed by extraction with ethyl acetate (50 mL), and subsequently the organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=50%-90%) to afford the desired compound (491 mg, yield 37%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.28 (3H, s), 2.49 (4H, t, J=4.9 Hz), 3.04 (4H, br s), 7.21 (2H, dd, J=9.4, 7.8 Hz), 7.76-7.79 (2H, m).

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(116b) N-[(2R)-2-Hydroxypropyl]-5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[(triisopropylsilyl)oxy]phenyl}-1H-pyrrole-2-carboxamide

5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[(triisopropylsilyl)oxy]phenyl}-1H-pyrrole-2-carboxylic acid (51.4 g, 115 mmol) synthesized in Example (106c) was dissolved in methanol (600 mL), and (R)-(-)-1-amino-2-propanol (19.9 mL, 253 mmol) and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride n hydrate (63.7 g, 230 mmol) were added, followed by stirring for 15 hours under nitrogen atmosphere. The solvent was distilled off under reduced pressure, and water (500 mL) was added, followed by extraction twice with ethyl acetate (500 mL). Subsequently, the organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=25%-67%) to afford the desired compound (48.7 g, yield 84%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.12 (18H, d, J=7.8 Hz), 1.27 (3H, q, J=8.3 Hz), 1.32 (3H, d, J=6.3 Hz), 2.60 (1H, s), 3.27-3.33 (1H, m), 3.42 (3H, s), 3.49 (1H, dd, J=10.3, 4.4 Hz), 3.56-3.65 (2H, m), 4.03 (1H, s), 4.53 (1H, td, J=6.1,4.4 Hz), 6.31 (1H, br s), 6.41 (1H, t, J=2.2 Hz), 6.46 (1H, t, J=3.2 Hz), 6.61 (1H, t, J=3.2 Hz), 6.67 (1H, t, J=1.7 Hz), 6.73 (1H, t, J=2.0 Hz), 9.51 (1H, br s).

(116c) (5S)-2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[(triisopropylsilyl)oxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-4,5-dihydro-1,3-oxazole

N-[(2R)-2-hydroxypropyl]-5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[(triisopropylsilyl)oxy]phenyl}-1H-pyrrole-2-carboxamide (48.7 g, 96.5 mmol) synthesized in Example (116b) was dissolved in tetrahydrofuran (600 mL), and anhydrous methanesulfonic acid (33.6 g, 193 mmol) and triethylamine (40.4 mL, 289 mmol) were added, followed by stirring at 50°C for 3

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hours under nitrogen atmosphere. To the reaction solution, a saturated aqueous ammonium chloride solution (500 mL) was added, and extraction was carried out twice with ethyl acetate (500 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, diisopropylether (300 mL) was added to the resulting residue, and the slurry was stirred to give a white solid, which was filtered off. Under reduced pressure, the solvent in the mother liquor was distilled off, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=10%-50%). This was vacuum-dried together with the filtered product to afford the desired compound (34.8 g, yield 74%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.11 (18H, d, J=7.8 Hz), 1.25-1.34 (3H, m), 1.38 (3H, d, J=6.3 Hz), 1.65 (3H, d, J=5.9 Hz), 3.43 (3H, s), 3.58-3.65 (2H, m), 3.76 (1H, dd, J=10.9, 7.8 Hz), 4.28 (1H, dd, J=11.3, 9.8 Hz), 4.81-4.87 (1H, m), 5.28-5.37 (1H, m), 6.51 (1H, t, J=2.2 Hz), 6.62 (1H, d, J=2.0 Hz), 6.91 (1H, s), 7.19 (1H, s), 7.35 (1H, s).

(116d) 3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenol

(5S)-2-(5-{3-[(1*S*)-2-Methoxy-1-methylethoxy]-5-[(triisopropylsilyl)oxy]phenyl}-1H-pyrrol-2-yl)-5-methyl-4,5-dihydro-1,3-oxazole (29.5 g, 60.7 mmol) synthesized in Example (116c) was dissolved in tetrahydrofuran (400 mL), and tetrabutylammonium fluoride (1.0 mol/L tetrahydrofuran solution, 66 mL, 66 mmol) was added, followed by stirring for 1 hour under nitrogen atmosphere. The solvent was distilled off under reduced pressure, water (400 mL) was added to the residue, and extraction was carried out twice with ethyl acetate (400 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column

chromatography (elution solvent: ethyl acetate/hexane=10%-50%) to afford the desired compound (16.7 g, yield 83%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J=6.3 Hz), 1.49 (4H, d, J=6.3 Hz), 3.42 (3H, s), 3.49 (1H, dd, J=10.2, 4.7 Hz), 3.59 (1H, dd, J=10.2, 5.5 Hz), 3.68 (1H, dd, J=13.3, 7.4 Hz), 4.22 (1H, dd, J=13.5, 9.2 Hz), 4.52-4.57 (1H, m), 4.97-4.88 (1H, m), 6.34 (1H, t, J=2.0 Hz), 6.47 (1H, d, J=3.5 Hz), 6.72 (1H, s), 6.76 (1H, d, J=3.5 Hz), 7.10 (1H, s).

(116e) 1-{[4-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)phenyl]sulfonyl}-4-methylpiperazine

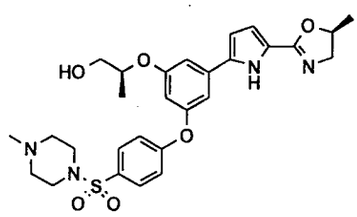
3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenol (40 mg, 0.12 mmol) synthesized in Example (116d) and 1-[(4-fluorophenyl)sulfonyl]-4-methylpiperazine (25 mg, 0.15 mmol) synthesized in Example (116a) were dissolved in N,N-dimethylformamide (2 mL), and potassium carbonate (51 mg, 0.37 mmol) was added, followed by stirring at 100°C for 1 hour under nitrogen atmosphere. 1-[(4-Fluorophenyl)sulfonyl]-4-methylpiperazine (30 mg) was added again, and the mixture was stirred at 90°C overnight. The reaction solution was cooled to room temperature, water (10 mL) was added, and extraction was carried out twice with ethyl acetate (10 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-5%) to afford the desired compound (25 mg, yield 35%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J=5.9 Hz), 1.43 (3H, d, J=6.3 Hz), 2.29 (3H, s), 2.50 (4H, br s), 3.06 (4H, br s), 3.43 (3H, d, J=2.4 Hz), 3.50-3.61 (3H, m), 4.10 (1H, dd, J=14.2, 9.3 Hz), 4.58 (1H, dd, J=10.5, 6.1 Hz), 4.82-4.86 (1H, m), 6.52 (1H, d, J=3.4 Hz), 6.55 (1H, t, J=2.2 Hz), 6.77 (1H, d, J=3.9 Hz),

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6.84 (1H, d, J=2.0 Hz), 6.98 (1H, s), 7.09 (2H, d, J=6.8 Hz), 7.71 (2H, d, J=9.3 Hz).
MS (FAB) m/z: 569.2418 $(M+H)^+$.

(Example 117)
(2S)-2-(3-{5-[(5S)-5-Methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenoxy}phenoxy)propan-1-ol



(117a) 3-[(1S)-2-Hydroxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenol

3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenol (60 mg, 0.18 mmol) synthesized in Example (116d) was dissolved in methylene chloride (4 mL), and boron tribromide (1.0 mol/L methylene chloride solution, 0.38 mL, 0.38 mmol) was added at -78°C under nitrogen atmosphere. Subsequently, the temperature was brought back to room temperature, followed by stirring for 1 hour. To the reaction solution, a saturated aqueous sodium hydrogencarbonate solution was added, and extraction was carried out with ethyl acetate. The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: hexane/ethyl acetate=50%-70%) to afford the desired compound (41 mg, yield 72%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.29 (3H, d, J=6.3 Hz), 1.49 (3H, d, J=5.9 Hz), 3.66-3.78 (3H, m), 4.23 (1H, dd, J=13.7, 9.3 Hz), 4.52 (1H, ddd, J=14.4, 8.1,4.6 Hz), 4.93 (1H, dq, J=17.7, 5.0 Hz), 6.32 (1H, t, J=2.0 Hz), 6.48 (1H, d, J=3.9 Hz), 6.71 (1H, s), 6.77 (1H, d, J=3.4 Hz), 7.11 (1H, s), 11.09 (1H, s).

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(117b) (2S)-2-(3-{5-[(5S)-5-Methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenoxy}phenoxy)propan-1-ol

3-[(1S)-2-Hydroxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenol (40 mg, 0.13 mmol) synthesized in Example (117a) and 1-[(4-fluorophenyl)sulfonyl]-4-methylpiperazine (49 mg, 0.19 mmol) synthesized in Example (116a) were dissolved in N,N-dimethylformamide (2 mL), and potassium carbonate (52 mg, 0.38 mmol) was added, followed by stirring at 100°C for 4 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, water (10 mL) was added, and extraction was carried out twice with ethyl acetate (10 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-5%) to afford the desired compound (17 mg, yield 25%) as a white solid.

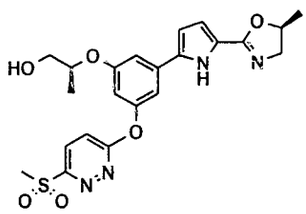
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.29 (3H, d, J=6.3 Hz), 1.43 (3H, d, J=6.3 Hz), 2.28 (3H, s), 2.48-2.51 (4H, br m), 3.03 (4H, br s), 3.55 (1H, dd, J=13.9, 7.2 Hz), 3.77 (2H, d, J=5.1 Hz), 4.09 (1H, dd, J=14.1, 9.4 Hz), 4.55-4.60 (1H, m), 4.87-4.81 (1H, m), 6.42 (1H, s), 6.50 (1H, d, J=3.9 Hz), 6.76 (1H, d, J=3.5 Hz), 6.83 (1H, s), 6.95 (1H, s), 7.07 (2H, d, J=8.6 Hz), 7.70 (2H, d, J=8.6 Hz).

MS (FAB) m/z: 555.2271 $(M+H)^+$.

(Example 118)

(2S)-2-(3-{5-[(5S)-5-Methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridazin-3-yl]oxy}phenoxy)propan-1-ol

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(118a) 6-Chloropyridazine-3-thiol

Under nitrogen atmosphere, dichloropyridazine (1.00 g, 6.71 mmol) was dissolved in methanol (20 mL), and 10-20% aqueous potassium hydrogen sulfide solution (20 mL) was added, followed by heating to reflux for 2 hours. The solvent was distilled off under reduced pressure, and the residue was diluted with water, followed by neutralization with 1N hydrochloric acid. The resulting yellow precipitate was filtered off, washed with water and hexane, and subsequently vacuum-dried to afford the desired compound (500 mg, yield 51%) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.00 (1H, d, J=9.4 Hz), 7.60 (1H, d, J=9.4 Hz), 11.68 (1H, br s).

(118b) 3-Chloro-6-(methylthio)pyridazine

6-Chloropyridazine-3-thiol (500 mg, 3.41 mmol) synthesized in Example (118a) was dissolved in methanol (20 mL), and sodium methoxide (203 mg, 3.75 mmol) and iodomethane (234 mL, 3.75 mmol) were added, followed by stirring at 60°C for 30 minutes under nitrogen atmosphere. The reaction solution was cooled to room temperature, water (50 mL) was added, and extraction was carried out twice with ethyl acetate (50 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=10%-50%) to afford the desired compound (515 mg, yield 94%) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.71 (3H, s), 7.25 (1H, d, J=9.6 Hz), 7.30 (1H, d, J=9.0 Hz).

(118c) 3-Chloro-6-(methylsulfonyl)pyridazine

3-Chloro-6-(methylthio)pyridazine (90 mg, 0.50 mmol) synthesized in Example (118b) was dissolved in methylene chloride (10 mL), and m-chloroperbenzoic acid (220 mg, 1.00 mmol) was added, followed by stirring at 0°C for 30 minutes under nitrogen atmosphere. Water (20 mL) was added to the reaction solution, and extraction was carried out twice with methylene chloride (10 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=10%-100%) to afford the desired compound (77 mg, yield 71%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.45 (3H, s), 7.81 (1H, d, J=8.2 Hz), 8.16 (1H, d, J=8.4 Hz).

(118d) 3-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-6-(methylsulfonyl)pyridazine

3-Chloro-6-(methylsulfonyl)pyridazine (41 mg, 0.27 mmol) synthesized in Example (118c) and 3-[(1S)-2-methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenol (80 mg, 0.24 mmol) synthesized in Example (116d) were dissolved in acetonitrile (2 mL), and cesium carbonate (158 mg, 0.48 mmol) was added, followed by stirring for 1 hour under nitrogen atmosphere. To the reaction solution, water (10 mL) was added, and extraction was carried out with ethyl acetate (10 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-4%) to afford the desired compound (116 mg, yield 98%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J=6.3 Hz), 1.42 (3H, d, J=6.3 Hz), 3.40 (3H, s), 3.42 (3H, s), 3.48-3.62 (3H, m), 4.07

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(1H, dd, J=13.9, 9.2 Hz), 4.58 (1H, td, J=6.2, 4.4 Hz), 4.82 (1H, dt, J=11.7, 4.6 Hz), 6.50 (1H, d, J=3.5 Hz), 6.69 (1H, t, J=2.2 Hz), 6.74 (1H, d, J=3.9 Hz), 6.99 (1H, q, J=2.0 Hz), 7.09 (1H, t, J=1.8 Hz), 7.40 (1H, d, J=9.0 Hz), 8.17 (1H, d, J=9.0 Hz).

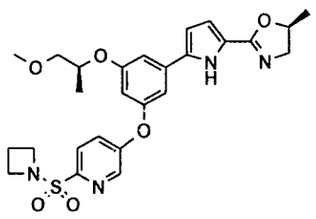
(118e) (2S)-2-(3-{5-[(5S)-5-Methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridazin-3-yl]oxy}phenoxy)propan-1-ol

3-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-6-(methylsulfonyl)pyridazine (116 mg, 0.24 mmol) synthesized in Example (118d) was dissolved in methylene chloride (5 mL), and boron tribromide (1.0 mol/L methylene chloride solution, 0.26 mL, 0.26 mmol) was added at -78°C under nitrogen atmosphere. Subsequently, the temperature was brought back to room temperature, followed by stirring for 4 hours. To the reaction solution, a saturated aqueous sodium hydrogencarbonate solution was added, and extraction was carried out with ethyl acetate. The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-5%) to afford the desired compound (100 mg, yield 89%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.30 (3H, d, J=6.3 Hz), 1.41 (3H, d, J=6.3 Hz), 3.39 (3H, s), 3.53 (1H, dd, J=13.7, 7.4 Hz), 3.76-3.77 (2H, m), 4.07 (1H, dd, J=13.9, 9.2 Hz), 4.56 (1H, dd, J=10.8, 6.1 Hz), 4.82 (1H, dt, J=12.0, 4.6 Hz), 6.47 (1H, d, J=3.5 Hz), 6.61 (1H, t, J=2.2 Hz), 6.74 (1H, d, J=3.9 Hz), 6.99 (1H, t, J=1.6 Hz), 7.03 (1H, t, J=1.6 Hz), 7.39 (1H, d, J=9.4 Hz), 8.16 (1H, d, J=9.4 Hz).
MS (ESI) m/z: 473.15056 $(M+H)^+$.

(Example 119)
2-(Azetidin-1-ylsulfonyl)-5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl}-1H-pyrrol-2-

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yl}phenoxy)-pyridine



(119a) 5-Chloropyridine-2-thiol

Under nitrogen atmosphere, 2,5-dichloropyridine (5.00 g, 33.8 mmol) was dissolved in dimethyl sulfoxide (35 mL), and sodium disulfide nonahydrate (9.00 g, 37.2 mmol) was added, followed by stirring at 120°C for 2 hours. The reaction solution was cooled to room temperature, and water (50 mL) was added, followed by neutralization with 5N hydrochloric acid. The resulting precipitate was filtered off, followed by washing with water and hexane, and subsequently the resulting solid was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-10%) to afford the desired compound (2.28 g, yield 46%) as a yellow solid. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.63 (1H, s), 7.34 (1H, dd, J=9.0, 2.2 Hz), 7.41 (1H, d, J=9.3 Hz), 7.70 (1H, s).

(119b) 2-(Azetidin-1-ylsulfonyl)-5-chloropyridine

5-Chloropyridine-2-thiol (1.00 g, 6.87 mmol) synthesized in Example (119a) was dissolved in methylene chloride (30 mL)/1N hydrochloric acid (30 mL), and cooled to -5°C. To the reaction solution, ice-cooled 7% aqueous sodium perchlorate solution (30 mL) was added dropwise while being kept at 0°C or below, and stirring was carried out as it is for 15 minutes. The organic layer was extracted with a separatory funnel ice-cooled in advance, and cooled to -78°C, a methylene chloride solution (10 mL) of commercially available azetidine hydrochloride (2.24 mg, 17.7 mmol) and triethylamine (1.8 mL, 12.9 mmol) was added, and the temperature was raised to 0°C, followed by stirring for 30 minutes. To the reaction solution, water (50 mL) was added, and extraction was carried out twice with ethyl acetate (30 mL).

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The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=5%-60%) to afford the desired compound (735 mg, yield 46%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.19-2.25 (2H, m), 4.10 (4H, t, J=7.8 Hz), 7.91 (1H, dd, J=8.3, 2.0 Hz), 7.95 (1H, d, J=7.8 Hz), 8.72 (1H, d, J=2.0 Hz).

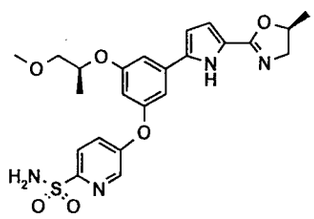
(119c) 2-(Azetidin-1-ylsulfonyl)-5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-pyridine

2-(Azetidin-1-ylsulfonyl)-5-chloropyridine (170 mg, 0.73 mmol) synthesized in Example (119b) and 3-[(1S)-2-methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenol (230 mg, 0.70 mmol) synthesized in Example (116d) were dissolved in N,N-dimethylformamide (3.5 mL), and cesium carbonate (454 mg, 1.39 mmol) was added, followed by stirring at 100°C for 2 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, water (20 mL) was added, and extraction was carried out twice with ethyl acetate (20 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=5%-50%) to afford the desired compound (273 mg, yield 75%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J=6.3 Hz), 1.43 (3H, d, J=6.3 Hz), 2.18-2.24 (2H, m), 3.42 (3H, s), 3.49-3.61 (3H, m), 4.10 (4H, t, J=7.6 Hz), 4.56-4.62 (1H, m), 4.82-4.86 (1H, m), 6.51 (1H, d, J=3.9 Hz), 6.58 (1H, t, J=2.0 Hz), 6.76 (1H, d, J=3.9 Hz), 6.88 (1H, s), 7.04 (1H, s), 7.43 (1H, dd, J=8.8, 2.9 Hz), 7.94 (1H, d, J=8.8 Hz), 8.53 (1H, d, J=2.9 Hz).
MS (ESI) m/z: 527.20527 $(M+H)^+$.

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(Example 120)

5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)pyridine-2-sulfonamide



(120a) 5-Chloro-N-(4-methoxybenzyl)pyridine-2-sulfonamide

5-Chloropyridine-2-thiol (1.00 g, 6.87 mmol) synthesized in Example (119a) was dissolved in methylene chloride (30 mL)/1N hydrochloric acid (30 mL), and cooled to -5°C. To the reaction solution, an ice-cooled 7% aqueous sodium perchlorate solution (35 mL) was added dropwise while being kept at 0°C or below, and stirring was carried out as it is for 15 minutes. The organic layer was extracted with a separatory funnel ice-cooled in advance, and cooled to -78°C, commercially available 4-methoxybenzylamine (2.24 mL, 17.7 mmol) was added, and the temperature was raised to 0°C, followed by stirring for 30 minutes. To the reaction solution, 0.1N hydrochloric acid (30 mL) was added, and extraction was carried out twice with methylene chloride (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=5%-100%) to afford the desired compound (983 mg, yield 46%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.78 (3H, s), 4.20 (2H, d, J=6.3 Hz), 5.07 (1H, s), 6.79 (2H, dt, J=9.4, 2.5 Hz), 7.14 (2H, d, J=8.6 Hz), 7.83 (1H, dd, J=8.6, 2.3 Hz), 7.90 (1H, d, J=7.8 Hz), 8.60 (1H, dd, J=2.3, 0.8 Hz).

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(120b) 5-Chloro-N,N-bis(4-methoxybenzyl)pyridine-2-sulfonamide

5-Chloro-N-(4-methoxybenzyl)pyridine-2-sulfonamide (983 mg, 3.14 mmol) synthesized in Example (120a) was dissolved in N,N-dimethylformamide (5 mL), and sodium hydride (132 mg, 3.30 mmol) was added. After ice cooling, p-methoxybenzyl chloride (1.02 mL, 3.37 mmol) was added, and the temperature was raised to room temperature, followed by stirring for 2 hours. Water (20 mL) was added to the reaction solution, and extraction was carried out twice with ethyl acetate (20 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=10%-100%) to afford the desired compound (1.14 g, yield 84%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.78 (6H, s), 4.40 (4H, s), 6.75 (4H, dt, J=9.3,2.5 Hz), 7.05 (4H, dt, J=8.2, 2.0 Hz), 7.78 (1H, dd, J=8.2, 2.3 Hz), 7.84 (1H, d, J=7.8 Hz), 8.55 (1H, d, J=2.7 Hz).

(120c) N,N-Bis(4-methoxybenzyl)-5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)pyridine-2-sulfonamide

5-Chloro-N,N-bis(4-methoxybenzyl)pyridine-2-sulfonamide (288 mg, 0.67 mmol) synthesized in Example (120b) and 3-[(1S)-2-methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenol (220 mg, 0.67 mmol) synthesized in Example (116d) were dissolved in N,N-dimethylformamide (3 mL), and cesium carbonate (434 mg, 1.33 mmol) was added, followed by stirring at 100°C for 1 hour under nitrogen atmosphere. The reaction solution was cooled to room temperature, water (20 mL) was added, and extraction was carried out twice with ethyl acetate (20 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent:

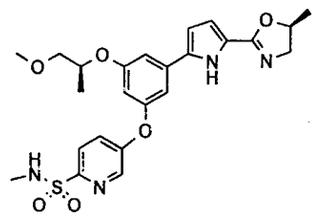
methanol/methylene chloride=0.5%-5%) to afford the desired compound (160 mg, yield 33%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J=5.9 Hz), 1.43 (3H, d, J=6.3 Hz), 3.42 (3H, s), 3.50-3.62 (3H, m), 3.77 (6H, s), 4.09 (1H, dd, J=13.9, 9.0 Hz), 4.41 (4H, s), 4.56-4.63 (1H, m), 4.81-4.86 (1H, m), 6.52 (1H, d, J=3.9 Hz), 6.56 (1H, t, J=2.0 Hz), 6.76 (4H, d, J=8.8 Hz), 7.07 (4H, d, J=8.8 Hz), 7.33 (1H, dd, J=8.5, 2.7 Hz), 7.88 (1H, d, J=8.8 Hz), 8.39 (1H, d, J=2.9 Hz).

(120d) 5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)pyridine-2-sulfonamide

N,N-Bis(4-methoxybenzyl)-5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)pyridine-2-sulfonamide (160 mg, 0.24 mmol) synthesized in Example (120c) was dissolved in trifluoroacetic acid (2 mL), and stirring was carried out at 40°C for 8 hours. The solvent was distilled off under reduced pressure, methylene chloride and triethylamine were added in small portions to the residue, and the solvent was distilled off again under reduced pressure. The resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-5%) to afford the desired compound (106 mg, yield 99%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.33 (3H, d, J=6.3 Hz), 1.42 (3H, d, J=5.9 Hz), 3.42 (3H, s), 3.49-3.53 (2H, m), 3.59 (1H, dd, J=10.3, 5.9 Hz), 4.05 (1H, dd, J=14.2, 9.3 Hz), 4.55-4.61 (1H, m), 4.79-4.86 (1H, m), 5.30 (2H, br s), 6.50 (1H, d, J=3.9 Hz), 6.56 (1H, t, J=2.2 Hz), 6.75 (1H, d, J=3.9 Hz), 6.85 (1H, t, J=1.7 Hz), 7.03 (1H, t, J=1.7 Hz), 7.42 (1H, dd, J=8.5, 2.7 Hz), 7.95 (1H, d, J=8.8 Hz), 8.42 (1H, d, J=2.4 Hz).
MS (ESI) m/z: 487.16619 $(M+H)^+$.

(Example 121)
5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-N-

methylpyridine-2-sulfonamide



(121a) 5-Chloro-N-methylpyridine-2-sulfonamide

5-Chloropyridine-2-thiol (1.00 g, 6.87 mmol) synthesized in Example (119a) was dissolved in methylene chloride (30 mL)/1N hydrochloric acid (30 mL), and cooled to -5°C. To the reaction solution, an ice-cooled 7% aqueous sodium perchlorate solution (30 mL) was added dropwise while being kept at 0°C or below, and stirring was carried out as it is for 15 minutes. The organic layer was extracted with a separatory funnel ice-cooled in advance, and cooled to -78°C, a methylene chloride solution (10 mL) of commercially available 40% methylamine/methanol solution (1.33 mL, 17.2 mmol) was added, and the temperature was raised to 0°C, followed by stirring for 2 hours. To the reaction solution, water (50 mL) was added, and extraction was carried out twice with ethyl acetate (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=30%-80%) to afford the desired compound (889 mg, yield 63%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.77 (3H, d, J=4.9 Hz), 4.81 (1H, s), 7.90 (1H, dd, J=8.3, 2.4 Hz), 7.97 (1H, d, J=8.3 Hz), 8.65 (1H, d, J=2.4 Hz).

(121b) 5-Chloro-N-(4-methoxybenzyl)-N-methylpyridine-2-sulfonamide

5-Chloro-N-methylpyridine-2-sulfonamide (889 mg, 4.30 mmol) synthesized in Example (121a) was dissolved in N,N-

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dimethylformamide (15 mL), and sodium hydride (172 mg, 4.30 mmol) was added. After ice cooling, p-methoxybenzyl chloride (0.70 mL, 5.16 mmol) was added, and the temperature was raised to room temperature, followed by stirring for 3 hours. Water (20 mL) was added to the reaction solution, and extraction was carried out twice with ethyl acetate (20 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-20%) to afford the desired compound (817 mg, yield 58%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.79 (3H, s), 3.81 (3H, s), 4.36 (2H, s), 6.87 (2H, dt, J=9.4, 2.4 Hz), 7.25 (2H, d, J=7.3 Hz), 7.88 (1H, dd, J=8.3,2.4 Hz), 7.94 (1H, d, J=8.3 Hz), 8.66 (1H, d, J=2.4 Hz).

(121c) N-(4-Methoxybenzyl)-5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-N-methylpyridine-2-sulfonamide

5-Chloro-N-(4-methoxybenzyl)-N-methylpyridine-2-sulfonamide (228 mg, 0.70 mmol) synthesized in Example (121b) and 3-[(1S)-2-methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenol (220 mg, 0.67 mmol) synthesized in Example (116d) were dissolved in N,N-dimethylformamide (3 mL), and cesium carbonate (434 mg, 1.33 mmol) was added, followed by stirring at 100°C for 3 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, water (20 mL) was added, and extraction was carried out twice with ethyl acetate (20 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0.5%-5%) to afford the desired compound (293 mg, yield 71%) as a white solid.

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^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J=6.3 Hz), 1.43 (3H, d, J=5.9 Hz), 2.79 (3H, s), 3.42 (3H, s), 3.49-3.61 (3H, m), 3.81 (3H, s), 4.08 (1H, dd, J=13.7, 9.3 Hz), 4.37 (2H, s), 4.55-4.62 (1H, m), 4.80-4.87 (1H, m), 6.51 (1H, d, J=3.9 Hz), 6.57 (1H, t, J=2.2 Hz), 6.75 (1H, d, J=3.9 Hz), 6.87-6.89 (3H, m), 7.03 (1H, s), 7.28 (2H, d, J=8.8 Hz), 7.41 (1H, dd, J=8.5, 2.7 Hz), 7.94 (1H, d, J=8.3 Hz), 8.47 (1H, d, J=2.4 Hz).

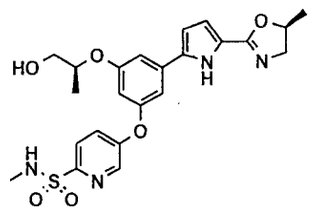
(121d) 5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-N-methylpyridine-2-sulfonamide

N-(4-Methoxybenzyl)-5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-N-methylpyridine-2-sulfonamide (292 mg, 0.47 mmol) synthesized in Example (121c) was dissolved in trifluoroacetic acid (2 mL), and stirring was carried out at 45°C for 1 hour. The solvent was distilled off under reduced pressure, methylene chloride and triethylamine were added in small portions to the residue, and the solvent was distilled off again under reduced pressure. The resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-4%) to afford the desired compound (208 mg, yield 88%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J=5.9 Hz), 1.43 (3H, d, J=6.3 Hz), 2.76 (3H, s), 3.41 (3H, s), 3.49-3.61 (3H, m), 4.08 (1H, dd, J=13.9, 9.0 Hz), 4.61-4.55 (1H, m), 4.84 (1H, dd, J=15.1, 7.3 Hz), 6.50 (1H, d, J=3.9 Hz), 6.56 (1H, t, J=2.2 Hz), 6.76 (1H, d, J=3.9 Hz), 6.86 (1H, s), 7.04 (1H, s), 7.41 (1H, dd, J=8.5, 2.7 Hz), 7.96 (1H, d, J=8.8 Hz), 8.45 (1H, d, J=2.4 Hz).
MS (ESI) m/z: 501.18090 $(M+H)^+$.

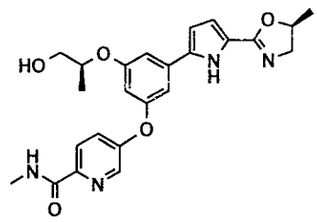
(Example 122)
5-(3-[(1S)-2-Hydroxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-N-methylpyridine-2-sulfonamide

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5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-N-methylpyridine-2-sulfonamide (166 mg, 0.32 mmol) synthesized in Example (121d) was dissolved in methylene chloride (5 mL), and boron tribromide (1.0 mol/L methylene chloride solution, 0.34 mL, 0.34 mmol) was added at -78°C under nitrogen atmosphere. Subsequently, the temperature was brought back to room temperature, followed by stirring for 1.5 hours. To the reaction solution, a saturated aqueous sodium hydrogencarbonate solution was added, and extraction was carried out with methylene chloride. The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-4%) to afford the desired compound (119 mg, yield 78%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.30 (3H, d, J=6.3 Hz), 1.43 (3H, d, J=6.8 Hz), 2.75 (3H, s), 3.54 (1H, dd, J=13.7, 7.3 Hz), 3.75-3.77 (2H, m), 4.08 (1H, dd, J=9.3, 13.7 Hz), 4.52-4.58 (1H, m), 4.81-4.88 (1H, m), 6.43 (1H, s), 6.47 (1H, d, J=3.9 Hz), 6.75 (1H, d, J=4.4 Hz), 6.83 (1H, s), 7.00 (1H, s), 7.39 (1H, dd, J=8.8, 2.0 Hz), 7.95 (1H, d, J=8.8 Hz), 8.39 (1H, s).
MS (ESI) m/z: 487.16369 $(M+H)^+$.

(Example 123)
5-(3-[(1S)-2-Hydroxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-N-methylpyridine-2-carboxamide



(123a) 5-Fluoro-N-methylpyridine-2-carboxamide

5-Fluoropyridine-2-carboxylic acid (495 mg, 3.51 mmol) was dissolved in methylene chloride (10 mL), and HOBt·H_2O (591 mg, 3.86 mmol), WSCI·HCl (1.35 g, 7.02 mmol), triethylamine (2.44 mL, 17.5 mmol) and 40% methylamine/methanol solution (0.82 mL, 10.5 mmol) were added, followed by stirring for 15 hours. To the reaction solution, water (30 mL) was added, and extraction was carried out twice with methylene chloride (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-50%) to afford the desired compound (490 mg, yield 91%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.03 (3H, d, J=5.5 Hz), 7.53 (1H, dt, J=2.7, 8.6 Hz), 7.85 (1H, br s), 8.24 (1H, dd, J=8.2, 4.7 Hz), 8.38 (1H, d, J=2.7 Hz).

(123b) 5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-N-methylpyridine-2-carboxamide

5-Fluoro-N-methylpyridine-2-carboxamide (122 mg, 0.79 mmol) synthesized in Example (123a) and 3-[(1S)-2-methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenol (275 mg, 0.83 mmol) synthesized in Example (116d) were dissolved in N,N-dimethylformamide (3 mL), and potassium carbonate (219 mg, 1.58 mmol) was added, followed by stirring at 100°C for 3 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, water (30 mL) was added, and extraction was carried out twice with ethyl acetate (30 mL). The organic layer was washed with saturated

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brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-5%) to afford the desired compound (283 mg, yield 77%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J=6.3 Hz), 1.42 (3H, d, J=6.3 Hz), 3.03 (3H, d, J=5.1 Hz), 3.41 (3H, s), 3.48-3.61 (3H, m), 4.08 (1H, dd, J=13.9, 9.2 Hz), 4.53-4.60 (1H, m), 4.80-4.86 (1H, m), 6.49 (1H, d, J=3.9 Hz), 6.53 (1H, t, J=2.2 Hz), 6.74 (1H, d, J=3.5 Hz), 6.83 (1H, d, J=1.6 Hz), 7.00 (1H, s), 7.41 (1H, dd, J=8.6, 2.7 Hz), 7.86 (1H, br s), 8.17 (1H, d, J=8.6 Hz), 8.31 (1H, d, J=2.7 Hz).

(123c) 5-(3-[(1S)-2-Hydroxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-N-methylpyridine-2-carboxamide

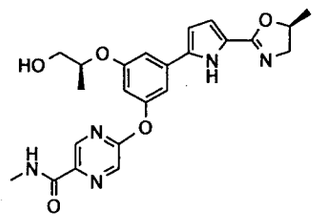
5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-N-methylpyridine-2-carboxamide (176 mg, 0.38 mmol) synthesized in Example (123b) was dissolved in methylene chloride (5 mL), and boron tribromide (1.0 mol/L methylene chloride solution, 0.50 mL, 0.50 mmol) was added at -78°C. Subsequently, the temperature was brought back to room temperature, followed by stirring for 1 hour. To the reaction solution, a saturated aqueous sodium hydrogencarbonate solution was added, and extraction was carried out with methylene chloride. The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-5%) to afford the desired compound (118 mg, yield 69%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.28 (3H, d, J=5.9 Hz), 1.42 (3H, d, J=6.3 Hz), 3.03 (3H, d, J=5.1 Hz), 3.54 (1H, dd, J=13.9, 7.2 Hz), 3.76 (2H, d, J=4.7 Hz), 4.07 (1H, dd, J=13.9, 9.2 Hz), 4.57 (1H,

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dd, J=11.1, 6.1 Hz), 4.83 (1H, dt, J=11.7, 4.6 Hz), 6.38 (1H, s), 6.45 (1H, d, J=3.5 Hz), 6.73 (1H, d, J=3.9 Hz), 6.80 (1H, s), 6.93 (1H, s), 7.35 (1H, dd, J=8.6, 2.7 Hz), 7.87 (1H, d, J=5.5 Hz), 8.15 (1H, d, J=8.6 Hz), 8.27 (1H, d, J=2.7 Hz).
MS (ESI) m/z: 451.19720 $(M+H)^+$.

(Example 124)
5-(3-[(1S)-2-Hydroxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-N-methylpyrazine-2-carboxamide



(124a) 5-Chloro-N-methylpyrazine-2-carboxamide

5-Chloropyrazine-2-carboxylic acid (1.99 g, 12.6 mmol) was dissolved in N,N-dimethylformamide (10 mL), and HOBt·H_2O (591 mg, 3.86 mmol), WSCI·HCl (1.35 g, 7.02 mmol), N-methylmorpholine (2.76 mL, 25.1 mmol) and 40% methylamine/methanol solution (2.92 mL, 37.6 mmol) were added, followed by stirring for 18 hours. To the reaction solution, water (50 mL) was added, and extraction was carried out twice with ethyl acetate (50 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-75%) to afford the desired compound (585 mg, yield 27%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.03 (3H, d, J=4.9 Hz), 7.60 (1H, br s), 8.09 (1H, d, J=1.5 Hz), 8.93 (1H, d, J=1.0 Hz).

(124b) 5-(3-[(1S)-2-Hydroxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-N-methylpyrazine-2-carboxamide

5-Chloro-N-methylpyrazine-2-carboxamide (171 mg, 1.00

mmol) synthesized in Example (124a) and 3-[(1S)-2-methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenol (300 mg, 0.91 mmol) synthesized in Example (116d) were dissolved in N,N-dimethylformamide (3 mL), and potassium carbonate (376 mg, 2.72 mmol) was added, followed by stirring at 100°C for 5 hours under nitrogen atmosphere. To the reaction solution, 5-chloro-N-methylpyrazine-2-carboxamide (110 mg, 0.64 mmol) was added further, and stirring was carried out for 3 hours. The reaction solution was cooled to room temperature, water (30 mL) was added, and extraction was carried out twice with ethyl acetate (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-5%) to afford a white solid (206mg).

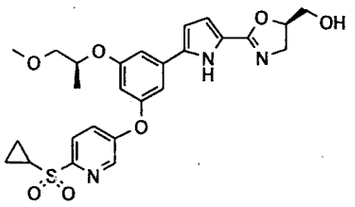
This product was dissolved in methylene chloride (5 mL), and boron tribromide (1.0 mol/L methylene chloride solution, 0.57 mL, 0.57 mmol) was added at -78°C. Subsequently, the temperature was brought back to room temperature, followed by stirring for 1.5 hours. The reaction solution was cooled again to -78°C, boron tribromide (1.0 mol/L methylene chloride solution, 1.00 mL, 1.00 mmol) was added, and the temperature was brought back to room temperature, followed by stirring for 3 hours. To the reaction solution, a saturated aqueous sodium hydrogencarbonate solution was added, and extraction was carried out with methylene chloride. The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-5%) to afford the desired compound (87.8 mg, yield 21%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J=5.9 Hz), 1.43 (3H, d, J=6.3 Hz), 3.05 (3H, d, J=5.4 Hz), 3.55 (1H, dd, J=13.9, 7.6 Hz),

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3.77 (2H, d, J=5.4 Hz), 4.09 (1H, dd, J=13.9, 9.0 Hz), 4.56 (1H, dd, J=11.2, 5.9 Hz), 4.87-4.80 (1H, m), 6.49 (1H, d, J=3.4 Hz), 6.60 (1H, s), 6.75 (1H, d, J=3.9 Hz), 6.93 (1H, s), 7.00 (1H, s), 7.62 (1H, d, J=4.9 Hz), 8.29 (1H, s), 8.93 (1H, d, J=1.0 Hz).
MS (ESI) m/z: 452.19252 $(M+H)^+$.

(Example 125)
{(5R)-2-[5-(3-{[6-(Cyclopropylsulfonyl)pyridin-3-yl]oxy}-5-[(1S)-2-methoxy-1-methylethoxy]phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-5-yl}methanol



(125a) (5-Chloro-2-[(3-chloropropyl)thio]pyridine

5-Chloropyridine-2-thiol (600 mg, 4.12 mmol) synthesized in Example (119a) was dissolved in methanol (15 mL), and 28% sodium methoxide/methanol solution (0.95 mL, 4.94 mmol) and 1-bromo-3-chloropropane (0.61 mL, 6.18 mmol) were added, followed by stirring at 60°C for 1.5 hours. The reaction solution was cooled to room temperature, water (40 mL) was added, and extraction was carried out twice with ethyl acetate (40 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and vacuum drying was carried out to afford the desired compound (849 mg, yield 92%) as a colorless oil.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.26-2.31 (2H, m), 3.55-3.58 (2H, m), 3.67 (2H, t, J=6.3 Hz), 7.96 (1H, dd, J=8.3,2.0 Hz), 8.06 (1H, d, J=7.8 Hz), 8.70 (1H, d, J=2.4 Hz).

(125b) 5-Chloro-2-[(3-chloropropyl)sulfonyl]pyridine

5-Chloro-2-[(3-chloropropyl)thio]pyridine (846 mg, 3.80 mmol) synthesized in Example (125a) was dissolved in methylene chloride (20 mL) and ice cooling, and subsequently m-

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chloroperbenzoic acid (2.02 g, 7.62 mmol) was added, followed by stirring as it is for 1 hour. To the reaction solution, saturated aqueous sodium hydrogencarbonate solution (40 mL) was added, and extraction was carried out twice with methylene chloride (40 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-20%) to afford the desired compound (733 mg, yield 76%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.21-2.14 (2H, m), 3.30 (2H, t, J=6.8 Hz), 3.67 (2H, t, J=6.3 Hz), 7.13 (1H, dd, J=8.6, 0.8 Hz), 7.45 (1H, dd, J=8.6, 2.3 Hz), 8.37 (1H, dd, J=5.1,3.1 Hz).

(125c) 5-Chloro-2-(cyclopropylsulfonyl)pyridine

5-Chloro-2-[(3-chloropropyl)sulfonyl]pyridine (732 mg, 3.05 mmol) synthesized in Example (125b) was dissolved in tetrahydrofuran (10 mL) and cooled to -30°C, and subsequently potassium-t-butoxide (582 mg, 5.18 mmol) was added, followed by stirring as it is for 30 minutes. To the reaction solution, a saturated aqueous ammonium chloride solution (40 mL) was added, and extraction was carried out twice with methylene chloride (40 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-25%) to afford the desired compound (397 mg, yield 60%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.07-1.12 (2H, m), 1.37-1.41 (2H, m), 2.76-2.83 (1H, m), 7.91 (1H, dd, J=8.2, 2.3 Hz), 7.98 (1H, d, J=8.2 Hz), 8.71 (1H, dd, J=2.3, 0.8 Hz).

(125d) N-[(2S)-2,3-Dihydroxypropyl]-5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[(triisopropylsilyl)oxy]phenyl}-1H-pyrrole-2-carboxamide

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5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[(triisopropylsilyl)oxy]phenyl}-1H-pyrrole-2-carboxylic acid (9.32 g, 20.8 mmol) synthesized in Example (106c) was dissolved in methanol (200 mL), and (S)-(-)-3-amino-1,2-propanediol (5.01 g, 55.0 mmol) and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride n hydrate (10.13 g, 32.3 mmol) were added, followed by stirring at room temperature overnight under nitrogen atmosphere. The solvent was distilled off under reduced pressure, water (300 mL) and ethyl acetate (200 mL) were added to the resulting residue, and the solution was separated. The organic layer was washed with saturated brine, subsequently dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=70%-100%) to afford the desired product (9.32 g, yield 86%) as a colorless oil.
^{1}H-NMR ($CDCl_3$, 400 Hz): δ 1.11 (18H, d, J=7.0 Hz), 1.22-1.29 (3H, m), 1.31 (3H, d, J=6.3 Hz), 3.07-3.14 (2H, m), 3.42 (3H, s), 3.50 (1H, dd, J=10.2, 4.3 Hz), 3.54-3.66 (5H, m), 3.83-3.90 (1H, m), 4.49-4.57 (1H, m), 6.34 (1H, t, J=6.5 Hz), 6.42 (1H, t, J=2.3 Hz), 6.46 (1H, dd, J=3.9, 2.7 Hz), 6.63 (1H, dd, J=3.9, 2.3 Hz), 6.67 (1H, t, J=1.6 Hz), 6.73 (1H, t, J=1.6 Hz), 9.55 (1H, br s).

(125e) N-{(2S)-2-Hydroxy-3-[(triisopropylsilyl)oxy]propyl}-5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[(triisopropylsilyl)oxy]phenyl}-1H-pyrrole-2-carboxamide

N-[(2S)-2,3-Dihydroxypropyl]-5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[(triisopropylsilyl)oxy]phenyl}-1H-pyrrole-2-carboxamide (9.30 g, 17.9 mmol) synthesized in Example (125d) was dissolved in methylene chloride (180 mL), and triisopropylsilyl chloride (4.25 mL, 19.9 mmol), triethylamine (7.45 mL, 53.5 mmol) and 4-dimethylaminopyridine (2.20 g, 18.0 mmol) were added, followed by stirring at room temperature for 2.5 hours under nitrogen atmosphere. Water (300 mL) was added to separate the solution, and the organic layer was washed with

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saturated brine and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=10%-35%) to afford the desired compound (10.56 g, yield 87%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 Hz): δ 1.18-1.06 (39H, m), 1.22-1.30 (3H, m), 1.32 (3H, d, J=6.3 Hz), 3.20 (1H, d, J=4.3 Hz), 3.38-3.44 (1H, m), 3.42 (3H, s), 3.49 (1H, dd, J=10.2, 4.3 Hz), 3.59 (1H, dd, J=10.2, 5.5 Hz), 3.66-3.79 (3H, m), 3.85-3.91 (1H, m), 4.49-4.56 (1H, m), 6.30 (1H, t, J=5.9 Hz), 6.41 (1H, t, J=2.0 Hz), 6.45 (1H, dd, J=3.9, 2.7 Hz), 6.59 (1H, dd, J=3.9, 2.3 Hz), 6.66 (1H, t, J=2.0 Hz), 6.72 (1H, t, J=2.0 Hz), 9.34 (1H, br s).

(125f) (5R)-2-{5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[(triisopropylsilyl)oxy]phenyl}-1H-pyrrol-2-yl)-5{[(triisopropylsilyl)oxy]methyl}-4,5-dihydro-1,3-oxazole

N-{(2S)-2-Hydroxy-3-[(triisopropylsilyl)oxy]propyl}-5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-[(triisopropylsilyl)oxy]phenyl}-1H-pyrrole-2-carboxamide (10.54 g, 15.6 mmol) synthesized in Example (125e) was dissolved in tetrahydrofuran (160 mL), and anhydrous methanesulfonic acid (5.51 g, 31.6 mmol) and triethylamine (8.70 mL, 62.4 mmol) were added, followed by stirring at room temperature for 3 hours under nitrogen atmosphere, and subsequently the temperature was raised to 60°C, followed by stirring for 3 hours. To the reaction solution, water (200 mL) was added, and extraction was carried out with ethyl acetate (300 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=5%-30%) to afford the desired compound (9.72 g, yield 95%) as a brown oil.

^{1}H-NMR ($CDCl_3$, 400 Hz): δ 1.04-1.14 (39H, m), 1.22-1.29 (3H, m), 1.32 (3H, d, J=6.3 Hz), 3.42 (3H, s), 3.48 (1H, dd, J=10.2, 4.3

Hz), 3.59 (1H, dd, J=10.2, 5.9 Hz), 3.85-3.90 (3H, m), 4.02 (1H, dd, J=14.1,9.8 Hz), 4.48-4.54 (1H, m), 4.72-4.78 (1H, m), 6.39 (1H, t, J=2.0 Hz), 6.45 (1H, d, J=3.9 Hz), 6.67 (1H, t, J=2.0 Hz), 6.71 (1H, t, J=2.0 Hz), 6.73 (1H, d, J=3.9 Hz).

(125g) 3-{5-[(5R)-5-(Hydroxylmethyl)-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-[(1S)-2-methoxy-1-methylethoxy]phenol

(5R)-2-(5-{3-[(1S)-2-Methoxy-1-methylethoxy]-5-[(triisopropylsilyl)oxy]phenyl}-1H-pyrrol-2-yl)-5{[(triisopropylsilyl)oxy]methyl}-4,5-dihydro-1,3-oxazole (9.69 g, 14.7 mmol) synthesized in Example (125f) was dissolved in tetrahydrofuran (150 mL), and tetrabutylammonium fluoride (1 mol/L tetrahydrofuran solution, 30.0 mL, 30 mmol) was added dropwise at 0°C, followed by stirring at 0°C for 30 minutes. A saturated aqueous ammonium chloride solution (200 mL) was added, and extraction was carried out with ethyl acetate (200 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=3%-7%) to afford the desired compound (6.50 g, yield ~100%) as a pale yellow solid. ^{1}H-NMR ($CDCl_3$, 400 Hz): δ 1.31 (3H, d, J=6.3 Hz), 3.41 (3H, s), 3.48 (1H, dd, J=10.2, 4.3 Hz), 3.58 (1H, dd, J=10.2, 5.9 Hz), 3.78 (1H, dd, J=12.5,5.5 Hz), 3.92-3.97 (2H, m), 4.12 (1H, dd, J=13.7, 9.8 Hz), 4.51-4.59 (1H, m), 4.88-4.94 (1H, m), 6.39 (1H, t, J=2.0 Hz), 6.47 (1H, d, J=3.5 Hz), 6.72 (1H, s), 6.82 (1H, d, J=3.9 Hz), 7.06 (1H, s), 11.05 (1H, br s).

(125h) {(5R)-2-[5-(3-{[6-(Cyclopropylsulfonyl)pyridin-3-yl]oxy}-5-[(1S)-2-methoxy-1-methylethoxy]phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-5-yl}methanol

5-Chloro-2-(cyclopropylsulfonyl)pyridine (168 mg, 0.77 mmol) synthesized in Example (125c) and 3-{5-[(5R)-5-(Hydroxylmethyl)-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-[(1S)-2-methoxy-1-methylethoxy]phenol (401 mg, 1.16 mmol)

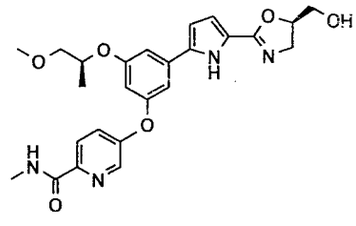
synthesized in Example (125g) were dissolved in N,N-dimethylformamide (2 mL), and potassium carbonate (213 mg, 154 mmol) was added, followed by stirring at 100°C for 3 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, water (30 mL) was added, and extraction was carried out twice with ethyl acetate (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0.5%-5%) to afford the desired compound (139 mg, yield 34%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.06-1.11 (2H, m), 1.31 (3H, d, J=6.3 Hz), 1.37-1.41 (2H, m), 2.76-2.83 (1H, m), 3.42 (3H, d, J=2.3 Hz), 3.50 (1H, dd, J=10.2, 3.9 Hz), 3.59 (1H, dd, J=10.2, 6.3 Hz), 3.68-3.79 (2H, m), 3.87 (1H, dd, J=12.3, 2.9 Hz), 4.03 (1H, dd, J=14.1, 9.8 Hz), 4.60-4.53 (1H, m), 4.84-4.77 (1H, m), 6.49 (1H, d, J=3.9 Hz), 6.57 (1H, t, J=2.2 Hz), 6.75 (1H, d, J=3.9 Hz), 6.86 (1H, t, J=1.8 Hz), 7.03 (1H, s), 7.42 (1H, dd, J=8.6, 2.7 Hz), 7.97 (1H, d, J=8.6 Hz), 8.51 (1H, d, J=2.7 Hz).

MS (ESI) m/z: 528.17975 $(M+H)^+$.

(Example 126)

5-(3-{5-[(5R)-5-(Hydroxymethyl)-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-[(1S)-2-methoxy-1-methylethoxy]phenoxy)-N-methylpyridine-2-carboxamide



5-Fluoro-N-methylpyridine-2-carboxamide (150 mg, 0.97 mmol) synthesized in Example (123a) and 3-{5-[(5R)-5-(hydroxylmethyl)-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-[(1S)-2-methoxy-1-methylethoxy]phenol (438 mg, 1.27 mmol) synthesized in Example (125 g) were dissolved in N,N-

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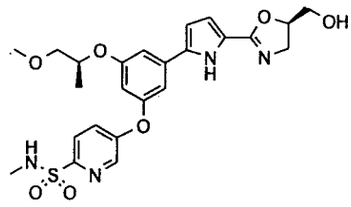
dimethylformamide (3 mL), and potassium carbonate (269 mg, 1.95 mmol) was added, followed by stirring at 100°C for 3 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, water (30 mL) was added, and extraction was carried out twice with ethyl acetate (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-5%) to afford the desired compound (281 mg, yield 60%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.30 (3H, d, J=6.3 Hz), 3.03 (3H, d, J=4.9 Hz), 3.41 (3H, s), 3.49 (1H, dd, J=10.3, 3.9 Hz), 3.58 (1H, dd, J=10.3, 6.3 Hz), 3.69 (1H, dd, J=11.7, 5.4 Hz), 3.76 (1H, dd, J=13.9, 7.1 Hz), 3.85 (1H, d, J=12.2 Hz), 4.02 (1H, dd, J=14.2, 9.3 Hz), 4.58-4.52 (1H, m), 4.78 (1H, s), 6.47 (1H, d, J=3.9 Hz), 6.54 (1H, t, J=2.2 Hz), 6.73 (1H, d, J=3.4 Hz), 6.83 (1H, t, J=1.7 Hz), 6.98 (1H, s), 7.40 (1H, dd, J=8.8, 2.9 Hz), 7.86 (1H, d, J=4.4 Hz), 8.16 (1H, d, J=8.3 Hz), 8.30 (1H, d, J=2.4 Hz).

MS (ESI) m/z: 481.20954 $(M+H)^+$.

(Example 127)

5-(3-{5-[(5R)-5-(Hydroxymethyl)-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-[(1S)-2-methoxy-1-methylethoxy]phenoxy)-N-methylpyridine-2-sulfonamide



(127a) 5-(3-{5-[(5R)-5-Hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-[(1S)-2-methoxy-1-methylethoxy]phenoxy)-N-(4-methoxybenzyl)-N-methylpyridine-2-sulfonamide

5-Chloro-N-(4-methoxybenzyl)-N-methylpyridine-2-sulfonamide (427 mg, 1.31 mmol) synthesized in Example (121b) and 3-{5-[(5R)-5-(hydroxylmethyl)-4,5-dihydro-1,3-oxazol-2-yl]-

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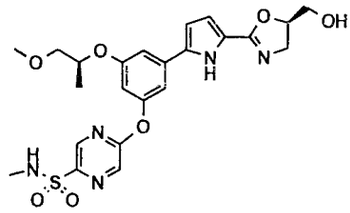
1H-pyrrol-2-yl}-5-[(1S)-2-methoxy-1-methylethoxy]phenol (568 mg, 1.64 mmol) synthesized in Example (125g) were dissolved in N,N-dimethylformamide (5 mL), and potassium carbonate (361 mg, 2.61 mmol) was added, followed by stirring at 100°C for 2 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, water (40 mL) was added, and extraction was carried out twice with ethyl acetate (40 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-3.5%) to afford the desired compound (228 mg, yield 27%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J=5.9 Hz), 2.79 (3H, s), 3.43 (3H, s), 3.51 (1H, dd, J=10.3, 3.9 Hz), 3.59 (1H, dd, J=10.3, 6.3 Hz), 3.69-3.73 (1H, m), 3.75-3.81 (4H, m), 3.87 (1H, d, J=12.2 Hz), 4.04 (1H, dd, J=14.2, 9.8 Hz), 4.37 (2H, s), 4.55-4.58 (1H, m), 4.79-4.84 (1H, m), 6.50 (1H, d, J=3.9 Hz), 6.58 (1H, t, J=2.2 Hz), 6.76 (1H, d, J=3.9 Hz), 6.85 (1H, s), 6.88 (2H, d, J=8.8 Hz), 6.99 (1H, s), 7.26 (3H, d, J=8.8 Hz), 7.42 (1H, dd, J=8.8, 2.9 Hz), 7.94 (1H, d, J=8.8 Hz), 8.47 (1H, d, J=2.4 Hz).

(127b) 5-(3-{5-[(5R)-5-(Hydroxymethyl)-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-[(1S)-2-methoxy-1-methylethoxy]phenoxy)-N-methylpyridine-2-sulfonamide

5-(3-{5-[(5R)-5-Hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-[(1S)-2-methoxy-1-methylethoxy]phenoxy)-N-(4-methoxybenzyl)-N-methylpyridine-2-sulfonamide (292 mg, 0.47 mmol) synthesized in Example (127a) was dissolved in trifluoroacetic acid (2 mL), and stirring was carried out at 45°C for 6 hours. The solvent was distilled off under reduced pressure, methylene chloride and triethylamine were added in small portions to the residue, and the solvent was distilled off again under reduced pressure. The resulting residue was purified using silica gel column chromatography (elution

solvent: methanol/methylene chloride=0%-4%) to afford the desired compound (184 mg, yield 100%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J=5.9 Hz), 1.43 (3H, d, J=6.3 Hz), 2.76 (3H, s), 3.41 (3H, s), 3.49-3.61 (3H, m), 4.08 (1H, dd, J=13.9, 9.0 Hz), 4.61-4.55 (1H, m), 4.84 (1H, dd, J=15.1, 7.3 Hz), 6.50 (1H, d, J=3.9 Hz), 6.56 (1H, t, J=2.2 Hz), 6.76 (1H, d, J=3.9 Hz), 6.86 (1H, s), 7.04 (1H, s), 7.41 (1H, dd, J=8.5, 2.7 Hz), 7.96 (1H, d, J=8.8 Hz), 8.45 (1H, d, J=2.4 Hz).
MS (ESI) m/z: 517.17549 $(M+H)^+$.

(Example 128)
5-(3-{5-[(5R)-5-(Hydroxymethyl)-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-[(1S)-2-methoxy-1-methylethoxy]phenoxy)-N-methylpyrazine-2-sulfonamide



(128a) 5-Bromopyrazine-2-thiol

Under nitrogen atmosphere, 2,5-dibromopyrazine (300 mg, 1.26 mmol) was dissolved in dimethyl sulfoxide (3 mL), and sodium disulfide nonahydrate (454 mg, 1.89 mmol) was added, followed by stirring at 100°C for 1.5 hours. The reaction solution was cooled to room temperature, and water (30 mL) was added, followed by neutralization with 5N hydrochloric acid. After the resulting precipitate was filtered off and washed with water, the resulting solid was dissolved in diethyl ether/tetrahydrofuran, and the insolubles were filtered off. The solvent was distilled off under reduced pressure, and vacuum drying was carried out to afford the desired compound (163 mg, yield 68%) as an orange solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.19 (1H, s), 7.97 (1H, d, J=1.0 Hz), 8.34 (1H, d, J=1.0 Hz).

(128b) 5-Bromo-N-methylpyrazine-2-sulfonamide

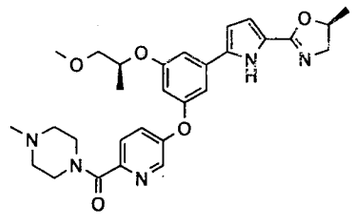
and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-3.5%) to afford the desired compound (161 mg, yield 54%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J=6.3 Hz), 2.81 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J=10.3, 3.9 Hz), 3.60 (1H, dd, J=10.3, 5.9 Hz), 3.68-3.76 (2H, m), 3.85 (1H, dd, J=12.2, 3.4 Hz), 4.00 (1H, dd, J=14.2, 9.8 Hz), 4.60-4.54 (1H, m), 4.76-4.82 (1H, m), 5.23 (1H, s), 6.49 (1H, d, J=3.9 Hz), 6.66 (1H, t, J=2.0 Hz), 6.75 (1H, d, J=3.4 Hz), 6.96 (1H, t, J=1.7 Hz), 7.06 (1H, t, J=2.0 Hz), 8.44 (1H, d, J=1.5 Hz), 8.70 (1H, d, J=1.0 Hz).

MS (ESI) m/z: 518.17036 $(M+H)^+$.

(Example 129)

1-{[5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)pyridin-2-yl]carbonyl}-4-methylpiperazine



(129a) Methyl 5-hydroxy pyridine-2-carboxylate

Commercially available 2-bromo-5-fluoro pyridine (3.80 g, 21.6 mmol) was dissolved in methanol (50 mL) and N,N-dimethylformamide (50 mL), and palladium acetate (484 mg, 2.16 mmol), 1,1-bis(diphenylphosphino)ferrocene (2.39 g, 4.32 mmol) and triethylamine (6.0 mL, 43.2 mmol) were added, followed by stirring at room temperature for 3 days under carbon monoxide atmosphere, and filtering off the insolubles in the reaction solution. Water (100 mL) was added, followed by extraction with ethyl acetate (100 mL), and the organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column

5-Bromopyrazine-2-thiol (988 mg, 5.17 mmol) synthesized in Example (128a) was dissolved in methylene chloride (15 mL)/1N hydrochloric acid (15 mL), and cooled to -10°C. To the reaction solution, ice-cooled 7% aqueous sodium perchlorate solution (15 mL) was added dropwise while being kept at -5°C or below, and stirring was carried out as it is for 1 hour. The organic layer was extracted with a separatory funnel ice-cooled in advance and cooled to 0°C, a commercially available 40% methylamine/methanol solution (1.00 mL, 12.9 mmol) was added, and the temperature was brought back to room temperature, followed by stirring for 17 hours. To the reaction solution, a saturated aqueous ammonium chloride solution (30 mL) was added, and extraction was carried out twice with methylene chloride (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-30%) to afford the desired compound (147 mg, yield 11%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.83 (3H, d, J=5.5 Hz), 4.80 (1H, s), 8.76 (1H, d, J=1.6 Hz), 8.96 (1H, d, J=1.2 Hz).

(128c) 5-(3-{5-[(5R)-5-(Hydroxymethyl)-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-[(1S)-2-methoxy-1-methylethoxy]phenoxy)-N-methylpyrazine-2-sulfonamide

5-Bromo-N-methylpyrazine-2-sulfonamide (147 mg, 0.58 mmol) synthesized in Example (128b) and 3-{5-[(5R)-5-(Hydroxylmethyl)-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-[(1S)-2-methoxy-1-methylethoxy]phenol (262 mg, 0.76 mmol) synthesized in Example (125g) were dissolved in acetonitrile (6 mL), and potassium carbonate (161 mg, 1.17 mmol) was added, followed by stirring for 4 hours under nitrogen atmosphere. Water (20 mL) was added to the reaction solution, and extraction was carried out twice with ethyl acetate (20 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure,

chromatography (elution solvent: ethyl acetate/hexane=0%-50%) to afford the desired compound (2.87 g, yield 86%) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.01 (3H, s), 7.54 (1H, dt, J=8.6, 3.9 Hz), 8.20 (1H, dd, J=8.6, 4.7 Hz), 8.59 (1H, d, J=2.7 Hz).

(129b) Methyl 5-(3-{5-[(benzyloxy)carbonyl]-1H-pyrrol-2-yl}-5-[(1S)-2-methoxy-1-methylethoxy]phenoxy)pyridine-2-carboxylate

2-Benzyl 1-t-butyl 5-{3-hydroxy-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrole-1,2-dicarboxylate (4.08 g, 8.47 mmol) synthesized in Example (78g) and methyl 5-fluoro pyridine-2-carboxylate (1.45 g, 9.32 mmol) synthesized in Example (129a) were dissolved in N,N-dimethylformamide (30 mL), and potassium carbonate (3.51 g, 25.4 mmol) was added, followed by stirring at 100°C for 3 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, water (100 mL) was added, and extraction was carried out with ethyl acetate (100 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: ethyl acetate/hexane=0%-35%).

The resulting yellow solid was dissolved in methylene chloride (5 mL), and trifluoroacetic acid (7.5 mL) was added, followed by stirring at room temperature for 1 hour. To the reaction solution, a saturated aqueous sodium hydrogencarbonate solution (50 mL) was added, and extraction was carried out twice with ethyl acetate (50 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-5%) to afford the desired compound (3.26 g, yield 75%) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J=6.3 Hz), 3.40 (3H, s), 3.50 (1H, dd, J=10.2, 3.9 Hz), 3.58 (1H, dd, J=10.4, 6.5 Hz),

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4.00 (3H, s), 4.52-4.59 (1H, m), 5.32 (2H, s), 6.50 (1H, t, J=2.9 Hz), 6.59 (1H, s), 6.83 (1H, s), 6.99-6.97 (2H, m), 7.34-7.44(5H, m), 8.12 (1H, d, J=8.6 Hz), 8.52 (1H, d, J=2.7 Hz), 9.22 (1H, s).

(129c) 5-(3-{[6-(Methoxycarbonyl)]pyridin-3-yl]oxy}-5-[(1S)-2-methoxy-1-methylethoxy]phenyl)-1H-pyrrole-2-carboxylic acid

Methyl 5-(3-{5-[(benzyloxy)carbonyl]-1H-pyrrol-2-yl}-5-[(1S)-2-methoxy-1-methylethoxy]phenoxy)pyridine-2-carboxylate (3.18 g, 6.16 mmol) synthesized in Example (129b) was dissolved in 5% formic acid/ethanol (200 mL), and a 10% palladium carbon catalyst (2.00 g) was added, followed by stirring for 2 hours under hydrogen atmosphere. The palladium carbon catalyst was removed by Celite filtration, followed by washing with tetrahydrofuran. The solvent was distilled off under reduced pressure, followed by dilution with methylene chloride (100 mL), washing with water, and drying over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure to afford the desired compound (2.41 g, yield 92%) as a white solid. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J=6.3 Hz), 3.46 (3H, s), 3.54 (1H, dd, J=10.2, 3.9 Hz), 3.66 (1H, dd, J=10.2, 6.6 Hz), 4.00 (3H, s), 4.71 (1H, td, J=6.3, 4.3 Hz), 6.49 (1H, dd, J=3.9, 2.7 Hz), 6.59 (1H, d, J=2.0 Hz), 6.92 (1H, t, J=1.6 Hz), 7.02 (1H, dd, J=3.9, 2.3 Hz), 7.39 (1H, dd, J=8.8, 2.9 Hz), 8.13 (1H, d, J=8.6 Hz), 8.57 (1H, d, J=2.7 Hz), 10.46 (1H, s).

(129d) Methyl 5-(3-{[(2R)-2-hydroxypropyl]carbamoyl}-1H-pyrrol-2-yl)-5-[(1S)-2-methoxy-1-methylethoxy]phenoxy}pyridine-2-carboxylate

5-(3-{[6-(Methoxycarbonyl)]pyridin-3-yl]oxy}-5-[(1S)-2-methoxy-1-methylethoxy]phenyl)-1H-pyrrole-2-carboxylic acid (800 mg, 1.87 mmol) synthesized in Example (129c) was dissolved in methanol (20 mL), and (R)-(-)-1-amino-2-propanol (339 μL, 4.30 mol) and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride n hydrate (829 mg, 2.99 mmol) were added, followed by stirring at room temperature for 16 hours

under nitrogen atmosphere. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-5%) to afford the desired compound (726 mg, yield 80%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.25 (3H, d, J=6.6 Hz), 1.32 (3H, d, J=6.3 Hz), 3.25-3.32 (1H, m), 3.41 (3H, s), 3.51 (1H, dd, J=10.2, 3.9 Hz), 3.57-3.65 (2H, m), 4.05 (3H, s), 4.58 (1H, td, J=6.3, 4.0 Hz), 6.35 (1H, s), 6.48 (1H, dd, J=3.9, 3.1 Hz), 6.57 (1H, t, J=2.2 Hz), 6.61 (1H, dd, J=3.9, 2.3 Hz), 6.85 (1H, t, J=1.8 Hz), 7.00 (1H, t, J=1.8 Hz), 7.36 (1H, dd, J=8.8, 2.9 Hz), 8.12 (1H, d, J=9.0 Hz), 8.53 (1H, d, J=2.7 Hz), 9.66 (1H, s).

(129e) Methyl 5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)pyridine-2-carboxylate

Methyl 5-(3-{[(2R)-2-hydroxypropyl]carbamoyl}-1H-pyrrol-2-yl)-5-[(1S)-2-methoxy-1-methylethoxy]phenoxy}pyridine-2-carboxylate (726 mg, 1.50 mmol) synthesized in Example (129d) was dissolved in tetrahydrofuran (20 mL), and anhydrous methanesulfonic acid (523 mg, 3.00 mmol) and triethylamine (0.63 mL, 4.50 mmol) were added, followed by stirring at 50°C for 5 hours under nitrogen atmosphere. To the reaction solution, a saturated aqueous ammonium chloride solution (30 mL) was added, and extraction was carried out with methylene chloride (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-7.5%) to afford the desired compound (264 mg, yield 38%) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J=6.3 Hz), 1.42 (3H, d, J=6.3 Hz), 3.41 (3H, d, J=3.1 Hz), 3.54 (3H, ddt, J=26.4, 11.3, 4.4 Hz), 4.01 (3H, s), 4.04-4.11 (1H, m), 4.60-4.53 (1H, m), 4.87-4.78 (1H, m), 6.49 (1H, d, J=3.9 Hz), 6.55 (1H, t, J=2.0

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Hz), 6.75 (1H, d, J=3.9 Hz), 6.83 (1H, t, J=1.8 Hz), 6.99 (1H, t, J=2.0 Hz), 7.35 (1H, dd, J=8.6, 2.7 Hz), 8.12 (1H, d, J=9.0 Hz), 8.53 (1H, d, J=2.7 Hz).

(129f) 5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)pyridine-2-carboxylic acid

Methyl 5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)pyridine-2-carboxylate (264 mg, 0.57 mmol) synthesized in Example (129e) was dissolved in methanol (20 mL), and water (3 mL) and lithium hydroxide monohydrate (71 mg, 1.70 mmol) were added, followed by stirring at 50°C for 1 hour under nitrogen atmosphere. To the reaction solution, a saturated aqueous ammonium chloride solution (50 mL) was added, followed by extraction twice with methylene chloride (40 mL), washing with saturated brine, and drying over sodium sulfate. The solvent was distilled off under reduced pressure, and vacuum drying was carried out to afford the desired compound (256 mg, yield 100%) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.40 (3H, d, J=6.3 Hz), 1.67 (3H, d, J=6.3 Hz), 3.43 (3H, s), 3.58-3.65 (2H, m), 3.78 (1H, dd, J=11.2, 7.8 Hz), 4.29 (1H, t, J=10.3 Hz), 4.84-4.90 (1H, m), 5.30-5.36 (1H, m), 6.65 (1H, d, J=3.9 Hz), 6.69 (1H, t, J=2.2 Hz), 7.21 (2H, s), 7.50 (1H, dd, J=7.3, 3.4 Hz), 7.56 (1H, s), 8.18 (1H, s), 8.39 (1H, d, J=2.4 Hz).

(129g) 1-{[5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)pyridin-2-yl]carbonyl}-4-methylpiperazine

5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)pyridine-2-carboxylic acid (270 mg, 0.60 mmol) synthesized in Example (129f) was dissolved in tetrahydrofuran (5 mL), and N-methylpiperazine (199 µl, 1.79 mmol), HATU (454 mg, 1.19 mmol) and N,N-diisopropylethylamine (624 µL, 3.58 mmol) were added,

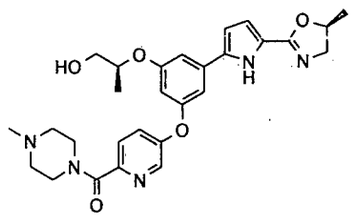
followed by stirring at room temperature for 3 days under nitrogen atmosphere. To the reaction solution, saturated brine (15 mL) was added, and extraction was carried out twice with ethyl acetate (15 mL), followed by drying over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-5%) to afford the desired compound (208 mg, yield 65%) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J=6.3 Hz), 1.42 (3H, d, J=5.9 Hz), 2.33 (3H, s), 2.44 (2H, t, J=4.9 Hz), 2.52 (2H, t, J=4.9 Hz), 3.41 (3H, d, J=0.8 Hz), 3.48-3.60 (3H, m), 3.73 (2H, br s), 3.84 (2H, br s), 4.08 (1H, dd, J=14.3, 9.2 Hz), 4.56 (1H, dd, J=10.2, 6.3 Hz), 4.83 (1H, dd, J=15.6, 6.6 Hz), 6.49 (1H, d, J=4.3 Hz), 6.54 (1H, t, J=2.0 Hz), 6.75 (1H, d, J=3.9 Hz), 6.81 (1H, t, J=1.8 Hz), 6.95 (1H, t, J=1.8 Hz), 7.38 (1H, dd, J=8.6, 2.7 Hz), 7.69 (1H, d, J=8.6 Hz), 8.36 (1H, d, J=2.7 Hz).

MS (ESI) m/z: 534.27234 $(M+H)^+$.

(Example 130)

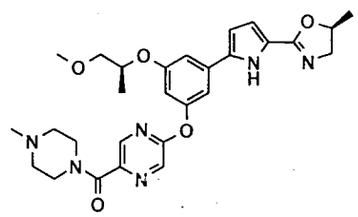
(2S)-2-[3-{5-[(5S)-5-Methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-({6-[(4-methylpiperazin-1-yl)carbonyl] pyridin-3-yl}oxy)phenoxy]propan-1-ol



1-{[5-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)pyridin-2-yl]carbonyl}-4-methylpiperazine (185 mg, 0.35 mmol) synthesized in Example (129g) was dissolved in methylene chloride (10 mL), and boron tribromide (1.0 mol/L methylene chloride solution, 694 μL, 0.694 mmol) was added at -78°C. Subsequently, the temperature was brought back to room temperature, followed by stirring for 50 minutes. To the

reaction solution, a saturated aqueous sodium hydrogencarbonate solution was added, and extraction was carried out with ethyl acetate. The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-10%) to afford the desired compound (51 mg, yield 28%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.28 (3H, d, J=6.3 Hz), 1.43 (3H, d, J=6.3 Hz), 2.34 (3H, s), 2.44 (2H, t, J=4.9 Hz), 2.53 (2H, t, J=4.9 Hz), 3.55 (1H, dd, J=13.9, 7.2 Hz), 3.72 (2H, t, J=4.7 Hz), 3.78 (2H, d, J=5.5 Hz), 3.84 (2H, s), 4.09 (1H, dd, J=13.9, 9.2 Hz), 4.60 (1H, dd, J=11.3, 5.5 Hz), 4.85 (1H, dt, J=11.6, 4.5 Hz), 6.35 (1H, s), 6.46 (1H, d, J=3.9 Hz), 6.75 (1H, d, J=3.9 Hz), 6.79 (1H, t, J=1.8 Hz), 6.90 (1H, s), 7.33 (1H, dd, J=8.6, 2.7 Hz), 7.67 (1H, dd, J=8.6, 0.8 Hz), 8.33 (1H, t, J=1.8 Hz).
MS (ESI) m/z: 520.25784 $(M+H)^+$.

(Example 131)
2-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-5-[(4-methylpiperazin-1-yl)carbonyl]pyrazine



(131a) 2-Chloro-5-[(4-methylpiperazin-1-yl)carbonyl]pyrazine

Commercially available 5-hydroxypyrazine-2-carboxylic acid (5.00 g, 39.0 mmol) was dissolved in thionyl chloride (64 mL), and a few drops of N,N-dimethylformamide were added, followed by heating to reflux for 5 hours under nitrogen atmosphere. The solvent was distilled off under reduced pressure, and the resulting residue was diluted with methylene chloride (50 mL). While being cooled in an ice bath, diisopropylethylamine (18.7 mL, 107 mmol) and 1-methylpiperazine (4.37 mL, 39.2 mmol) were

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added, and stirring was carried out at room temperature for 3 days under nitrogen atmosphere. To the reaction solution, water (100 mL) was added, and extraction was carried out with methylene chloride (100 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=3%-5%) to afford the desired compound (5.32 g, yield 62%) as a brown solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.34 (3H, s), 2.44 (2H, t, J=5.1 Hz), 2.53 (2H, t, J=5.1 Hz), 3.64 (2H, t, J=5.1 Hz), 3.84 (2H, t, J=4.9 Hz), 8.55 (1H, d, J=1.2 Hz), 8.76 (1H, d, J=1.6 Hz).

(131b) Benzyl 5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-({5-[(4-methylpiperazin-1-yl)carbonyl]pyrazin-2-yl}oxy)phenyl}-1H-pyrrole-2-carboxylate

2-Benzyl 1-t-butyl 5-{3-hydroxy-5-[(1S)-2-methoxy-1-methylethoxy]phenyl}-1H-pyrrole-1,2-dicarboxylate (2.00 g, 4.15 mmol) synthesized in Example (78g) and 2-chloro-5-[(4-methylpiperazin-1-yl)carbonyl]pyrazine (1.10 g, 4.57 mmol) synthesized in Example (131a) were dissolved in N,N-dimethylformamide (20 mL), and potassium carbonate (1.72 g, 12.5 mmol) was added, followed by stirring at 80°C for 4 hours under nitrogen atmosphere. The reaction solution was cooled to room temperature, water (80 mL) was added, and extraction was carried out twice with ethyl acetate (50 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-7.5%) to afford a compound (2.88 g) as a brown oil.

This was dissolved in methylene chloride (5 mL), and trifluoroacetic acid (5 mL) was added, followed by stirring at room temperature for 2 hours. To the reaction solution, a

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saturated aqueous sodium hydrogencarbonate solution (50 mL) was added, and extraction was carried out twice with methylene chloride (50 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-7.5%) to afford the desired compound (1.96 g, yield 81%) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ1.34 (3H, d, J=6.3 Hz), 2.34 (3H, s), 2.45 (2H, t, J=4.5 Hz), 2.53 (2H, t, J=4.9 Hz), 3.41 (3H, s), 3.51 (1H, dd, J=10.9, 3.7 Hz), 3.59 (1H, dd, J=9.8, 5.5 Hz), 3.71 (2H, br s), 3.84 (2H, br s), 4.53-4.60 (1H, m), 5.33 (2H, s), 6.51 (1H, dd, J=3.9, 2.7 Hz), 6.69 (1H, t, J=2.0 Hz), 6.93 (1H, s), 6.98 (1H, dd, J=3.7, 2.5 Hz), 7.02 (1H, s), 7.34-7.44(5H, m), 8.35 (1H, t, J=1.4 Hz), 8.54 (1H, d, J=0.8 Hz), 9.21 (1H, br s).

(131c) N-[(2R)-2-Hydroxypropyl]-5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-({5-[(4-methylpiperazin-1-yl)carbonyl]pyrazin-2-yl}oxy)phenyl}-1H-pyrrole-2-carboxamide

Benzyl 5-{3-[(1S)-2-methoxy-1-methylethoxy]-5-({5-[(4-methylpiperazin-1-yl)carbonyl]pyrazin-2-yl}oxy)phenyl}-1H-pyrrole-2-carboxylate (1.94 g, 3.32 mmol) synthesized in Example (131b) was dissolved in methanol (100 mL), and a 10% palladium carbon catalyst (1.20 g) was added, followed by stirring at room temperature for 2.5 hours under hydrogen atmosphere. The palladium carbon catalyst was removed by Celite filtration, followed by washing with tetrahydrofuran. The solvent was distilled off under reduced pressure to afford a white solid (1.45 g).

This white solid (700 mg, 1.41 mmol) and 4-dimethylaminopyridine (86 mg, 0.71 mmol) were dissolved in methylene chloride (30 mL), and WSCI·HCl (625 mg, 2.26 mmol) and (R)-1-amino-2-propanol (256 μL, 3.25 mmol) were added at room temperature, followed by stirring for 3 days under nitrogen

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atmosphere. The reaction solution was diluted with methylene chloride (60 mL), washed with saturated aqueous sodium hydrogencarbonate solution and saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-10%) to afford the desired product (447 mg, 50%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.23 (3H, d, J=6.3 Hz), 1.33 (3H, d, J=8.0 Hz), 2.34 (3H, s), 2.45 (2H, t, J=4.7 Hz), 2.53 (2H, t, J=4.7 Hz), 3.23-3.30 (1H, m), 3.42 (3H, s), 3.51 (1H, dd, J=10.2, 4.3 Hz), 3.58-3.63 (2H, m), 3.71 (2H, t, J=4.7 Hz), 3.84 (2H, t, J=5.5 Hz), 4.00 (1H, br s), 4.53-4.60 (1H, m), 6.37 (1H, s), 6.49 (1H, t, J=3.3 Hz), 6.61 (1H, dd, J=3.9, 2.3 Hz), 6.66 (1H, s), 6.93 (1H, t, J=1.8 Hz), 7.02 (1H, t, J=2.0 Hz), 8.34 (1H, s), 8.53 (1H, s), 9.66 (1H, br s).

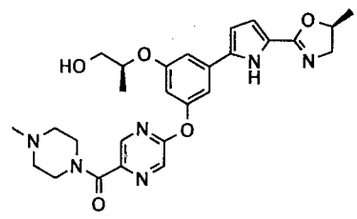
(131d) 2-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-5-[(4-methylpiperazin-1-yl)carbonyl]pyrazine

N-[(2R)-2-Hydroxypropyl]-5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-({5-[(4-methylpiperazin-1-yl)carbonyl]pyrazin-2-yl}oxy)phenyl}-1H-pyrrole-2-carboxamide (447 mg, 0.81 mmol) synthesized in Example (131c) was dissolved in tetrahydrofuran (20 mL), and anhydrous methanesulfonic acid (282 mg, 1.62 mmol) and triethylamine (0.34 mL, 2.43 mmol) were added, followed by stirring at 50°C for 4 hours under nitrogen atmosphere. To the reaction solution, a saturated aqueous ammonium chloride solution (30 mL) was added, and extraction was carried out twice with methylene chloride (30 mL). The organic layer was washed with saturated brine, and subsequently dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=0%-5%) to afford the desired compound (279 mg, yield 65%) as a pale yellow solid.

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^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J=6.3 Hz), 1.42 (3H, d, J=6.3 Hz), 2.34 (3H, s), 2.46 (2H, t, J=4.7 Hz), 2.53 (2H, t, J=4.7 Hz), 3.42 (3H, s), 3.49-3.62 (3H, m), 3.72 (2H, t, J=4.3 Hz), 3.84 (2H, t, J=5.1 Hz), 4.08 (1H, dd, J=14.1, 9.0 Hz), 4.53-4.60 (1H, m), 4.87-4.78 (1H, m), 6.50 (1H, d, J=3.9 Hz), 6.65 (1H, t, J=2.2 Hz), 6.75 (1H, d, J=3.9 Hz), 6.91 (1H, t, J=1.8 Hz), 7.02 (1H, t, J=2.0 Hz), 8.34 (1H, d, J=1.2 Hz), 8.54 (1H, d, J=1.2 Hz).
MS (ESI) m/z: 535.26585 $(M+H)^+$.

(Example 132)
(2S)-2-[3-{5-[(5S)-5-Methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-({5-[(4-methylpiperazin-1-yl)carbonyl]pyrazin-2-yl}oxy)phenoxy]propan-1-ol



2-(3-[(1S)-2-Methoxy-1-methylethoxy]-5-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}phenoxy)-5-[(4-methylpiperazin-1-yl)carbonyl]pyrazine (259 mg, 0.48 mmol) synthesized in Example (131d) was dissolved in methylene chloride (15 mL), and boron tribromide (1.0 mol/L methylene chloride solution, 0.81 mL, 0.81 mmol) was added at -78°C. Subsequently, the temperature was brought back to room temperature, followed by stirring for 3 hours. To the reaction solution, a saturated aqueous sodium hydrogencarbonate solution was added, and extraction was carried out with ethyl acetate. The organic layer was washed with saturated brine, and subsequently dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified using silica gel column chromatography (elution solvent: methanol/methylene chloride=2%-8%) to afford the desired compound (62.4 mg, yield 25%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.28 (4H, d, J=6.3 Hz), 1.41 (3H, d,

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J=6.3 Hz), 2.34 (3H, s), 2.45 (2H, t, J=4.5 Hz), 2.52 (2H, t, J=4.7 Hz), 3.53 (1H, dd, J=13.7, 7.4 Hz), 3.71 (2H, t, J=4.7 Hz), 3.77-3.79 (2H, m), 3.83 (2H, t, J=4.7 Hz), 4.07 (1H, dd, J=13.7, 9.4 Hz), 4.59 (1H, td, J=11.5, 5.7 Hz), 4.83 (1H, dq, J=17.8, 5.1 Hz), 6.44 (1H, d, J=3.9 Hz), 6.47 (1H, s), 6.72 (1H, d, J=3.9 Hz), 6.88 (1H, s), 6.94 (1H, s), 8.30 (1H, s), 8.52 (1H, d, J=0.8 Hz).

MS (ESI) m/z: 521.25002 $(M+H)^+$.

(Test Example 1)

(1) GK Preparation

cDNA encoding human pancreatic GK polypeptide (GenBank Accession No. NM_000162, human glucokinase variant 1) was cloned from a human cDNA library by polymerase chain reaction (PCR), and introduced into a glutathione S-transferase (GST)-fused protein expression vector (GEX4T, GE Healthcare Bioscience). The vector was introduced into Escherichia coli (such as BL21 or JM109, Invitrogen), and the transformed E. coli was cultured overnight at 37°C followed by recovery of the cells. After freezing and thawing the recovered cells, the cells were suspended in phosphate buffer containing Triton-X at a final concentration of 1% followed by disrupting the cells with an ultrasonic homogenizer. The supernatant obtained by low-speed centrifugation treatment of the homogenate (10,000 x g, 30 minutes) was further subjected to high-speed centrifugation (100,000 x g, 10 minutes) followed by recovering the supernatant and purifying the fused protein using a GST fused protein purification system (Bulk GST Purification Module, GE Healthcare Bioscience). The GK fused protein was divided into smaller aliquots and stored at -80°C.

(2) GK Activity Test

GK activity was measured using the GK purified in (1) above. More specifically, an enzyme solution was prepared by adding the purified GK of (1) above and glucose-6-phosphate dehydrogenase (Sigma) to solution 1 of a glucose assay kit (D-Glucose UV Method, Roche Diagnostics). The enzyme solution, a

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test compound diluent and glucose (final concentration: 5 mM) were mixed in a 96-well ELISA plate, and allowed to react for 30 minutes at room temperature. Following completion of the reaction, absorbance at a wavelength of 340 nm was measured using SpectraMax Plus (Molecular Probe). Furthermore, unreacted (when glucose was not added) absorbance was used for the background.

GK activation rates were indicated with values represented by the following numerical formula: (absorbance after reacting for 30 minutes when test compound added)/(absorbance after reacting for 30 minutes when test compound not added). The results for GK activation rates obtained at a test compound concentration of 1 μM are shown in Table 1.

(Table 1)

Example	GK Activation Rate
1	2.0
2	1.9
3	1.9
15	1.6
20	2.0
21	2.0
25	2.0
26	2.3
29	2.0
31	2.0
32	2.0
33	1.7
35	2.1
41	2.1
47	2.0
60	2.0
64	1.9
65	2.4

On the basis of the above results, compounds of the present invention have superior GK activating activity, and are useful as a therapeutic and/or preventive of a disease selected from the group consisting of diabetes, impaired glucose tolerance, gestational diabetes, chronic complications of diabetes (including diabetic peripheral neuropathy, diabetic nephropathy, diabetic retinopathy and diabetic macroangiopathy) and metabolic syndrome.

Preparation Example 1: Capsule

Compound of Example 1 or 78	50 mg
Lactose	128 mg
Cornstarch	70 mg
Magnesium stearate	2 mg
	250 mg

Powders of the above formulation were mixed and passed through a 60 mesh sieve followed by filling the powders into a 250 mg gelatin capsule to obtain a capsule.

Preparation Example 2: Tablet

Compound of Example 1 or 78	50 mg
Lactose	126 mg
Cornstarch	23 mg
Magnesium stearate	1 mg
	200 mg

Powders of the above formulation were mixed, granulated using cornstarch paste and dried, followed by forming into tablets with a tableting machine to obtain a 200 mg tablet. This tablet can be provided with a sugar coating as necessary.

INDUSTRIAL APPLICABILITY

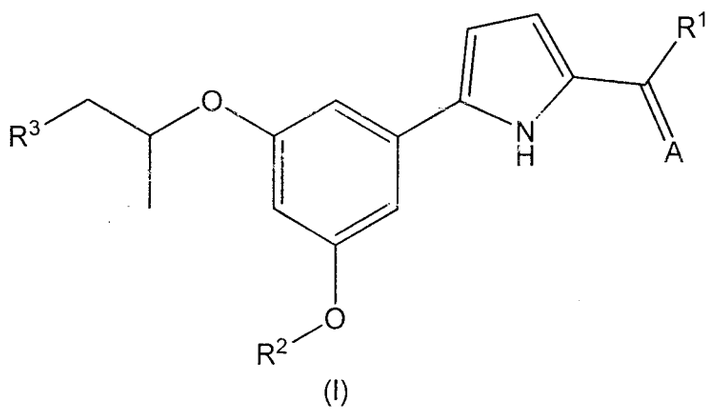
A compound represented by general formula (I) of the present invention, or a pharmacologically acceptable salt thereof, has superior GK activating activity, and is useful as a therapeutic or preventive (and particularly a therapeutic) for diabetes, impaired glucose tolerance, gestational diabetes, chronic complications of diabetes (including diabetic peripheral

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neuropathy, diabetic nephropathy, diabetic retinopathy and diabetic macroangiopathy) or metabolic syndrome (and particularly diabetes or impaired glucose tolerance) for use in warm-blooded animals (and particularly humans).

Claims

1. A compound having the general formula (I):



(I)

[wherein,

A represents a group represented by the formula $=NOR^4$, an oxygen atom or a sulfur atom,

R^4 represents a hydrogen atom or a C_1-C_6 alkyl group,

R^1 represents a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a C_1-C_6 halogenated alkyl group, a C_1-C_6 halogenated alkoxy group, an amino group, a mono-C_1-C_6 alkylamino group, a mono-C_1-C_6 halogenated alkylamino group, a di-(C_1-C_6 alkyl)amino group or a di-(C_1-C_6 halogenated alkyl)amino group, or

A and R^1 together with the carbon atom bonded thereto form a heterocyclic group that may be substituted with 1 to 3 group(s) independently selected from Substituent Group α,

R^2 represents a phenyl group that may be substituted with 1 to 5 group(s) independently selected from Substituent Group α or a heterocyclic group that may be substituted with 1 to 3 group(s) independently selected from Substituent Group α,

R^3 represents a hydroxy group or a C_1-C_6 alkoxy group, and

Substituent Group α represents the group of substituents selected from a halogen atom, a C_1-C_6 alkyl group, a C_1-C_6 halogenated alkyl group, a C_2-C_6 alkenyl group, a C_2-C_6 alkynyl group, a hydroxy group, a C_1-C_6 alkyl group substituted with 1 or 2 hydroxy group(s), a C_1-C_6 alkoxy group, a C_1-C_6 halogenated alkoxy group, a (C_1-C_6 alkoxy)-(C_1-C_6 alkyl) group, a (C_1-C_6 alkoxy)-(C_1-C_6 alkoxy) group, a formyl group, a carboxyl group, a

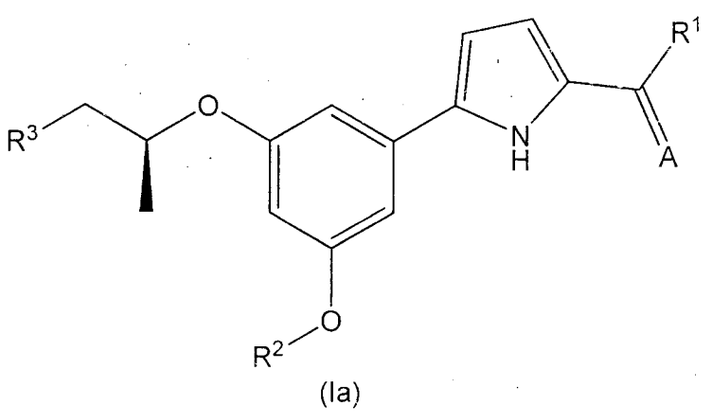
C_2-C_7 alkylcarbonyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 alkylcarbonyloxy group, a C_2-C_7 alkoxycarbonyloxy group, a nitro group, an amino group, a mono-C_1-C_6 alkylamino group, a di-(C_1-C_6 alkyl)amino group, a C_1-C_6 alkylthio group, a C_1-C_6 alkylsulfonyl group, a C_3-C_6 cycloalkylsulfonyl group, a C_1-C_6 hydroxyalkylsulfonyl group, a (C_1-C_6 alkoxy)-(C_1-C_6 alkylsulfonyl) group, a group represented by the formula -V-NR^5R^6 (wherein V represents a carbonyl group or a sulfonyl group, and R^5 and R^6 may be the same or different and respectively represent a hydrogen atom or a C_1-C_6 alkyl group, or R^5 and R^6 together with the nitrogen atom bonded thereto form a 4- to 6-membered saturated heterocycle that may be substituted with 1 or 2 group(s) independently selected from a C_1-C_6 alkyl group and a hydroxy group, and the 4- to 6-membered saturated heterocycle may further contain one oxygen atom or nitrogen atom), a mono-C_2-C_7 alkylcarbonylamino group, a mono-C_1-C_6 alkylaminocarbonyloxy group, a di-(C_1-C_6 alkyl)aminocarbonyloxy group, a mono-C_2-C_7 alkoxycarbonylamino group, a mono-C_1-C_6 alkylsulfonylamino group, a cyano group, a 1,3,4-oxadiazol-2-yl group optionally substituted with a C_1-C_6 alkyl group at the 5-position, a 1,3,4-thiadiazol-2-yl group optionally substituted with a C_1-C_6 alkyl group at the 5-position, and an oxo group] or a pharmacologically acceptable salt thereof.

2. The compound or pharmacologically acceptable salt thereof according to claim 1, wherein

Substituent Group α represents the group of substituents selected from a halogen atom, a C_1-C_6 alkyl group, a C_1-C_6 halogenated alkyl group, a C_2-C_6 alkenyl group, a C_2-C_6 alkynyl group, a hydroxy group, a C_1-C_6 alkyl group substituted with 1 or 2 hydroxy group(s), a C_1-C_6 alkoxy group, a C_1-C_6 halogenated alkoxy group, a (C_1-C_6 alkoxy)-(C_1-C_6 alkyl) group, a (C_1-C_6 alkoxy)-(C_1-C_6 alkoxy) group, a formyl group, a carboxyl group, a C_2-C_7 alkylcarbonyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 alkylcarbonyloxy group, a C_2-C_7 alkoxycarbonyloxy group, a nitro group, an amino group, a mono-C_1-C_6 alkylamino group, a di-(C_1-C_6

alkyl)amino group, a C_1-C_6 alkylthio group, a C_1-C_6 alkylsulfonyl group, a C_3-C_6 cycloalkylsulfonyl group, a C_1-C_6 hydroxyalkylsulfonyl group, a (C_1-C_6 alkoxy)-(C_1-C_6 alkylsulfonyl) group, a group represented by the formula -V-NR^5R^6 (wherein V represents a carbonyl group or a sulfonyl group, and R^5 and R^6 may be the same or different and respectively represent a hydrogen atom or a C_1-C_6 alkyl group, or R^5 and R^6 together with the nitrogen atom bonded thereto form a 4- to 6-membered saturated heterocycle that may be substituted with 1 or 2 group(s) independently selected from a C_1-C_6 alkyl group and a hydroxy group, and the 4- to 6-membered saturated heterocycle may further contain one oxygen atom or nitrogen atom), a mono-C_2-C_7 alkylcarbonylamino group, a mono-C_1-C_6 alkylaminocarbonyloxy group, a di-(C_1-C_6 alkyl)aminocarbonyloxy group, a mono-C_2-C_7 alkoxycarbonylamino group, a mono-C_1-C_6 alkylsulfonylamino group, a cyano group, a 1,3,4-oxadiazol-2-yl group optionally substituted with a C_1-C_6 alkyl group at the 5-position, and a 1,3,4-thiadiazol-2-yl group optionally substituted with a C_1-C_6 alkyl group at the 5-position.

3. The compound or pharmacologically acceptable salt thereof according to claim 1 or 2, wherein the general formula (I) is a general formula (Ia);



(Ia)

4. The compound or pharmacologically acceptable salt thereof according to any one of claims 1 to 3, wherein A is an oxygen

atom.

5. The compound or pharmacologically acceptable salt thereof according to any one of claims 1 to 4, wherein R^1 is a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group or a mono-C_1-C_6 halogenated alkylamino group.

6. The compound or pharmacologically acceptable salt thereof according to any one of claims 1 to 4, wherein R^1 is a methyl group or a 2-chloroethylamino group.

7. The compound or pharmacologically acceptable salt thereof according to any one of claims 1 to 3, wherein the heterocyclic group formed by A and R^1 together with the carbon atom bonded thereto and which may be substituted with 1 to 3 group(s) independently selected from Substituent Group α is a 2-pyridyl group, 5,6-dihydro-4H-1,3-oxazin-2-yl group, 1,3-thiazol-2-yl group, 1,3-oxazol-2-yl group, 1,3,4-oxadiazol-2-yl group, 1,3,4-thiadiazol-2-yl group, 4,5-dihydro-1,3-thiazol-2-yl group, 4,5-dihydro-1,3-oxazol-2-yl group or 4,5-dihydro-1,3-benzothiazol-2-yl group that may be substituted with 1 to 3 group(s) independently selected from Substituent Group γ, and

Substituent Group γ indicates the group consisting of a halogen atom, a C_1-C_6 alkyl group, a C_1-C_6 halogenated alkyl group, a C_1-C_6 alkyl group substituted with 1 or 2 hydroxy group(s), a C_1-C_6 alkoxy group, a carboxyl group, a mono-C_1-C_6 alkylaminocarbonyl group, a di-(C_1-C_6 alkyl)aminocarbonyl group and a hydroxy group.

8. The compound or pharmacologically acceptable salt thereof according to any one of claims 1 to 3, wherein the heterocyclic group formed by A and R^1 together with the carbon atom bonded thereto and which may be substituted with 1 to 3 group(s) independently selected from Substituent Group α is a 1,3-thiazol-2-yl group, a 5-methyl-1,3-thiazol-2-yl group, a 5-methyl-1,3,4-oxadiazol-2-yl group, a 4,5-dihydro-1,3-thiazol-2-

yl group, a 4,5-dihydro-1,3-oxazol-2-yl group, a (5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5R)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a 5-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5R)-5-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-ethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4S)-4-[(1R)-1-hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl group, a (4S)-4-[(1S)-1-hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5S)-4,5-dimethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5S)-4-hydroxy-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5S)-4-hydroxymethyl-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5R)-5-hydroxymethyl-4-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a 5-carboxyl-1,3-thiazol-2-yl group, a 5-dimethylaminocarbonyl-1,3-thiazol-2-yl group, a 5-methyl-1,3,4-thiadiazol-2-yl group or a 5,6-dihydro-4H-1,3-oxazin-2-yl group.

9. The compound or pharmacologically acceptable salt thereof according to any one of claims 1 to 3, wherein the heterocyclic group formed by A and R^1 together with the carbon atom bonded thereto and which may be substituted with 1 to 3 group(s) independently selected from Substituent Group α is a 4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-ethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5R)-5-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4S)-4-[(1R)-1-hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl group, a (4S)-4-[(1S)-1-hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5S)-4,5-dimethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5S)-4-hydroxymethyl-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5R)-5-hydroxymethyl-4-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a 1,3-thiazol-2-yl group, 5-carboxyl-1,3-thiazol-2-yl group, a 5-dimethylaminocarbonyl-1,3-thiazol-2-yl group, a 5-methyl-1,3,4-thiadiazol-2-yl group, a 5-methyl-1,3,4-oxadiazol-2-yl group, a 4,5-dihydro-1,3-thiazol-2-yl group or a

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5,6-dihydro-4H-1,3-oxazin-2-yl group.

10. The compound or pharmacologically acceptable salt thereof according to any one of claims 1 to 3, wherein the heterocyclic group formed by A and R^1 together with the carbon atom bonded thereto and which may be substituted with 1 to 3 group(s) independently selected from Substituent Group α is a 4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-ethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R)-4-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (5R)-5-hydroxymethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4S)-4-[(1R)-1-hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl group, a (4S)-4-[(1S)-1-hydroxyethyl]-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5S)-4,5-dimethyl-4,5-dihydro-1,3-oxazol-2-yl group, a (4R,5S)-4-hydroxymethyl-5-methyl-4,5-dihydro-1,3-oxazol-2-yl group or a (4R,5R)-5-hydroxymethyl-4-methyl-4,5-dihydro-1,3-oxazol-2-yl group.

11. The compound or pharmacologically acceptable salt thereof according to any one of claims 1 to 10, wherein R^2 is a phenyl group that may be substituted with 1 to 5 group(s) independently selected from Substituent Group δ or a 2-pyridyl group, 3-pyridyl group or 2-pyrazinyl group that may be substituted with 1 to 3 group(s) independently selected from Substituent Group δ, and

Substituent Group δ indicates the group consisting of a halogen atom, a C_1-C_6 alkyl group, a C_1-C_6 halogenated alkyl group, a C_1-C_6 alkyl group substituted with 1 or 2 hydroxy group(s), a C_2-C_7 alkylcarbonyl group, a C_2-C_7 alkoxycarbonyl group, a C_1-C_6 alkylsulfonyl group, a group represented by the formula $-V-NR^5R^6$ (wherein V represents a carbonyl group or a sulfonyl group, and R^5 and R^6 may be the same or different and respectively represent a hydrogen atom or a C_1-C_6 alkyl group, or R^5 and R^6 together with the nitrogen atom bonded thereto form a 4- to 6-membered saturated heterocycle that may be substituted

with 1 or 2 group(s) independently selected from a C_1-C_6 alkyl group and a hydroxy group, and the 4- to 6-membered saturated heterocycle may further contain one oxygen atom or nitrogen atom), a 1,3,4-oxadiazol-2-yl group optionally substituted with a C_1-C_6 alkyl group at the 5-position, and a 1,3,4-thiadiazol-2-yl group optionally substituted with a C_1-C_6 alkyl group at the 5-position.

12. The compound or pharmacologically acceptable salt thereof according to any one of claims 1 to 10, wherein R^2 is a 4-methylsulfonylphenyl group, a 4-(1-azetidinyl)carbonyl-2-fluorophenyl group, a 2-fluoro-4-(1-pyrrolidinyl)carbonylphenyl group, a 5-(1-azetidinyl)carbonyl-3-chloro-2-pyridyl group, a 2-methylsulfonyl-5-pyridyl group, a 5-(4-methyl-1-piperazinyl)carbonyl-2-pyrazinyl group, a 2-methylaminocarbonyl-5-pyridyl group, a 2-methylaminosulfonyl-5-pyridyl group or a 5-methylsulfonyl-2-pyrazinyl group.

13. The compound or pharmacologically acceptable salt thereof according to any one of claims 1 to 10, wherein R^2 is a 4-methylsulfonylphenyl group, a 2-methylsulfonyl-5-pyridyl group, a 5-methylsulfonyl-2-pyrazinyl group or a 5-(1-azetidinyl)carbonyl-3-chloro-2-pyridyl group.

14. The compound or pharmacologically acceptable salt thereof according to any one of claims 1 to 13, wherein R^3 is a hydroxy group or a methoxy group.

15. The compound or pharmacologically acceptable salt thereof according to claim 1, wherein the compound represented by the general formula (I) is:
(2S)-2-{3-[5-(4,5-dihydro-1,3-oxazol-2-yl)-1H-pyrrol-2-yl]-5-[4-(methylsulfonyl)phenoxy]phenoxy}propan-1-ol,
(2S)-2-(3-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-[4-(methylsulfonyl)phenoxy]phenoxy)propan-1-ol,
(2S)-2-(3-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-

pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol,
{(5R)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-5-yl}methanol,
(2S)-2-(3-{5-[(4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol,
(2S)-2-(3-{5-[(4R)-4-ethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol,
{(4R)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}methanol,
(2S)-2-(3-{5-[(4R,5S)-4,5-dimethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol,
{(4R,5R)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4-methyl-4,5-dihydro-1,3-oxazol-5-yl}methanol,
{(4R,5S)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazol-4-yl}methanol,
(1S)-1-{(4S)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol,
(1R)-1-{(4S)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol,
(2S)-2-(3-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol,
{(5R)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-5-yl}methanol,
(2S)-2-(3-{5-[(4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-

pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol,
(2S)-2-(3-{5-[(4R)-4-ethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol,
(2S)-2-(3-{5-[(4R,5S)-4,5-dimethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol,
{(4R,5S)-2-[5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazol-4-yl}methanol,
(1S)-1-{(4S)-2-[5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol, or
(1R)-1-{(4S)-2-[5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol.

16. The compound according to claim 1, wherein the compound represented by the general formula (I) is:
(2S)-2-{3-[5-(4,5-dihydro-1,3-oxazol-2-yl)-1H-pyrrol-2-yl]-5-[4-(methylsulfonyl)phenoxy]phenoxy}propan-1-ol,
(2S)-2-(3-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-[4-(methylsulfonyl)phenoxy]phenoxy)propan-1-ol,
(2S)-2-(3-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol,
{(5R)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-5-yl}methanol,
(2S)-2-(3-{5-[(4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol,
(2S)-2-(3-{5-[(4R)-4-ethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol,

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{(4R)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}methanol,
(2S)-2-(3-{5-[(4R,5S)-4,5-dimethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenoxy)propan-1-ol,
{(4R,5R)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4-methyl-4,5-dihydro-1,3-oxazol-5-yl}methanol,
{(4R,5S)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazol-4-yl}methanol,
(1S)-1-{(4S)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol,
(1R)-1-{(4S)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[6-(methylsulfonyl)pyridin-3-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol,
(2S)-2-(3-{5-[(5S)-5-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol,
{(5R)-2-[5-(3-[(1S)-2-methoxy-1-methylethoxy]-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-5-yl}methanol,
(2S)-2-(3-{5-[(4R)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol,
(2S)-2-(3-{5-[(4R)-4-ethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol,
(2S)-2-(3-{5-[(4R,5S)-4,5-dimethyl-4,5-dihydro-1,3-oxazol-2-yl]-1H-pyrrol-2-yl}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenoxy)propan-1-ol,
{(4R,5S)-2-[5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-5-methyl-4,5-dihydro-1,3-oxazol-4-yl}methanol,

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(1S)-1-{(4S)-2-[5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol, or
(1R)-1-{(4S)-2-[5-(3-{[(2S)-1-methoxypropan-2-yl]oxy}-5-{[5-(methylsulfonyl)pyrazin-2-yl]oxy}phenyl)-1H-pyrrol-2-yl]-4,5-dihydro-1,3-oxazol-4-yl}ethanol.

17. A glucokinase activator containing as an active ingredient thereof a compound or pharmacologically acceptable salt thereof according to any one of claims 1 to 16.

18. A pharmaceutical composition containing as an active ingredient thereof a compound or pharmacologically acceptable salt thereof according to any one of claims 1 to 16.

19. The pharmaceutical composition according to claim 18, wherein the pharmaceutical composition has glucokinase activating activity.

20. The pharmaceutical composition according to claim 18, wherein the pharmaceutical composition is for treating and/or preventing a disease that is treatable and/or preventable by glucokinase activating activity.

21. The pharmaceutical composition according to claim 18, wherein the pharmaceutical composition is for treating and/or preventing a disease for which the symptoms thereof are treated, improved, diminished and/or prevented by activation of glucokinase and maintenance of glucose homeostasis or regulation of blood glucose level.

22. The pharmaceutical composition according to claim 18, the pharmaceutical composition is for treating and/or preventing diabetes, impaired glucose tolerance, gestational diabetes, chronic complications of diabetes (including diabetic peripheral neuropathy, diabetic nephropathy, diabetic retinopathy and

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diabetic macroangiopathy) or metabolic syndrome.

23. The pharmaceutical composition according to claim 18, wherein the pharmaceutical composition is for treating and/or preventing diabetes or impaired glucose tolerance.

24. A use of a compound or pharmacologically acceptable salt thereof according to any one of claims 1 to 16, for producing a pharmaceutical composition.

25. The use according to claim 24, wherein the pharmaceutical composition is a composition for activating glucokinase.

26. The use according to claim 24, wherein the pharmaceutical composition is a composition for treating and/or preventing diabetes, impaired glucose tolerance, gestational diabetes, chronic complications of diabetes (including diabetic peripheral neuropathy, diabetic nephropathy, diabetic retinopathy and diabetic macroangiopathy) or metabolic syndrome.

27. The use according to claim 24, wherein the pharmaceutical composition is a composition for treating and/or preventing diabetes or impaired glucose tolerance.

28. A glucokinase activation method, comprising administering a pharmacologically effective amount of a compound or pharmacologically acceptable salt thereof according to any one of claims 1 to 16 to a warm-blooded animal.

29. A method for treating and/or preventing a disease, comprising administering a pharmacologically effective amount of a compound or pharmacologically acceptable salt thereof according to any one of claims 1 to 16 to a warm-blooded animal.

30. The method according to claim 29, wherein the disease is diabetes, impaired glucose tolerance, gestational diabetes,

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chronic complications of diabetes (including diabetic peripheral neuropathy, diabetic nephropathy, diabetic retinopathy and diabetic macroangiopathy) or metabolic syndrome.

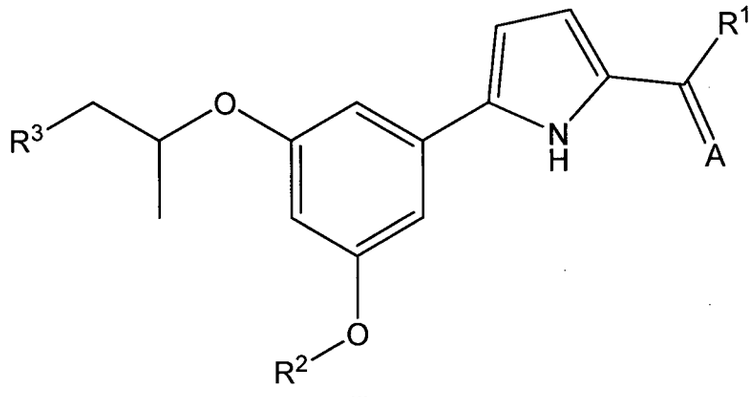
31. The method according to claim 29, wherein the disease is diabetes or impaired glucose tolerance.

32. The method according to any one of claims 28 to 31, wherein the warm-blooded animal is a human.

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ABSTRACT

The present invention relates to a compound or a pharmacologically acceptable salt thereof having superior glucokinase activating activity, and is a compound represented by general formula (I), or pharmacologically acceptable salt thereof:



(I)

[wherein,

A represents, for example, an oxygen atom or sulfur atom, R^1 represents, for example, a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group or a C_1-C_6 halogenated alkyl group, A and R^1 together with the carbon atom bonded thereto form a heterocyclic group that may be substituted with 1 to 3 group(s) independently selected from Substituent Group α, R^2 represents a phenyl group that may be substituted with 1 to 5 group(s) independently selected from Substituent Group α or a heterocyclic group that may be substituted with 1 to 3 group(s) independently selected from Substituent Group α, R^3 represents a hydroxy group or a C_1-C_6 alkoxy group, and Substituent Group α consists of, for example, a halogen atom, a C_1-C_6 alkyl group, a C_1-C_6 alkyl group substituted with 1 or 2 hydroxy group(s), a C_1-C_6 alkylsulfonyl group, and a group represented by the formula $-V-NR^5R^6$ (wherein, V represents a carbonyl group or a sulfonyl group, and R^5 and R^6 may be the same or different and respectively represent a hydrogen atom or a C_1-C_6 alkyl group, or R^5 and R^6 together with the nitrogen atom bonded thereto form a 4- to 6-membered

saturated heterocycle that may be substituted with 1 or 2 group(s) independently selected from a C_1-C_6 alkyl group and a hydroxy group, and the 4- to 6-membered saturated heterocycle may further contain one oxygen atom or nitrogen atom)].

DERIVADO DE FENILPIRROL NOVEDOSO

CAMPO TECNICO

La presente invención se refiere a un compuesto de fenilpirrol y las sales farmacológicamente aceptables del mismo, que tienen una actividad activadora de glucocinasa superior y son útiles como agentes terapéuticos para la diabetes y similares.

ANTECEDENTES DE LA INVENCION

La glucocinasa (abreviada como GK en la presente descripción, EC 2.7.1.1) es uno de los cuatro tipos de hexocinasas (hexocinasa IV) encontradas en los mamíferos. Las hexocinasas son enzimas que catalizan la conversión de glucosa a glucosa-6-fosfato en la primera etapa del sistema de glucólisis en las células, y la expresión de GK se localiza principalmente en el hígado y las células beta pancreáticas. En las células beta pancreáticas, la GK funciona como un mecanismo de detección de la concentración extracelular de glucosa, que regula la secreción de insulina estimulada por glucosa, mientras que en el hígado la reacción enzimática de GK sirve como el paso limitativo de velocidad para regular reacciones subsiguientes tales como glucólisis y síntesis de glucógeno. Aunque la GK encontrada en el hígado y la encontrada en las células beta pancreáticas difieren en su

secuencia que consiste en 15 aminoácidos desde el extremo N, debido a una diferencia de empalme, sus propiedades enzimáticas son idénticas. A diferencia de las actividades enzimáticas de los tres tipos de hexocinasas diferentes de GK (tipos I, II y III), que se saturan a una concentración de glucosa de 1 mM o menor, la GK presenta baja afinidad por la glucosa y su valor de Km es cercano al nivel fisiológico de la glucosa en la sangre de 8-15 mM. De esta manera, ocurre una aceleración del metabolismo de la glucosa intracelular mediada por GK en respuesta a cambios de concentración de la glucosa sanguínea que varían de las concentraciones normales (aproximadamente 5 mM) a concentraciones postprandiales (10 mM a 15 mM).

Durante mucho tiempo se ha afirmado la hipótesis de que la GK funciona como un sensor de glucosa en el hígado y las células beta pancreáticas (documentos no patentes 1 a 3). Recientes hallazgos de investigación han mostrado que la GK desempeña realmente una función importante en el mantenimiento de la homeostasis de la glucosa sistémica, verificando así esta hipótesis. Por ejemplo, unos ratones en los que se ha trastocado el gen de glucocinasa mostraron síntomas prominentes de hiperglucemia y murieron poco después del nacimiento, mientras que se observó que unos ratones heterodeficientes en GK tienen una tolerancia defectuosa a la glucosa y deterioro de la secreción de insulina estimulada por glucosa (documento no patente 4). Por otra parte, se observó que ratones normales que expresan excesivamente la GK muestran una disminución de la

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concentración de glucosa en la sangre y un aumento del contenido de glucógeno en el hígado, y estos fenómenos fueron similares a los observados en ratones en los que se indujo artificialmente la diabetes (documento no patente 5).

Además, la GK también funciona como un sensor de glucosa en los humanos y una investigación reciente ha mostrado que desempeña una función importante en el mantenimiento de homeostasis de la glucosa. Se han descubierto anormalidades en los genes de GK de linajes de familia que muestran una forma de diabetes de aparición juvenil, llamada diabetes de tipo MODY 2 (*maturity onset diabetes of the young*), y se observó claramente una correlación entre estos casos y la actividad de GK (documento no patente 6). Por otra parte, también se han encontrado linajes de familia que tienen una mutación que aumenta la actividad de GK, y en dichos linajes de familia se han observado síntomas de hipoglucemia en ayunas acompañados por elevación de la concentración de la insulina plasmática (documento no patente 7). Basándose en estos reportes, la GK desempeña una función importante en la regulación de glucosa en la sangre, funcionando como un sensor de glucosa en los mamíferos incluyendo los humanos. De esta manera, las sustancias que tienen actividad activadora de GK se consideran útiles como fármacos para el tratamiento de enfermedades glucometabólicas que incluyen la diabetes mellitus de tipo II. Puesto que es de esperar que las sustancias activadoras de GK muestren simultáneamente actividad promotora de la captación de glucosa, actividad inhibitoria de la liberación de glucosa en el

hígado, y también actividad promotora de secreción de insulina, en particular en las células beta pancreáticas, se prevé que serán capaces de mostrar potentes efectos terapéuticos que no pueden ser obtenidos con los fármacos existentes.

Recientemente se ha determinado que la GK de tipo célula beta pancreática se expresa en el hipotálamo ventromedial (VMH) del cerebro de la rata. Convencionalmente se sabe que el VMH es el sitio de las neuronas que responden a la concentración de glucosa. En contraste con la disminución de la ingestión de alimento cuando se administra glucosa al ventrículo de la rata, cuando se inhibe el metabolismo de la glucosa por administración del análogo de glucosa glucosamina, la ingestión de alimento se acelera (documento no patente 8). Experimentos electrofisiológicos han mostrado que las neuronas sensibles a la glucosa se activan respondiendo a cambios fisiológicos de la concentración de glucosa (5 mM a 20 mM), y se ha determinado que la glucocinasa funciona similarmente como un sensor de glucosa en el tejido periférico (documento no patente 9). De esta manera, se puede esperar que las sustancias que activen la glucocinasa no solo en el hígado y las células beta pancreáticas, sino también en el VMH, muestren actividad reductora de glucosa en la sangre y también actividad que corrija la obesidad, que se considera un problema asociado con muchos pacientes de diabetes mellitus de tipo II.

Basándose en las descripciones anteriormente mencionadas, las sustancias que tienen actividad activadora de GK son útiles como agentes

terapéuticos y preventivos para la diabetes, o como agentes terapéuticos y preventivos para las complicaciones crónicas de la diabetes que incluyen retinopatía diabética, nefropatía diabética, neuropatía diabética, enfermedad isquémica cardiaca y arteriosclerosis.

Además, aunque en el pasado se ha reportado una pluralidad de compuestos que tiene actividad activadora de GK, todos estos tienen estructuras diferentes a las del compuesto de la presente invención. Por ejemplo, aunque el documento de patente 1 describe un compuesto que tiene una estructura de amida como constituyente esencial del mismo, el compuesto de la presente invención tiene una estructura de pirrol en lugar de una estructura de amida como constituyente esencial. Además, aunque el documento de patente 2 describe un compuesto que tiene un pirrol condensado, el compuesto de la presente invención tiene un pirrol no condensado como constituyente esencial. Además, aunque el documento de patente 3 describe un compuesto que tiene una porción de pirazol o 1,2,4-triazol 3,5-di-sustituidos, ésta difiere de la estructura de pirrol 2,5-di-sustituido de la presente invención. Aunque se ha reportado una pluralidad de compuestos que tienen actividad activadora de GK además de los descritos en las publicaciones anteriores, todos ellos tienen estructuras diferentes del compuesto de la presente invención (véanse por ejemplo los documentos de patente 4 a 15 y los documentos no patentes 10 y 11).

Documento de patente 1: Publicación internacional No. WO2005/080359

Documento de patente 2: Publicación internacional No. WO2007/031739

Documento de patente 3: Publicación internacional No. WO2007/061923

Documento de patente 4: Publicación internacional No. WO2000/058293

Documento de patente 5: Publicación internacional No. WO2003/080585

Documento de patente 6: Publicación internacional No. WO2005/066145

Documento de patente 7: Publicación internacional No. WO2005/090332

Documento de patente 8: Publicación internacional No. WO2006/112549

Documento de patente 9: Publicación internacional No. WO2007/007886

Documento de patente 10: Publicación internacional No. WO2007/037534

Documento de patente 11: Publicación internacional No. WO2007/053765

Documento de patente 12: Publicación internacional No. WO2007/117381

Documento de patente 13: Publicación internacional No.

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WO2005/044801

Documento de patente 14: Publicación internacional No. WO2007/053662

Documento de patente 15: Publicación internacional No. WO2008/136428

Documento no patente 1: *Am J Physiol.*, septiembre de 1984; 247(3 Pt 2):R527-36.

Documento no patente 2: *Diabetes*, enero de 1986; 35(1):61-7.

Documento no patente 3: *Diabetes*, octubre de 1986; 35(10):1163-73.

Documento no patente 4: *Cell*, 6 de octubre de 1995; 83(1):69-78.

Documento no patente 5: *Proc Natl Acad Sci U S A*, 9 de julio de 1996; 93(14):7225-30.

Documento no patente 6: *Nature*, 23 de abril de 1992; 356(6371):721-2.

Documento no patente 7: *N Engl J Med.*, 22 de enero de 1998; 338(4):226-30.

Documento no patente 8: *Life Sci.*, 30 de diciembre de 1985; 37(26):2475-82.

Documento no patente 9: *Diabetes*, febrero de 2006; 55(2):412-20; fe de erratas en: *Diabetes*, marzo de 2006; 55(3):862.

Documento no patente 10: *Science*, 18 de julio de 2003;

301(5631):370-3.

Documento no patente 11: *J Biol Chem.*, 8 de diciembre de 2006; 281(49):37668-74. Epub 6 de octubre de 2006.

BREVE DESCRIPCION DE LA INVENCION

Problemas que intenta resolver la invención

Un objeto de la presente invención es proveer un derivado de fenilpirrol novedoso y un activador de GK que utiliza este derivado de fenilpirrol novedoso, y particularmente proveer un agente terapéutico y preventivo para la diabetes y el deterioro de la tolerancia a la glucosa. Como resultado de la realización de extensos estudios sobre compuestos que tienen actividad activadora de GK, los inventores de la presente invención encontraron que un compuesto de fenilpirrol que tiene una estructura química específica tiene una actividad activadora de GK superior. Además, el compuesto de la presente invención tiene una selectividad de GK superior, baja toxicidad y pocos efectos secundarios adversos. Los inventores de la presente invención también encontraron que este compuesto de fenilpirrol es útil como ingrediente activo de una composición farmacéutica para el tratamiento o prevención de enfermedades seleccionadas del conjunto que consiste en diabetes, deterioro de tolerancia a la glucosa, diabetes gestacional, complicaciones crónicas de la diabetes (que incluyen neuropatía periférica diabética, nefropatía diabética, retinopatía diabética y

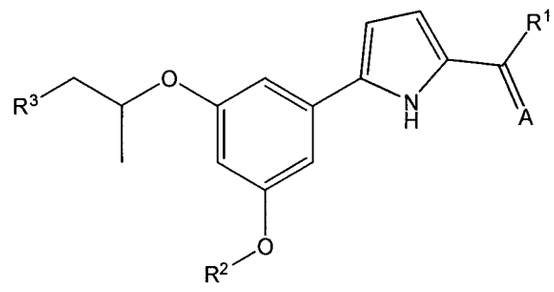
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macroangiopatía diabética), y síndrome metabólico. La presente invención se cumplió basándose en los hallazgos anteriormente mencionados.

Medios para resolver los problemas

La presente invención se refiere a:

(1) un compuesto que tiene la fórmula general (I):



(I)

[en donde:

A representa un grupo representado por la fórmula $=NOR^4$, un átomo de oxígeno o un átomo de azufre,

R^4 representa un átomo de hidrógeno o un grupo alquilo de C_1-C_6,

R^1 representa un grupo alquilo de C_1-C_6, un grupo alcoxi de C_1-C_6, un grupo alquilo de C_1-C_6 halogenado, un grupo alcoxi de C_1-C_6 halogenado, un grupo amino, un grupo mono-alquil(C_1-C_6)-amino, un grupo mono-alquilo halogenado (C_1-C_6)-amino, un grupo di-alquil(C_1-C_6)-amino, o un grupo di-alquilo halogenado (C_1-C_6)-amino, o

A y R^1, junto con el átomo de carbono al que están unidos, forman un grupo heterocíclico que puede estar sustituido con 1 a 3 grupos

seleccionados independientemente del conjunto de sustituyentes α,

R^2 representa un grupo fenilo que puede estar sustituido con 1 a 5 grupos seleccionados independientemente del conjunto de sustituyentes α, o un grupo heterocíclico que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α,

R^3 representa un grupo hidroxi o un grupo alcoxi de C_1-C_6, y

el conjunto de sustituyentes α comprende un átomo de halógeno, un grupo alquilo de C_1-C_6, un grupo de alquilo de C_1-C_6 halogenado, un grupo alquenilo de C_2-C_6, un grupo alquinilo de C_2-C_6, un grupo hidroxi, un grupo alquilo de C_1-C_6 sustituido con 1 o 2 grupos hidroxi, un grupo alcoxi de C_1-C_6, un grupo alcoxi de C_1-C_6 halogenado, un grupo alcoxi(C_1-C_6)-alquilo(C_1-C_6), un grupo alcoxi(C_1-C_6)-alcoxi(C_1-C_6), un grupo formilo, un grupo carboxilo, un grupo alquilcarbonilo de C_2-C_7, un grupo alcoxicarbonilo de C_2-C_7, un grupo alquilcaboniloxi de C_2-C_7, un grupo alcoxicarboniloxi de C_2-C_7, un grupo nitro, un grupo amino, un grupo mono-alquil(C_1-C_6)-amino, un grupo di-alquil(C_1-C_6)-amino, un grupo alquiltio de C_1-C_6, un grupo alquilsulfonilo de C_1-C_6, un grupo cicloalquilsulfonilo de C_3-C_6, un grupo hidroxialquilsulfonilo de C_1-C_6, un grupo alcoxi(C_1-C_6)-alquilsulfonilo(C_1-C_6), un grupo representado por la fórmula -V-NR^5R^6 (en donde V representa un grupo carbonilo o un grupo sulfonilo, y R^5 y R^6 pueden ser iguales o diferentes y representan respectivamente un átomo de hidrógeno o un grupo alquilo de C_1-C_6, o R^5 y R^6, junto con el átomo de nitrógeno al que están

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unidos, forman un heterociclo saturado de 4 a 6 miembros que puede estar sustituido con 1 o 2 grupos seleccionados independientemente de un grupo alquilo de C_1-C_6 y un grupo hidroxi, y el heterociclo saturado de 4 a 6 miembros puede contener también un átomo de oxígeno o un átomo de nitrógeno), un grupo mono-alquilcarbonilamino de C_2-C_7, un grupo mono-alquil(C_1-C_6)-aminocarboniloxi, un grupo di-alquil(C_1-C_6)-aminocarboniloxi, un grupo mono-alcoxicarbonilamino de C_2-C_7, un grupo mono-alquilsulfonilamino de C_1-C_6, un grupo ciano, un grupo 1,3,4-oxadiazol-2-ilo sustituido opcionalmente con un grupo alquilo de C_1-C_6 en la posición 5, un grupo 1,3,4-tiadiazol-2-ilo sustituido opcionalmente con un grupo alquilo de C_1-C_6 en la posición 5, y un grupo oxo],

y las sales farmacológicamente aceptables del mismo;

(2) el compuesto o sal farmacológicamente aceptable del inciso (1) anterior, en donde:

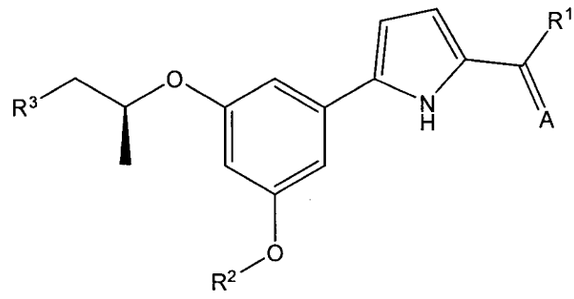
el conjunto de sustituyentes α comprende un átomo de halógeno, un grupo alquilo de C_1-C_6, un grupo alquilo de C_1-C_6 halogenado, un grupo alquenilo de C_2-C_6, un grupo alquinilo de C_2-C_6, un grupo hidroxi, un grupo alquilo de C_1-C_6 sustituido con 1 o 2 grupos hidroxi, un grupo alcoxi de C_1-C_6, un grupo alcoxi de C_1-C_6 halogenado, un grupo alcoxi(C_1-C_6)-alquilo(C_1-C_6), un grupo alcoxi(C_1-C_6)-alcoxi(C_1-C_6), un grupo formilo, un grupo carboxilo, un grupo alquilcarbonilo de C_2-C_7, un grupo alcoxicarbonilo de C_2-C_7, un grupo alquilcaboniloxi de C_2-C_7, un grupo alcoxicarboniloxi de C_2-C_7, un grupo nitro, un grupo amino, un grupo mono-alquil(C_1-C_6)-amino, un

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grupo di-alquil(C_1-C_6)-amino, un grupo alquiltio de C_1-C_6, un grupo alquilsulfonilo de C_1-C_6, un grupo cicloalquilsulfonilo de C_3-C_6, un grupo hidroxialquilsulfonilo de C_1-C_6, un grupo alcoxi(C_1-C_6)-alquilsulfonilo(C_1-C_6), un grupo representado por la fórmula -V-NR^5R^6 (en donde V representa un grupo carbonilo o un grupo sulfonilo, y R^5 y R^6 pueden ser iguales o diferentes y representan respectivamente un átomo de hidrógeno o un grupo alquilo de C_1-C_6, o R^5 y R^6, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros que puede estar sustituido con 1 o 2 grupos seleccionados independientemente de un grupo alquilo de C_1-C_6 y un grupo hidroxi, y el heterociclo saturado de 4 a 6 miembros puede contener también un átomo de oxígeno o un átomo de nitrógeno), un grupo mono-alquilcarbonilamino de C_2-C_7, un grupo mono-alquil(C_1-C_6)-aminocarboniloxi, un grupo di-alquil(C_1-C_6)-aminocarboniloxi, un grupo mono-alcoxicarbonilamino de C_2-C_7, un grupo mono-alquilsulfonilamino de C_1-C_6, un grupo ciano, un grupo 1,3,4-oxadiazol-2-ilo sustituido opcionalmente con un grupo alquilo de C_1-C_6 en la posición 5, y un grupo 1,3,4-tiadiazol-2-ilo sustituido opcionalmente con un grupo alquilo de C_1-C_6 en la posición 5;

(3) el compuesto o sal farmacológicamente aceptable del inciso (1) o (2) anteriores, en donde:

la fórmula general (I) es la fórmula general (Ia):



(Ia)

(4) el compuesto o sal farmacológicamente aceptable de cualquiera de los incisos (1) a (3) anteriores, en donde A es un átomo de oxígeno;

(5) el compuesto o sal farmacológicamente aceptable de cualquiera de los incisos (1) a (4) anteriores, en donde R^1 es un grupo alquilo de C_1-C_6, un grupo alcoxi de C_1-C_6 o un grupo mono-alquilo halogenado (C_1-C_6)-amino;

(6) el compuesto o sal farmacológicamente aceptable de cualquiera de los incisos (1) a (4) anteriores, en donde R^1 es un grupo metilo o un grupo 2-cloroetilamino;

(7) el compuesto o sal farmacológicamente aceptable de cualquiera de los incisos (1) a (4) anteriores, en donde el grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están unidos, y que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, es un grupo 2-piridilo, un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo, un grupo 1,3-tiazol-2-ilo, un grupo 1,3-oxazol-2-ilo, un grupo 1,3,4-oxadiazol-2-ilo, un grupo 1,3,4-tiadiazol-2-ilo, un grupo 4,5-dihidro-

1,3-tiazol-2-ilo, un grupo 4,5-dihidro-1,3-oxazol-2-ilo, o un grupo 4,5-dihidro-1,3-benzotiazol-2-ilo, que pueden estar sustituidos con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes γ, y

el conjunto de sustituyentes γ comprende un átomo de halógeno, un grupo alquilo de C_1-C_6, un grupo alquilo de C_1-C_6 halogenado, un grupo alquilo de C_1-C_6 sustituido con 1 o 2 grupos hidroxi, un grupo alcoxi de C_1-C_6, un grupo carboxilo, un grupo mono-alquil(C_1-C_6)-aminocarbonilo, un grupo di-alquil(C_1-C_6)-aminocarbonilo y un grupo hidroxi;

(8) el compuesto o sal farmacológicamente aceptable de cualquiera de los incisos (1) a (3) anteriores, en donde el grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están unidos, y que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, es un grupo 1,3-tiazol-2-ilo, un grupo 5-metil-1,3-tiazol-2-ilo, un grupo 5-metil-1,3,4-oxadiazol-2-ilo, un grupo 4,5-dihidro-1,3-tiazol-2-ilo, un grupo 4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo 5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-etil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1R)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1S)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-4-hidroxi-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4-

hidroximetil-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5R)-5-hidroximetil-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo 5-carboxil-1,3-tiazol-2-ilo, un grupo 5-dimetilaminocarbonil-1,3-tiazol-2-ilo, un grupo 5-metil-1,3,4-tiadiazol-2-ilo, o un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo;

(9) el compuesto o sal farmacológicamente aceptable de cualquiera de los incisos (1) a (3) anteriores, en donde el grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están unidos, y que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, es un grupo 4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-etil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1R)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1S)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4-hidroximetil-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5R)-5-hidroximetil-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo 1,3-tiazol-2-ilo, un grupo 5-carboxil-1,3-tiazol-2-ilo, un grupo 5-dimetilaminocarbonil-1,3-tiazol-2-ilo, un grupo 5-metil-1,3,4-tiadiazol-2-ilo, un grupo 5-metil-1,3,4-oxadiazol-2-ilo, un grupo 4,5-dihidro-1,3-tiazol-2-ilo, o un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo;

(10) el compuesto o sal farmacológicamente aceptable de cualquiera de los incisos (1) a (3) anteriores, en donde el grupo heterocíclico

formado por A y R^1 junto con el átomo de carbono al que están unidos, y que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, es un grupo 4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-etil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1R)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1S)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4-hidroximetil-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, o un grupo (4R,5R)-5-hidroximetil-4-metil-4,5-dihidro-1,3-oxazol-2-ilo;

(11) el compuesto o sal farmacológicamente aceptable de cualquiera de los incisos (1) a (10) anteriores, en donde R^2 es un grupo fenilo que puede estar sustituido con 1 a 5 grupos seleccionados independientemente del conjunto de sustituyentes δ o un grupo 2-piridilo, 3-piridilo o 2-pirazinilo que pueden estar sustituidos con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes δ, y

el conjunto de sustituyentes δ comprende un átomo de halógeno, un grupo alquilo de C_1-C_6, un grupo alquilo de C_1-C_6 halogenado, un grupo alquilo de C_1-C_6 sustituido con 1 o 2 grupos hidroxi, un grupo alquilcarbonilo de C_2-C_7, un grupo alcoxicarbonilo de C_2-C_7, un grupo alquilsulfonilo de C_1-C_6, un grupo representado por la fórmula –V-NR^5R^6 (en donde V representa un

grupo carbonilo o un grupo sulfonilo, y R^5 y R^6 pueden ser iguales o diferentes y representan, respectivamente, un átomo de hidrógeno o un grupo alquilo de C_1-C_6, o R^5 y R^6, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros que puede estar sustituido con 1 o 2 grupos seleccionados independientemente de un grupo alquilo de C_1-C_6 y un grupo hidroxi, y el heterociclo saturado de 4 a 6 miembros puede contener también un átomo de oxígeno o un átomo de nitrógeno), un grupo 1,3,4-oxadiazol-2-ilo sustituido opcionalmente con un grupo alquilo de C_1-C_6 en la posición 5, y un grupo 1,3,4-tiadiazol-2-ilo sustituido opcionalmente con un grupo alquilo de C_1-C_6 en la posición 5;

(12) el compuesto o sal farmacológicamente aceptable de cualquiera de los incisos (1) a (10) anteriores, en donde R^2 es un grupo 4-metilsulfonilfenilo, un grupo 4-(1-azetidinil)carbonil-2-fluorofenilo, un grupo 2-fluoro-4-(1-pirrolidinil)carbonilfenilo, un grupo 5-(1-azetidinil)carbonil-3-cloro-2-piridilo, un grupo 2-metilsulfonil-5-piridilo, un grupo 5-(4-metil-1-piperazinil)carbonil-2-pirazinilo, un grupo 2-metilaminocarbonil-5-piridilo, un grupo 2-metilaminosulfonil-5-piridilo, o un grupo 5-metilsulfonil-2-pirazinilo;

(13) el compuesto o sal farmacológicamente aceptable de cualquiera de los incisos (1) a (10) anteriores, en donde R^2 es un grupo 4-metilsulfonilfenilo, un grupo 2-metilsulfonil-5-piridilo, un grupo 5-metilsulfonil-2-pirazinilo, o un grupo 5-(1-azetidinil)carbonil-3-cloro-2-piridilo.

(14) el compuesto o sal farmacológicamente aceptable de cualquiera de los incisos (1) a (13) anteriores, en donde R^3 es un grupo hidroxi

o un grupo metoxi;

(15) el compuesto o sal farmacológicamente aceptable del inciso (1) anterior, en donde la fórmula general (I) es la fórmula general (Ia), A es un átomo de oxígeno, R^1 es un grupo alquilo de C_1-C_6, un grupo alcoxi de C_1-C_6 o un grupo mono-alquilo halogenado (C_1-C_6)-amino, R^2 es un grupo fenilo que puede estar sustituido con 1 a 5 grupos seleccionados independientemente del conjunto de sustituyentes δ o un grupo 2-piridilo, un grupo 3-piridilo o un grupo 2-pirazinilo, que pueden estar sustituidos con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes δ, y R^3 es un grupo hidroxi o un grupo metoxi;

(16) el compuesto o sal farmacológicamente aceptable del inciso (1) anterior, en donde la fórmula general (I) es la fórmula general (Ia), A es un átomo de oxígeno, R^1 es un grupo metilo o un grupo 2-cloroetilamino, R^2 es un grupo 4-metilsulfonilfenilo, un grupo 4-(1-azetidinil)carbonil-2-fluorofenilo, un grupo 2-fluoro-4-(1-pirrolidinil)carbonilfenilo, un grupo 5-(1-azetidinil)carbonil-3-cloro-2-piridilo, un grupo 2-metilsulfonil-5-piridilo, un grupo 5-(4-metil-1-piperazinil)carbonil-2-pirazinilo, un grupo 2-metilaminocarbonil-5-piridilo, un grupo 2-metilaminosulfonil-5-piridilo, o un grupo 5-metilsulfonil-2-pirazinilo, y R^3 es un grupo hidroxi o un grupo metoxi;

(17) el compuesto o sal farmacológicamente aceptable del inciso (1) anterior, en donde la fórmula general (I) es la fórmula general (Ia), A es un átomo de oxígeno, R^1 es un grupo metilo o un grupo 2-cloroetilamino, R^2 es un grupo 4-metilsulfonilfenilo, un grupo 2-metilsulfonil-5-piridilo, un grupo 5-

metilsulfonil-2-pirazinilo, o un grupo 5-(1-azetidinil)carbonil-3-cloro-2-piridilo, y R^3 es un grupo hidroxi o un grupo metoxi;

(18) el compuesto o sal farmacológicamente aceptable del inciso (1) anterior, en donde la fórmula general (I) es la fórmula general (Ia), el grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están unidos y que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, es un grupo 2-piridilo, un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo, un grupo 1,3-tiazol-2-ilo, un grupo 1,3-oxazol-2-ilo, un grupo 1,3,4-oxadiazol-2-ilo, un grupo 1,3,4-tiadiazol-2-ilo, un grupo 4,5-dihidro-1,3-tiazol-2-ilo, un grupo 4,5-dihidro-1,3-oxazol-2-ilo, o un grupo 4,5-dihidro-1,3-benzotiazol-2-ilo, que pueden estar sustituidos con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes γ, R^3 es un grupo fenilo que puede estar sustituido con 1 a 5 grupos seleccionados independientemente del conjunto de sustituyentes δ, o un grupo 2-piridilo, un grupo 3-piridilo, o un grupo 2-pirazinilo que pueden estar sustituidos con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes δ, y R^3 es un grupo hidroxi o un grupo metoxi;

(19) el compuesto o sal farmacológicamente aceptable del inciso (1) anterior, en donde la fórmula general (I) es la fórmula general (Ia), el grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están unidos y que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, es un grupo 1,3-tiazol-2-

ilo, un grupo 5-metil-1,3-tiazol-2-ilo, un grupo 5-metil-1,3,4-oxadiazol-2-ilo, un grupo 4,5-dihidro-1,3-tiazol-2-ilo, un grupo 4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo 5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-etil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1R)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1S)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-4-hidroxi-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4-hidroximetil-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5R)-5-hidroximetil-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo 5-carboxil-1,3-tiazol-2-ilo, un grupo 5-dimetilaminocarbonil-1,3-tiazol-2-ilo, un grupo 5-metil-1,3,4-tiadiazol-2-ilo, o un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo, R^2 es un grupo 4-metilsulfonilfenilo, un grupo 4-(1-azetidinil)carbonil-2-fluorofenilo, un grupo 2-fluoro-4-(1-pirrolidinil)carbonilfenilo, un grupo 5-(1-azetidinil)carbonil-3-cloro-2-piridilo, un grupo 2-metilsulfonil-5-piridilo, un grupo 5-(4-metil-1-piperazinil)carbonil-2-pirazinilo, un grupo 2-metilaminocarbonil-5-piridilo, un grupo 2-metilaminosulfonil-5-piridilo, o un grupo 5-metilsulfonil-2-pirazinilo, y R^3 es un grupo hidroxi o un grupo metoxi;

(20) el compuesto o sal farmacológicamente aceptable del inciso (1) anterior, en donde la fórmula general (I) es la fórmula general (Ia), el grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están

unidos y que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, es un grupo 4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-etil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1R)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1S)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4-hidroximetil-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5R)-5-hidroximetil-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo 1,3-tiazol-2-ilo, un grupo 5-carboxil-1,3-tiazol-2-ilo, un grupo 5-dimetilaminocarbonil-1,3-tiazol-2-ilo, un grupo 5-metil-1,3,4-tiadiazol-2-ilo, un grupo 5-metil-1,3,4-oxadiazol-2-ilo, un grupo 4,5-dihidro-1,3-tiazol-2-ilo, o un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo, R^2 es un grupo 4-metilsulfonilfenilo, un grupo 2-metilsulfonil-5-piridilo, un grupo 5-metilsulfonil-2-pirazinilo, o un grupo 5-(1-azetidinil)carbonil-3-cloro-2-piridilo, y R^3 es un grupo hidroxi o un grupo metoxi;

(21) el compuesto o sal farmacológicamente aceptable del inciso (1) anterior, en donde la fórmula general (I) es la fórmula general (Ia), el grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están unidos y que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, es un grupo 4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo

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(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1R)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1S)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4-hidroximetil-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, o un grupo (4R,5R)-5-hidroximetil-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, R^2 es un grupo 4-metilsulfonilfenilo, un grupo 2-metilsulfonil-5-piridilo, un grupo 5-metilsulfonil-2-pirazinilo, o un grupo 5-(1-azetidinil)carbonil-3-cloro-2-piridilo, y R^3 es un grupo hidroxi o un grupo metoxi;

(22) el compuesto o sal farmacológicamente aceptable del inciso (1) anterior, en donde el compuesto representado por la fórmula general (I) es:

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-1,3-tiazol,

(2S)-2-{3-[4-(metilsulfonil)fenoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}propan-1-ol,

ácido 2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol-5-carboxílico,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-N,N-dimetil-1,3-tiazol-5-carboxamida,

1-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)etanona,

(2S)-2-{3-[5-(4,5-dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[4-

(metilsulfonil)fenoxi]fenoxi}propan-1-ol,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-5-metil-1,3,4-tiadiazol,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-tiazol,

(2S)-2-{3-[5-(4,5-dihidro-1,3-tiazol-2-il)-1H-pirrol-2-il]-5-[4-(metilsulfonil)fenoxi]fenoxi}propan-1-ol,

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[4-(metilsulfonil)fenoxi]fenoxi)propan-1-ol,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-5,6-dihidro-4H-1,3-oxazina,

(2S)-2-(3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]fenoxi)propan-1-ol,

(2S)-2-(3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

{(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}-metanol,

(2S)-2-(3-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-

il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

{(4R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}metanol,

(2S)-2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

{(4R,5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4-metil-4,5-dihidro-1,3-oxazol-5-il}metanol,

{(4R,5S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol,

(1S)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol,

(1R)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol,

(2S)-2-(3-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

{(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol,

(2S)-2-(3-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

{(4R,5S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol,

(1S)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol, o

(1R)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol;

(23) el compuesto o sal farmacológicamente aceptable del inciso (1) anterior, en donde el compuesto representado por la fórmula general (I) es:

(2S)-2-{3-[5-(4,5-dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[4-(metilsulfonil)fenoxi]fenoxi}propan-1-ol,

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[4-(metilsulfonil)fenoxi]fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

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{(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol,

(2S)-2-(3-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

{(4R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}metanol,

(2S)-2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

{(4R,5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4-metil-4,5-dihidro-1,3-oxazol-5-il}metanol,

{(4R,5S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol,

(1S)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol,

(1R)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol,

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

{(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)-

pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol,

(2S)-2-(3-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

{(4R,5S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol,

(1S)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol, o

(1R)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol;

(24) el compuesto descrito en el inciso (1) anterior, en donde el compuesto representado por la fórmula general (I) es:

(2S)-2-{3-[5-(4,5-dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[4-(metilsulfonil)fenoxi]fenoxi}propan-1-ol,

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[4-(metilsulfonil)fenoxi]fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-

il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

{(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol,

(2S)-2-(3-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

{(4R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}metanol,

(2S)-2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

{(4R,5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4-metil-4,5-dihidro-1,3-oxazol-5-il}metanol,

{(4R,5S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol,

(1S)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol,

(1R)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol,

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

{(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol,

(2S)-2-(3-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

{(4R,5S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol,

(1S)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol, o

(1R)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol;

(25) el compuesto o sal farmacológicamente aceptable del inciso (1) anterior, en donde el compuesto representado por la fórmula general (I) es:

1-(4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}fenil)etanona,

1-(4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}fenil)etanol,

1-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)etanona,

N-(2-cloroetil)-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida,

ácido 6-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)nicotínico,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-5,6-dihidro-4H-1,3-oxazina,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-1,3-tiazol,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-5-metil-1,3-tiazol,

[2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-1,3-tiazol-5-il]metanol,

ácido 2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]-fenil}-1H-pirrol-2-il)-1,3-tiazol-5-carboxílico,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-N,N-dimetil-1,3-tiazol-5-carboxamida,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-1,3-oxazol,

5-metoxi-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-1,3-oxazol,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-

fenil}-1H-pirrol-2-il)-5-metil-1,3,4-oxadiazol,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-5-metil-1,3,4-tiadiazol,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-tiazol,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol,

(5S)-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol,

(5R)-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5,5-dimetil-4,5-dihidro-1,3-oxazol,

[2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol-5-il]metanol,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-1,3-benzotiazol,

2-(5-{3-[4-(azetidin-1-ilsulfonil)fenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol,

3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzoato de metilo,

3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzamida,

3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-N-metilbenzamida,

3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-N,N-dimetilbenzamida,

2-(5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol,

2-(5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-5-metil-1,3,4-oxadiazol,

2-(5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol,

(5S)-2-(5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol,

2-(5-{3-[2-fluoro-4-(pirrolidin-1-ilcarbonil)fenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol,

4-(3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzoil)morfolina,

3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-N-metilbencenosulfonamida,

2-(5-{3-[4-(azetidin-1-ilsulfonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol,

2-(3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}fenil)-5-metil-1,3,4-oxadiazol,

2-(3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-

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1H-pirrol-2-il]fenoxi}fenil)-5-metil-1,3,4-tiadiazol,

2-(5-{3-[4-(azetidin-1-ilcarbonil)-2-metilfenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol,

2-(5-{3-[4-(azetidin-1-ilcarbonil)-2-(trifluorometil)fenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol,

5-(azetidin-1-ilcarbonil)-2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}piridina,

5-(azetidin-1-ilcarbonil)-3-cloro-2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}piridina,

5-(azetidin-1-ilcarbonil)-3-cloro-2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]fenoxi}piridina,

5-(azetidin-1-ilcarbonil)-3-cloro-2-{3-[5-(4,5-dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi}piridina,

5-(azetidin-1-ilcarbonil)-3-cloro-2-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)piridina,

5-(azetidin-1-ilcarbonil)-2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-3-metilpiridina,

5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-2-(metilsulfonil)piridina,

5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-2-(metilsulfonil)piridina,

2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-5-[(4-metilpiperazin-1-il)carbonil]pirazina,

5-(fluorometil)-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol,

(5R)-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5-(trifluorometil)-4,5-dihidro-1,3-oxazol,

[(5R)-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol-5-il]metanol,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-N,N-dimetil-4,5-dihidro-1,3-oxazol-5-carboxamida,

N-(2-cloroetil)-5-{3-[(1S)-2-hidroxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida,

(2S)-2-{3-[4-(metilsulfonil)fenoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}propan-1-ol,

(2S)-2-{3-[5-(4,5-dihidro-1,3-tiazol-2-il)-1H-pirrol-2-il]-5-[4-(metilsulfonil)fenoxi]fenoxi}propan-1-ol,

(2S)-2-{3-[5-(4,5-dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[4-(metilsulfonil)fenoxi]fenoxi}propan-1-ol,

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[4-(metilsulfonil)fenoxi]fenoxi)propan-1-ol,

(2S)-2-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]fenoxi}propan-1-ol,

(2S)-2-(3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)propan-1-ol,

(2S)-2-(3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[5-(5-

metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]fenoxi)propan-1-ol,

(2S)-2-(3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)propan-1-ol, o

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol;

(26) el compuesto o sal farmacológicamente aceptable del inciso (1) anterior, en donde el compuesto representado por la fórmula general (I) es:

1-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)etanona,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-1,3-tiazol,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-5-metil-1,3-tiazol,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-tiazol,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol,

(5S)-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol,

(5R)-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol,

[2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol-5-il]metanol,

2-(5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol,

2-(5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol,

(5S)-2-(5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol,

2-(5-{3-[2-fluoro-4-(pirrolidin-1-ilcarbonil)fenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol,

5-(azetidin-1-ilcarbonil)-3-cloro-2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}piridina,

5-(azetidin-1-ilcarbonil)-3-cloro-2-{3-[5-(4,5-dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi}piridina,

5-(azetidin-1-ilcarbonil)-3-cloro-2-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)piridina,

5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-2-(metilsulfonil)piridina,

5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-2-(metilsulfonil)piridina,

2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-5-[(4-metilpiperazin-1-il)carbonil]pirazina,

[(5R)-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol-5-il]metanol,

(2S)-2-{3-[4—(metilsulfonil)fenoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-

2-il)]fenoxi_]}propan-1-ol,

(2S)-2-{3-[5-(4,5-dihidro-1,3-tiazol-2-il)-1H-pirrol-2-il]-5-[4-(metilsulfonil)fenoxi]fenoxi}propan-1-ol,

(2S)-2-{3-[5-(4,5-dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[4-(metilsulfonil)fenoxi]fenoxi}propan-1-ol,

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[4-(metilsulfonil)fenoxi]fenoxi)propan-1-ol,

(2S)-2-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]fenoxi}propan-1-ol,

(2S)-2-(3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)propan-1-ol,

(2S)-2-(3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)propan-1-ol, o

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol;

(27) el compuesto descrito en el inciso (1) anterior, en donde el compuesto representado por la fórmula general (I) es:

1-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)etanona,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-1,3-tiazol,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-5-metil-1,3-tiazol,

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2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-tiazol,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol,

(5S)-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol,

(5R)-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol,

[2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol-5-il]metanol,

2-(5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol,

2-(5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol,

(5S)-2-(5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol,

2-(5-{3-[2-fluoro-4-(pirrolidin-1-ilcarbonil)fenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol,

5-(azetidin-1-ilcarbonil)-3-cloro-2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}piridina,

5-(azetidin-1-ilcarbonil)-3-cloro-2-{3-[5-(4,5-dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi}piridina,

5-(azetidin-1-ilcarbonil)-3-cloro-2-(3-[(1S)-2-metoxi-1-metiletoxi]-

5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)piridina,

5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-2-(metilsulfonil)piridina,

5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-2-(metilsulfonil)piridina,

2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-5-[(4-metilpiperazin-1-il)carbonil]pirazina,

[(5R)-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol-5-il]metanol,

(2S)-2-{3-[4-(metilsulfonil)fenoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]}fenoxi]}propan-1-ol,

(2S)-2-{3-[5-(4,5-dihidro-1,3-tiazol-2-il)-1H-pirrol-2-il]-5-[4-(metilsulfonil)fenoxi]fenoxi}propan-1-ol,

(2S)-2-{3-[5-(4,5-dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[4-(metilsulfonil)fenoxi]fenoxi}propan-1-ol,

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[4-(metilsulfonil)fenoxi]fenoxi)propan-1-ol,

(2S)-2-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]fenoxi}propan-1-ol,

(2S)-2-(3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)propan-1-ol,

(2S)-2-(3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)propan-1-ol, o

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(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol;

(28) el compuesto o sal farmacológicamente aceptable del inciso (1) anterior, en donde el compuesto representado por la fórmula general (I) es:

(2S)-2-(3-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

{(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol,

(2S)-2-(3-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

{(4R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}metanol,

(2S)-2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

{(4R,5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4-metil-4,5-dihidro-1,3-oxazol-5-il}metanol,

{(4R,5S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol,

(1S)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol,

(1R)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol,

(2S)-2-(3-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

{(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol,

(5S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-ol,

(2S)-2-(3-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

{(4R,5S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol,

(1S)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol,

(1R)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol,

5-(3-[(1S)-2-Hidroxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-N-metilpiridin-2-sulfonamida,

5-(3-[(1S)-2-hidroxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-N-metilpiridin-2-carboxamida,

5-(3-{5-[(5R)-5-(hidroximetil)-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)-N-metilpiridin-2-carboxamida, o

5-(3-{5-[(5R)-5-(hidroximetil)-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)-N-metilpiridin-2-sulfonamida;

(29) el compuesto o sal farmacológicamente aceptable del inciso (1) anterior, en donde el compuesto representado por la fórmula general (I) es:

{(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol,

(2S)-2-(3-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

{(4R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}metanol,

(2S)-2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

{(4R,5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4-metil-4,5-dihidro-1,3-oxazol-5-il}metanol,

{(4R,5S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol,

(1S)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol,

(1R)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol,

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

{(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol,

(2S)-2-(3-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

{(4R,5S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol,

(1S)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol, o

(1R)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol;

(30) el compuesto descrito en el inciso (1) anterior, en donde el compuesto representado por la fórmula general (I) es:

{(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol,

(2S)-2-(3-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

{(4R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}metanol,

(2S)-2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

{(4R,5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4-metil-4,5-dihidro-1,3-oxazol-5-il}metanol,

{(4R,5S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol,

(1S)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-

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(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol,

(1R)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol,

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

{(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol,

(2S)-2-(3-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

{(4R,5S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol,

(1S)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol, o

(1R)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-

il}etanol;

(31) un activador de glucocinasa que contiene como ingrediente activo un compuesto o sal farmacológicamente aceptable que se describen en cualquiera de los incisos (1) a (30) anteriores;

(32) una composición farmacéutica que contiene como ingrediente activo un compuesto o sal farmacológicamente aceptable que se describen en cualquiera de los incisos (1) a (30) anteriores

(33) la composición farmacéutica que se describe en el inciso (32) anterior, que tiene actividad activadora de glucocinasa;

(34) la composición farmacéutica que se describe en el inciso (32) anterior, para el tratamiento o prevención de una enfermedad que se puede tratar o prevenir activando la glucocinasa;

(35) la composición farmacéutica que se describe en el inciso (32) anterior, para el tratamiento o prevención de una enfermedad cuyos síntomas se tratan, mejoran, disminuyen o se previenen por activación de la glucocinasa y mantenimiento de la homeostasis de la glucosa o regulación de la concentración de glucosa en la sangre;

(36) la composición farmacéutica que se describe en el inciso (32) anterior, para el tratamiento o prevención de la diabetes, deterioro de tolerancia a la glucosa, diabetes gestacional, complicaciones crónicas de la diabetes (que incluyen neuropatía periférica diabética, nefropatía diabética, retinopatía diabética y macroangiopatía diabética), o síndrome metabólico;

(37) la composición farmacéutica que se describe en el inciso

(32) anterior, para el tratamiento o prevención de la diabetes o el deterioro de tolerancia a la glucosa;

(38) el uso de un compuesto o sal farmacológicamente aceptable que se describen en cualquiera de los incisos (1) a (30) anteriores, para producir una composición farmacéutica;

(39) el uso que se describe en el inciso (38) anterior, en donde la composición farmacéutica es una composición para activar la glucocinasa;

(40) el uso que se describe en el inciso (38) anterior, en donde la composición farmacéutica es una composición para el tratamiento o prevención de la diabetes, deterioro de tolerancia a la glucosa, diabetes gestacional, complicaciones crónicas de la diabetes (que incluyen neuropatía periférica diabética, nefropatía diabética, retinopatía diabética y macroangiopatía diabética), o síndrome metabólico;

(41) el uso que se describe en el inciso (38) anterior, en donde la composición farmacéutica es una composición para el tratamiento o prevención de la diabetes o el deterioro de tolerancia a la glucosa;

(42) un método de activación de glucocinasa, que comprende administrar a un animal de sangre caliente una cantidad farmacológicamente efectiva de un compuesto o sal farmacológicamente aceptable que se describen en cualquiera de los incisos (1) a (30) anteriores;

(43) un método de tratamiento o prevención de una enfermedad, que comprende administrar a un animal de sangre caliente una cantidad farmacológicamente efectiva de un compuesto o sal farmacológicamente

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aceptable que se describen en cualquiera de los incisos (1) a (30) anteriores;

(44) el método que se describe en el inciso (43) anterior, en donde la enfermedad es la diabetes, deterioro de tolerancia a la glucosa, diabetes gestacional, complicaciones crónicas de la diabetes (que incluyen neuropatía periférica diabética, nefropatía diabética, retinopatía diabética y macroangiopatía diabética), o síndrome metabólico;

(45) el método que se describe en el inciso (43) anterior, en donde la enfermedad es la diabetes o el deterioro de tolerancia a la glucosa; y

(46) el método que se describe en cualquiera de los incisos (42) a (45) anteriores, en donde el animal de sangre caliente es un humano.

En la presente invención, un "átomo de halógeno" se refiere a un átomo de flúor, un átomo de cloro, un átomo de bromo o un átomo yodo. Preferiblemente, el átomo de halógeno es un átomo de flúor o un átomo de cloro, de preferencia un átomo de cloro.

En la presente invención, un "grupo alquilo de C_1-C_6" se refiere a un grupo alquilo lineal o ramificado que tiene de 1 a 6 átomos de carbono. Ejemplos del grupo alquilo incluyen un grupo metilo, un grupo etilo, un grupo propilo, un grupo isopropilo, un grupo butilo, un grupo isobutilo, un grupo s-butilo, un grupo t-butilo, un grupo pentilo, un grupo isopentilo, un grupo 2-metilbutilo, un grupo neopentilo, un grupo 1-etilpropilo, un grupo hexilo, un grupo isohexilo, un grupo 4-metilpentilo, un grupo 3-metilpentilo, un grupo 2-metilpentilo, un grupo 1-metilpentilo, un grupo 3,3-dimetilbutilo, un grupo 2,2-dimetilbutilo, un grupo 1,1-dimetilbutilo, y un grupo 1,2-dimetilbutilo, y

preferiblemente el grupo alquilo de C_1-C_6 es un grupo alquilo lineal o ramificado que tiene de 1 a 4 átomos de carbono (grupo alquilo de C_1-C_4), de preferencia un grupo metilo o un grupo etilo (grupo alquilo de C_1-C_2), y muy de preferencia un grupo metilo.

En la presente invención, un "grupo de alquilo de C_1-C_6 halogenado" se refiere a un grupo en el cual están unidos de 1 a 5 de los "átomos de halógeno" anteriormente mencionados, iguales o diferentes, al "grupo alquilo de C_1-C_6" anteriormente mencionado. Ejemplos de los grupos de alquilo de C_1-C_6 halogenado incluyen un grupo trifluorometilo, un grupo triclorometilo, un grupo difluorometilo, un grupo diclorometilo, un grupo dibromometilo, un grupo fluorometilo, un grupo 2,2,2-trifluoroetilo, un grupo 2,2,2-tricloroetilo, un grupo 2-bromoetilo, un grupo 2-cloroetilo y un grupo 2-fluoroetilo; preferiblemente, el grupo alquilo de C_1-C_6 halogenado es un grupo en el que están unidos de 1 a 5 de los "átomos de halógeno" anteriormente mencionados, iguales o diferentes, al "grupo alquilo de C_1-C_4" anteriormente mencionado (grupo alquilo de C_1-C_4 halogenado), de preferencia un grupo en el que están unidos de 1 a 5 de los "átomos de halógeno" anteriormente mencionados, iguales o diferentes, al "grupo alquilo de C_1-C_2" anteriormente mencionado (grupo alquilo de C_1-C_2 halogenado), muy de preferencia un grupo trifluorometilo o un grupo fluorometilo.

En la presente invención, un "grupo alquenilo de C_2-C_6" se refiere a un "grupo alquilo de C_1-C_6" anteriormente mencionado que tiene un enlace doble y de 2 a 6 átomos de carbono. Ejemplos del grupo alquenilo de C_2-C_6

incluyen un grupo etenilo, un grupo 1-propenilo, un grupo 2-propenilo, un grupo 1-metil-2-propenilo, un grupo 1-metil-1-propenilo, un grupo 2-metil-1-propenilo, un grupo 2-metil-2-propenilo, un grupo 1-butenilo, un grupo 2-butenilo, un grupo 3-butenilo, un grupo 1-pentenilo, un grupo 4-pentenilo, un grupo 1-metil-4-pentenilo y un grupo 5-hexenilo; preferiblemente, el grupo alquenilo de C_2-C_6 es un grupo alquenilo que tiene de 2 a 4 átomos de carbono (grupo alquenilo de C_2-C_4), y muy de preferencia un grupo 2-propenilo.

En la presente invención, un "grupo alquinilo de C_2-C_6" se refiere a un "grupo alquilo de C_1-C_6" anteriormente mencionado que tiene un enlace triple y de 2 a 6 átomos de carbono. Ejemplos del grupo alquinilo de C_2-C_6 incluyen un grupo etinilo, un grupo 1-propinilo, un grupo 2-propinilo, un grupo 1-metil-2-propinilo, un grupo 1-butinilo, un grupo 2-butinilo, un grupo 1-metil-2-butinilo, un grupo 3-butinilo, un grupo 2-pentinilo y un grupo 5-hexinilo; preferiblemente, el grupo alquinilo de C_2-C_6 es un grupo alquinilo que tiene de 2 a 4 átomos de carbono (grupo alquinilo de C_2-C_4), y muy de preferencia un grupo 2-propinilo o un grupo 2-butinilo.

En la presente invención, un "grupo alquilo de C_1-C_6 sustituido con 1 o 2 grupos hidroxi" se refiere a un grupo en el que están unidos 1 o 2 grupos hidroxi al "grupo alquilo de C_1-C_6" anteriormente mencionado. Ejemplos del grupo alquilo de C_1-C_6 sustituido con 1 o 2 grupos hidroxi incluyen un grupo hidroximetilo, un grupo 2-hidroxietilo, un grupo 1-hidroxietilo, un grupo 3-hidroxipropilo, un grupo 1,2-dihidroxietilo y un grupo

2,3-dihidroxipropilo; preferiblemente, el grupo alquilo de C_1-C_6 sustituido con 1 o 2 grupos hidroxi es un grupo en el que 1 o 2 grupos hidroxi están unidos al "grupo alquilo de C_1-C_4" anteriormente mencionado, de preferencia un grupo en el que están unidos 1 o 2 grupos hidroxi al "grupo alquilo de C_1-C_2" anteriormente mencionado, de preferencia un grupo hidroximetilo o un grupo hidroxietilo.

En la presente invención, un "grupo alcoxi de C_1-C_6" se refiere a un grupo en donde el "grupo alquilo de C_1-C_6" anteriormente mencionado está unido a un átomo de oxígeno, y es un grupo alcoxi lineal o ramificado que tiene de 1 a 6 átomos de carbono. Ejemplos del grupo alcoxi de C_1-C_6 incluyen un grupo metoxi, un grupo etoxi, un grupo propoxi, un grupo isopropoxi, un grupo butoxi, un grupo isobutoxi, un grupo s-butoxi, un grupo t-butoxi, un grupo pentoxi, un grupo 2-metilbutoxi, un grupo 3-etilpropoxi, un grupo neopentoxi, un grupo hexiloxi y un grupo 2,3-dimetilbutoxi; preferiblemente, el grupo alcoxi de C_1-C_6 es un grupo alcoxi lineal o ramificado que tiene de 1 a 4 átomos de carbono (grupo alcoxi de C_1-C_4), de preferencia un grupo metoxi, un grupo etoxi, un grupo propoxi o un grupo isopropoxi (grupo alcoxi de C_1-C_3), de preferencia un grupo metoxi o un grupo etoxi (grupo alcoxi de C_1-C_2), y en particular preferiblemente un grupo metoxi.

En la presente invención, un "grupo alcoxi de C_1-C_6 halogenado" se refiere a un grupo en donde están unidos de 1 a 5 de los "átomos de halógeno" anteriormente mencionados, iguales o diferentes, al "grupo alcoxi de C_1-C_6" anteriormente mencionado. Ejemplos del grupo alcoxi de C_1-C_6

halogenado incluyen un grupo trifluorometoxi, un grupo triclorometoxi, un grupo difluorometoxi, un grupo diclorometoxi, un grupo dibromometoxi, un grupo fluorometoxi, un grupo 2,2,2-trifluoroetoxi, un grupo 2,2,2-tricloroetoxi, un grupo 2-cloroetoxi, un grupo 2-fluoroetoxi y un grupo pentafluoroetoxi; preferiblemente, el grupo alcoxi de C_1-C_6 halogenado es un grupo en el que están unidos de 1 a 5 de los "átomos de halógeno" anteriormente mencionados, iguales o diferentes, al grupo "alcoxi de C_1-C_4" anteriormente mencionado (grupo alcoxi de C_1-C_4 halogenado), de preferencia un grupo en el que están unidos de 1 a 5 de los "átomos de halógeno" anteriormente mencionados, iguales o diferentes, al "grupo alcoxi de C_1-C_2" anteriormente mencionado (grupo alcoxi de C_1-C_2 halogenado), muy de preferencia un grupo trifluorometoxi.

En la presente invención, un "grupo alcoxi(C_1-C_6)-alquilo(C_1-C_6)" se refiere a un grupo en donde un "grupo alcoxi de C_1-C_6" anteriormente mencionado está unido al "grupo alquilo de C_1-C_6" anteriormente mencionado. Ejemplos del grupo alcoxi(C_1-C_6)-alquilo(C_1-C_6) incluyen un grupo metoximetilo, un grupo etoximetilo, un grupo propoximetilo, un grupo isopropoximetilo, un grupo butoximetilo, un grupo s-butoximetilo, un grupo t-butoximetilo, un grupo 2-metoxietilo y un grupo 3-isopropoxipropilo; preferiblemente, el grupo alcoxi(C_1-C_6)-alquilo(C_1-C_6) es un grupo en donde un "grupo alcoxi de C_1-C_4" anteriormente mencionado está unido al "grupo alquilo de C_1-C_4" anteriormente mencionado (grupo alcoxi(C_1-C_4)-alquilo(C_1-C_4)), de preferencia un grupo en donde un "grupo alcoxi de C_1-C_2" anteriormente

mencionado está unido al "grupo alquilo de C_1-C_2" anteriormente mencionado (grupo alcoxi(C_1-C_2)-alquilo(C_1-C_2)), muy de preferencia un grupo metoximetilo.

En la presente invención, un "grupo alcoxi(C_1-C_6)-alcoxi(C_1-C_6) se refiere a un grupo en donde un "grupo alcoxi de C_1-C_6" anteriormente mencionado está unido al "grupo alcoxi de C_1-C_6" anteriormente mencionado. Ejemplos del grupo alcoxi(C_1-C_6)-alcoxi(C_1-C_6) incluyen un grupo etoximetiloxi, un grupo propoximetiloxi, un grupo butoximetiloxi, un grupo 2-metoxietiloxi y un grupo 3-isopropoxipropiloxi; preferiblemente, el grupo alcoxi(C_1-C_6)-alcoxi(C_1-C_6) es un grupo en donde un "grupo alcoxi de C_1-C_4" anteriormente mencionado está unido al "grupo alcoxi de C_1-C_4" anteriormente mencionado (grupo alcoxi(C_1-C_4)-alcoxi(C_1-C_4)), de preferencia un grupo en donde un "grupo alcoxi de C_1-C_2" anteriormente mencionado está unido al "grupo alcoxi de C_1-C_2" anteriormente mencionado (grupo alcoxi(C_1-C_2)-alcoxi(C_1-C_2)), muy de preferencia un grupo metoximetiloxi.

En la presente invención, un "grupo alquilcarbonilo de C_2-C_7" se refiere a un grupo en donde un "grupo alquilo de C_1-C_6" anteriormente mencionado está unido a un grupo carbonilo. Ejemplos del grupo alquilcarbonilo de C_2-C_7 incluyen un grupo acetilo, un grupo propionilo, un grupo butirilo, un grupo isobutirilo, un grupo pentanoilo, un grupo pivaloilo y un grupo valerilo; preferiblemente, el grupo alquilcarbonilo de C_2-C_7 es un grupo en donde un "grupo alquilo de C_1-C_4" anteriormente mencionado está unido a un grupo carbonilo (grupo alquilcarbonilo de C_2-C_5), de preferencia un grupo

acetilo o un grupo propionilo (grupo alquilcarbonilo de C_2-C_3), de preferencia un grupo acetilo.

En la presente invención, un "grupo alcoxicarbonilo de C_2-C_7" se refiere a un grupo en donde un "grupo alcoxi de C_1-C_6" anteriormente mencionado está unido a un grupo carbonilo. Ejemplos del grupo alcoxicarbonilo de C_2-C_7 incluyen un grupo metoxicarbonilo, un grupo etoxicarbonilo, un grupo propoxicarbonilo, un grupo isopropoxicarbonilo, un grupo butoxicarbonilo, un grupo isobutoxicarbonilo, un grupo s-butoxicarbonilo y un grupo t-butoxicarbonilo; preferiblemente, el grupo alcoxicarbonilo de C_2-C_7 es un grupo en donde un "grupo alcoxi de C_1-C_4" anteriormente mencionado está unido a un grupo carbonilo (grupo alcoxicarbonilo de C_2-C_5), de preferencia un grupo metoxicarbonilo o un grupo etoxicarbonilo (grupo alcoxicarbonilo de C_2-C_3), de preferencia un grupo metoxicarbonilo.

En la presente invención, un "grupo alquilcarboniloxi de C_2-C_7" se refiere a un grupo en donde el grupo carbonilo al que está unido un "grupo alquilo de C_1-C_6" anteriormente mencionado, está unido a un átomo de oxígeno. Ejemplos del grupo alquilcarboniloxi de C_2-C_7 incluyen un grupo acetoxi, un grupo propioniloxi, un grupo butiriloxi, un grupo isobutiriloxi, un grupo pentanoiloxi, un grupo pivaloiloxi, un grupo valeriloxi y un grupo isovaleriloxi; preferiblemente, el grupo alquilcarboniloxi de C_2-C_7 es un grupo en donde el grupo carbonilo al que está unido un "grupo alquilo de C_1-C_4" anteriormente mencionado está unido a un átomo de oxígeno (grupo alquilcarboniloxi de C_2-C_5), de preferencia un grupo acetoxi o un grupo

propioniloxi (grupo alquilcarboniloxi de C_2-C_3), muy de preferencia un grupo acetoxi.

En la presente invención, un "grupo alcoxicarboniloxi de C_2-C_7" se refiere a un grupo en donde el grupo carbonilo al que está unido el "grupo alcoxi de C_1-C_6" anteriormente mencionado, está unido a un átomo de oxígeno. Ejemplos del grupo alcoxicarboniloxi de C_2-C_7 incluyen un grupo metoxicarboniloxi, un grupo etoxicarboniloxi, un grupo propoxicarboniloxi, un grupo isopropoxicarboniloxi, un grupo butoxicarboniloxi, un grupo s-butoxicarboniloxi y un grupo t-butoxicarboniloxi; preferiblemente, el grupo alcoxicarboniloxi de C_2-C_7 es un grupo en donde un grupo carbonilo al que está unido un "grupo alcoxi de C_1-C_4" anteriormente mencionado, está unido a un átomo de oxígeno (grupo alcoxicarboniloxi de C_2-C_5), de preferencia un grupo metoxicarboniloxi o un grupo etoxicarboniloxi (grupo alcoxicarboniloxi de C_2-C_3), muy de preferencia un grupo metoxicarboniloxi.

En la presente invención, un "grupo mono-alquil(C_1-C_6)-amino" se refiere a un grupo en donde un "grupo alquilo de C_1-C_6" anteriormente mencionado está unido a un grupo amino. Ejemplos del grupo mono-alquil(C_1-C_6)-amino incluyen un grupo metilamino, un grupo etilamino, un grupo propilamino, un grupo isopropilamino, un grupo butilamino, un grupo isobutilamino, un grupo s-butilamino, un grupo t-butilamino, un grupo pentilamino, un grupo isopentilamino, un grupo 2-metilbutilamino, un grupo neopentilamino, un grupo 1-etilpropilamino, un grupo hexilamino y un grupo isohexilamino; preferiblemente, el grupo mono-alquil(C_1-C_6)-amino es un

grupo en donde el "grupo alquilo de C_1-C_4" anteriormente mencionado está unido a un grupo amino (grupo mono-alquil(C_1-C_4)-amino), de preferencia un grupo metilamino o un grupo etilamino (grupo mono-alquil(C_1-C_2)-amino), muy de preferencia un grupo metilamino.

En la presente invención, un "grupo mono-alquilo halogenado (C_1-C_6)-amino" se refiere a un grupo en donde un "grupo alquilo de C_1-C_6 halogenado" anteriormente mencionado está unido a un grupo amino. Ejemplos del grupo mono-alquilo halogenado (C_1-C_6)-amino incluyen un grupo trifluorometilamino, un grupo triclorometilamino, un grupo difluorometilamino, un grupo diclorometilamino, un grupo dibromometilamino, un grupo fluorometilamino, un grupo 2,2,2-trifluoroetilamino, un grupo 2,2,2-tricloroetilamino, un grupo 2-bromoetilamino, un grupo 2-cloroetilamino y un grupo 2-fluoroetilamino; preferiblemente, el grupo mono-alquilo halogenado (C_1-C_6)-amino es un grupo en donde un "grupo alquilo de C_1-C_4 halogenado" está unido a un grupo amino (grupo mono-alquilo halogenado (C_1-C_4)-amino), de preferencia un grupo en donde un "grupo alquilo de C_1-C_2 halogenado" anteriormente mencionado está unido a un grupo amino (grupo mono-alquilo halogenado (C_1-C_2)-amino), muy de preferencia un grupo 2-cloroetilamino.

En la presente invención, un "grupo di-alquil(C_1-C_6)-amino" se refiere a un grupo en donde dos grupos "alquilo de C_1-C_6" anteriormente mencionados, iguales o diferentes, están unidos a un grupo amino. Ejemplos del grupo di-alquil(C_1-C_6)-amino incluyen un grupo dimetilamino, un grupo dietilamino, un grupo dipropilamino, un grupo diisopropilamino, un grupo

dibutilamino, un grupo diisobutilamino, un grupo dipentilamino, un grupo diisopentilamino, un grupo dineopentilamino, un grupo dihexilamino, un grupo N-etil-N-metilamino, un grupo N-metil-N-propilamino, un grupo N-isopropil-N-metilamino, un grupo N-butil-N-metilamino, un grupo N-isobutil-N-metilamino, un grupo N-metil-N-pentilamino, un grupo N-isopentil-N-metilamino, un grupo N-etil-N-propilamino, un grupo N-etil-N-isopropilamino, un grupo N-butil-N-etilamino y un grupo N-etil-N-isopentilamino; preferiblemente, el grupo di-alquil(C_1-C_6)-amino es un grupo en donde dos grupos "alquilo de C_1-C_4" anteriormente mencionados están unidos a un grupo amino (grupo di-alquil(C_1-C_4)-amino), de preferencia un grupo dimetilamino, dietilamino o N-etil-N-metilamino (grupo di-alquil(C_1-C_2)-amino), y muy de preferencia un grupo dimetilamino.

En la presente invención, un "grupo di-alquilo halogenado (C_1-C_6)-amino" se refiere a un grupo en donde dos grupos de "alquilo de C_1-C_6 halogenado" anteriormente mencionados, iguales o diferentes, están unidos a un grupo amino. Ejemplos del grupo "di-alquilo halogenado (C_1-C_6)-amino" incluyen un grupo di-(trifluorometil)amino, un grupo di-(fluorometil)amino, un grupo di-(2,2,2-tricloroetil)amino, un grupo di-(2-cloroetil)amino y un grupo N-(2-cloroetil)-N-(2-fluoroetil)amino; preferiblemente, el grupo di-alquilo halogenado (C_1-C_6)-amino es un grupo en donde dos grupos de "alquilo de C_1-C_4 halogenado" anteriormente mencionados, iguales o diferentes, están unidos a un grupo amino (grupo di-alquilo halogenado (C_1-C_4)-amino), de preferencia un grupo di-(2-cloroetil)-amino.

En la presente invención, un "grupo alquiltio de C_1-C_6" se refiere a un grupo en donde un "grupo alquilo de C_1-C_6" anteriormente mencionado está unido a un átomo de azufre, y es un grupo alquiltio lineal o ramificado que tiene de 1 a 6 átomos de carbono. Ejemplos del grupo alquiltio de C_1-C_6 incluyen un grupo metiltio, un grupo etiltio, un grupo propiltio, un grupo isopropiltio, un grupo butiltio, un grupo isobutiltio, un grupo s-butiltio, un grupo pentiltio, un grupo 1-etilpropiltio y un grupo hexiltio; preferiblemente, el grupo alquiltio de C_1-C_6 es un alquiltio lineal o ramificado que tiene de 1 a 4 átomos de carbono (grupo alquiltio de C_1-C_4), de preferencia un grupo metiltio o un grupo etiltio (grupo alquiltio de C_1-C_2), y muy de preferencia un grupo metiltio.

En la presente invención, un "grupo alquilsulfonilo de C_1-C_6" se refiere a un grupo en donde un "grupo alquilo de C_1-C_6" anteriormente mencionado está unido a un grupo sulfonilo, y es un grupo alquilsulfonilo lineal o ramificado que tiene de 1 a 6 átomos de carbono. Ejemplos del grupo alquilsulfonilo de C_1-C_6 incluyen un grupo metilsulfonilo, un grupo etilsulfonilo, un grupo propilsulfonilo, un grupo isopropilsulfonilo, un grupo butilsulfonilo, un grupo isobutilsulfonilo, un grupo s-butilsulfonilo y un grupo pentilsulfonilo; preferiblemente, el grupo alquilsulfonilo de C_1-C_6 es un grupo alquilsulfonilo lineal o ramificado que tiene de 1 a 4 átomos de carbono (grupo alquilsulfonilo de C_1-C_4), de preferencia un grupo metilsulfonilo o un grupo etilsulfonilo (grupo alquilsulfonilo de C_1-C_2), y muy de preferencia un grupo metilsulfonilo.

En la presente invención, un "grupo cicloalquilsulfonilo de C_3-C_6" se refiere a un grupo ciclopropilsulfonilo, un grupo ciclobutilsulfonilo, un grupo

ciclopentilsulfonilo, o un grupo ciclohexilsulfonilo. El grupo cicloalquilsulfonilo de C_3-C_6 es preferiblemente un grupo ciclopropilsulfonilo.

En la presente invención, un "grupo hidroxialquilsulfonilo de C_1-C_6" se refiere a un grupo en donde un "grupo alquilo de C_1-C_6" anteriormente mencionado que está unido a un grupo hidroxi, está unido a un grupo sulfonilo, y es un grupo hidroxialquilsulfonilo lineal o ramificado que tiene de 1 a 6 átomos de carbono. Ejemplos del grupo hidroxialquilsulfonilo de C_1-C_6 incluyen un grupo hidroximetilsulfonilo, un grupo 2-hidroxietilsulfonilo, un grupo 1-hidroxietilsulfonilo y un grupo 3-hidroxipropilsulfonilo; preferiblemente, el grupo hidroxialquilsulfonilo es un grupo hidroxialquilsulfonilo lineal o ramificado que tiene de 1 a 4 átomos de carbono (grupo hidroxialquilsulfonilo de C_1-C_4), de preferencia un grupo hidroximetilsulfonilo o un grupo hidroxietilsulfonilo (grupo hidroxialquilsulfonilo de C_1-C_2), muy de preferencia un grupo hidroximetilsulfonilo.

En la presente invención, un "grupo alcoxi(C_1-C_6)-alquilsulfonilo(C_1-C_6)" se refiere a un grupo en donde un "grupo alcoxi de C_1-C_6" anteriormente mencionado está unido al "grupo alquilsulfonilo de C_1-C_6" anteriormente mencionado. Ejemplos del grupo alcoxi(C_1-C_6)-alquilsulfonilo(C_1-C_6) incluyen un grupo metoximetilsulfonilo, un grupo etoximetilsulfonilo, un grupo propoximetilsulfonilo, un grupo isopropoximetilsulfonilo, un grupo butoximetilsulfonilo y un grupo s-butoximetilsulfonilo; preferiblemente, el grupo alcoxi(C_1-C_6)-alquilsulfonilo(C_1-C_6) es un grupo en donde el "grupo alcoxi de C_1-C_4" anteriormente

mencionado está unido al "grupo alquilsulfonilo de C_1-C_4" anteriormente mencionado (grupo alcoxi(C_1-C_4)-alquilsulfonilo(C_1-C_4)), de preferencia un grupo en donde un "grupo alcoxi de C_1-C_2" anteriormente mencionado está unido al "grupo alquilsulfonilo de C_1-C_2" anteriormente mencionado (grupo alcoxi(C_1-C_2)-alquilsulfonilo(C_1-C_2)), muy de preferencia un grupo metoximetilsulfonilo.

En la presente invención, un "grupo representado por la fórmula –V-NR^5R^6 (en donde V representa un grupo carbonilo o un grupo sulfonilo y R^5 y R^6 pueden ser iguales o diferentes y representan respectivamente un átomo de hidrógeno o un grupo alquilo de C_1-C_6, o R^5 y R^6, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros que puede estar sustituido con 1 o 2 grupos seleccionados independientemente de un grupo alquilo de C_1-C_6 y un grupo hidroxi, y el heterociclo saturado de 4 a 6 miembros puede contener también un átomo de oxígeno o un átomo de nitrógeno)", se refiere a un "grupo representado por la fórmula –C(=O)-NR^5R^6" o un "grupo representado por la fórmula –SO_2-NR^5R^6", el "grupo representado por la fórmula –C(=O)-NR^5R^6" es un grupo carbamoilo, un grupo "mono-alquil(C_1-C_6)aminocarbonilo (grupo en donde un grupo amino al que está unido un "grupo alquilo de C_1-C_6" anteriormente mencionado, está unido a un grupo carbonilo)", un grupo "di-alquil(C_1-C_6)-aminocarbonilo (grupo en donde un grupo amino al que están unidos dos de los "grupos alquilo de C_1-C_6" anteriormente mencionados, iguales o diferentes, está unido a un grupo carbonilo)", o un "grupo en donde un átomo de

nitrógeno de un heterociclo saturado de 4 a 6 miembros, que puede estar sustituido con 1 o 2 grupos seleccionados independientemente de un grupo alquilo de C_1-C_6 y un grupo hidroxi (grupo heterocíclico saturado de 4 a 6 miembros completamente reducido que contiene un átomo de nitrógeno y puede contener también un átomo de oxígeno o un átomo de nitrógeno), está unido a un grupo carbonilo", y el "grupo representado por la fórmula $-SO_2-NR^5R^6$" es un grupo sulfamoilo, un "grupo mono-alquil(C_1-C_6)-aminosulfonilo (grupo en donde un grupo amino al que está unido un "grupo alquilo de C_1-C_6" anteriormente mencionado está unido a un grupo sulfonilo", un "grupo di-alquil(C_1-C_6)-aminosulfonilo (grupo en donde un grupo amino al que están unidos dos de los "grupos alquilo de C_1-C_6" anteriormente mencionados, iguales o diferentes, está unido a un grupo sulfonilo", o un "grupo en donde un átomo de nitrógeno de un heterociclo saturado de 4 a 6 miembros, que puede estar sustituido con 1 o 2 grupos seleccionados independientemente de un grupo alquilo de C_1-C_6 y un grupo hidroxi (grupo heterocíclico saturado de 4 a 6 miembros completamente reducido que contiene un átomo de nitrógeno y puede contener también un átomo de oxígeno o un átomo de nitrógeno), está unido a un grupo sulfonilo". Ejemplos del grupo anteriormente mencionado incluyen un grupo carbamoilo, un grupo metilaminocarbonilo, un grupo etilaminocarbonilo, un grupo propilaminocarbonilo, un grupo dimetilaminocarbonilo, un grupo dietilaminocarbonilo, un grupo dipropilaminocarbonilo, un grupo N-etil-N-metilaminocarbonilo, un grupo N-metil-N-propilaminocarbonilo, un grupo (1-azetidinil)carbonilo, un grupo (3-

hidroxi-1-azetidinil)carbonilo, un grupo (1-pirrolidinil)carbonilo, un grupo (4-morfolinil)carbonilo, un grupo (4-metil-1-piperazinil)carbonilo, un grupo sulfamoilo, un grupo metilaminosulfonilo, un grupo etilaminosulfonilo, un grupo propilaminosulfonilo, un grupo dimetilaminosulfonilo, un grupo dietilaminosulfonilo, un grupo dipropilaminosulfonilo, un grupo N-etil-N-metilaminosulfonilo, un grupo N-metil-N-propilaminosulfonilo y un grupo (1-azetidinil)sulfonilo; preferiblemente, el grupo anteriormente mencionado es un grupo carbamoilo, un grupo metilaminocarbonilo, un grupo dimetilaminocarbonilo, un grupo (1-azetidinil)carbonilo, un grupo (1-pirrolidinil)carbonilo, un grupo (4-morfolinil)carbonilo, un grupo (4-metil-1-piperazinil)carbonilo, un grupo metilaminosulfonilo, o un grupo (1-azetidinil)sulfonilo, de preferencia un grupo dimetilaminocarbonilo, un grupo (1-azetidinil)carbonilo, un grupo (1-pirrolidinil)carbonilo, o un grupo (4-metil-1-piperazinil)carbonilo, muy de preferencia un grupo dimetilaminocarbonilo o un grupo (1-azetidinil)carbonilo.

En la presente invención, un "grupo mono-alquilcarbonilamino de C_2-C_7" se refiere a un grupo en donde un grupo carbonilo al que está unido un "grupo alquilo de C_{1-6}" anteriormente mencionado, está unido a un grupo amino. Ejemplos del grupo mono-alquilcarbonilamino de C_2-C_7 incluyen un grupo acetamido, un grupo etilcarbonilamino, un grupo propilcarbonilamino, un grupo isopropilcarbonilamino, un grupo butilcarbonilamino y un grupo isobutilcarbonilamino; preferiblemente, el grupo mono-alquilcarbonilamino de C_2-C_7 es un grupo en donde un grupo carbonilo al que está unido un "grupo

alquilo de C_1-C_4" está unido a un grupo amino (grupo mono-alquilcarbonilamino de C_2-C_5), de preferencia un grupo acetamido o un grupo etilcarbonilamino (grupo mono-alquilcarbonilamino de C_2-C_3), muy de preferencia un grupo acetamido.

En la presente invención, un "grupo mono-alquil(C_1-C_6)-aminocarboniloxi" se refiere a un grupo en donde un grupo carbonilo al que está unido un grupo amino unido a un "grupo alquilo de C_1-C_6" anteriormente mencionado, está unido a un átomo de oxígeno. Ejemplos del grupo mono-alquil(C_1-C_6)-aminocarboniloxi incluyen un grupo metilaminocarboniloxi, un grupo etilaminocarboniloxi, un grupo propilaminocarboniloxi, un grupo isopropilaminocarboniloxi y un grupo butilaminocarboniloxi; preferiblemente, el grupo mono-alquil(C_1-C_6)-aminocarboniloxi es un grupo metilaminocarboniloxi o un grupo etilaminocarboniloxi (grupo mono-alquil(C_1-C_2)-aminocarboniloxi), de preferencia un grupo metilaminocarboniloxi.

En la presente invención, un "grupo di-alquil(C_1-C_6)-aminocarboniloxi" se refiere a un grupo en donde un grupo carbonilo, que está unido a un grupo amino unido a dos "grupos alquilo de C_1-C_6" anteriormente mencionados, iguales o diferentes, está unido a un átomo de oxígeno. Ejemplos del grupo di-alquil(C_1-C_6)-aminocarboniloxi incluyen un grupo dimetilaminocarboniloxi, un grupo dietilaminocarboniloxi, un grupo dipropilaminocarboniloxi, un grupo N-etil-N-metilaminocarboniloxi y un grupo N-metil-N-propilaminocarboniloxi; preferiblemente, el grupo di-alquil(C_1-C_6)-aminocarboniloxi es un grupo dimetilaminocarboniloxi, un grupo

dietilaminocarboniloxi o un grupo N-etil-N-metilaminocarboniloxi (grupo di-alquil(C_1-C_2)-aminocarboniloxi), de preferencia un grupo dimetilaminocarboniloxi.

En la presente invención, un "grupo mono-alcoxicarbonilamino de C_2-C_7" se refiere a un grupo en donde un grupo carbonilo al que está unido un "grupo alcoxi de C_1-C_6" anteriormente mencionado está unido a un grupo amino. Ejemplos del grupo mono-alcoxicarbonilamino de C_2-C_7 incluyen un grupo metoxicarbonilamino, un grupo etoxicarbonilamino, un grupo propoxicarbonilamino, un grupo isopropoxicarbonilamino y un grupo butoxicarbonilamino; preferiblemente, el grupo mono-alcoxicarbonilamino de C_2-C_7 es un grupo metoxicarbonilamino o un grupo etoxicarbonilamino (grupo alcoxicarbonilamino de C_2-C_3), de preferencia un grupo metoxicarbonilamino.

En la presente invención, un "grupo mono-alquilsulfonilamino de C_1-C_6" se refiere a un grupo en donde un grupo sulfonilo al que está unido un "grupo alquilo de C_1-C_6" anteriormente mencionado, está unido a un grupo amino. Ejemplos del grupo mono-alquilsulfonilamino de C_1-C_6 incluyen un grupo metilsulfonilamino, un grupo etilsulfonilamino, un grupo propilsulfonilamino, un grupo isopropilsulfonilamino, un grupo butilsulfonilamino, un grupo t-butilsulfonilamino y un grupo 2-etilbutilsulfonilamino; preferiblemente, el grupo mono-alquilsulfonilamino de C_1-C_6 es un grupo en donde un grupo sulfonilo al que está unido un "grupo alquilo de C_1-C_4" anteriormente mencionado, está unido a un grupo amino (grupo mono-alquilsulfonilamino de C_1-C_4), de preferencia un grupo

metilsulfonilamino o un grupo etilsulfonilamino (grupo mono-alquilsulfonilamino de C_1-C_2), muy de preferencia un grupo metilsulfonilamino.

En la presente invención, un "grupo 1,3,4-oxadiazol-2-ilo" sustituido opcionalmente con un grupo alquilo de C_1-C_6 en la posición 5" se refiere a un grupo en donde un grupo alquilo de C_1-C_6 está como sustituyente en la posición 5 de un grupo 1,3,4-oxadiazol-2-ilo. Ejemplos del grupo anteriormente mencionado incluyen un grupo 5-metil-1,3,4-oxadiazol-2-ilo y un grupo 5-etil-1,3,4-oxadiazol-2-ilo; preferiblemente, el grupo anteriormente mencionado es un grupo 5-metil-1,3,4-oxadiazol-2-ilo.

En la presente invención, un "grupo 1,3,4-tiadiazol-2-ilo sustituido opcionalmente con un grupo alquilo de C_1-C_6 en la posición 5" se refiere a un grupo en donde un grupo alquilo de C_1-C_6 está como sustituyente en la posición 5 de un grupo 1,3,4-tiadiazol-2-ilo. Ejemplos del grupo anteriormente mencionado incluyen un grupo 5-metil-1,3,4-tiadiazol-2-ilo y un grupo 5-etil-1,3,4-tiadiazol-2-ilo; preferiblemente, el grupo anteriormente mencionado es un grupo 5-metil-1,3,4-tiadiazol-2-ilo.

En la presente invención, un "grupo heterocíclico" se refiere a un grupo heterocíclico de 4 a 7 miembros que contiene de 1 a 3 átomos de azufre, oxígeno o nitrógeno, y puede contener además 1 o 2 átomos de nitrógeno, y en donde el átomo de azufre puede estar unido a 2 átomos de oxígeno. Ejemplos del grupo heterocíclico incluyen un "grupo heterocíclico aromático", tal como un grupo furilo, un grupo tienilo, un grupo pirrolilo, un grupo azepinilo, un grupo pirazolilo, un grupo imidazolilo, un grupo oxazolilo,

un grupo isoxazolilo, un grupo tiazolilo, un grupo isotiazolilo, un grupo 1,3,4-oxadiazolilo, un grupo 1,3,4-tiadiazolilo, un grupo triazolilo, un grupo tetrazolilo, un grupo tiadiazolilo, un grupo piranilo, un grupo piridilo, un grupo piridazinilo, un grupo pirimidinilo y un grupo pirazinilo; y un "grupo heterocíclico saturado, parcial o totalmente reducido", tal como un grupo tetrahidropiranilo, un grupo tetrahidrotienilo, un grupo morfolinilo, un grupo tiomorfolinilo, un grupo pirrolidinilo, un grupo pirrolinilo, un grupo imidazolidinilo, un grupo pirazolidinilo, un grupo piperidinilo, un grupo piperazinilo, un grupo oxazolinilo, un grupo oxazolidinilo, un grupo isoxazolidinilo, un grupo tiazolinilo, un grupo tiazolidinilo, un grupo pirazolidinilo, un grupo dioxolanilo, un grupo dioxanilo y un grupo 5,6-dihidro-4H-1,3-oxazina; y el grupo heterocíclico anterior puede estar fusionado con otro grupo cíclico tal como un anillo de benceno ("grupo heteroarilo bicíclico fusionado"), por ejemplo un grupo benzotienilo, un grupo benzotiazolilo, un grupo benzoxazolilo, un grupo isobenzofuranilo, un grupo 1,3-dihidroisobenzofuranilo, un grupo quinolilo, un grupo 1,3-benzodioxolanilo, un grupo 1,4-benzodioxanilo, un grupo indolilo, un grupo isoindolilo y un grupo indolinilo. Los grupos heterocíclicos formados por A y R^1 junto con el átomo de carbono al que están unidos, que pueden estar sustituidos con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, son preferiblemente un grupo 2-piridilo, un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo, un grupo 1,3-tiazol-2-ilo, un grupo 1,3-oxazol-2-ilo, un grupo 1,3,4-oxadiazol-2-ilo, un grupo 1,3,4-tiadiazol-2-ilo, un grupo 4,5-dihidro-1,3-tiazol-2-

ilo, un grupo 4,5-dihidro-1,3-oxazol-2-ilo, o un grupo 4,5-dihidro-1,3-benzotiazol-2-ilo, preferiblemente un grupo 1,3-tiazol-2-ilo, un grupo 1,3,4-oxadiazol-2-ilo, un grupo 4,5-dihidro-1,3-tiazol-2-ilo, un grupo 4,5-dihidro-1,3-oxazol-2-ilo, un grupo 1,3,4-tiadiazol-2-ilo, o un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo, de preferencia un grupo 4,5-dihidro-1,3-oxazol-2-ilo. En R^2, el grupo heterocíclico es preferiblemente un grupo heterocíclico de 6 miembros que contiene 1 o 2 átomos de nitrógeno, de preferencia un grupo piridilo o un grupo pirazinilo, muy de preferencia un grupo 2-piridilo, un grupo 3-piridilo, o un grupo 2-pirazinilo.

En la presente invención, un "grupo representado por la fórmula $=NOR^4$" se refiere a un grupo en donde un grupo hidroxi o un "grupo alcoxi de C_1-C_6" anteriormente mencionado está unido a un grupo imino. Preferiblemente, el grupo representado por la fórmula $=NOR^4$ es un grupo representado por la fórmula =NOH.

En la presente invención, un "grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están unidos, y que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α", se refiere al "grupo heterocíclico" anteriormente mencionado o al "grupo heterocíclico" anteriormente mencionado que está sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α. El grupo anteriormente mencionado es, preferiblemente, un grupo 2-piridilo, un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo, un grupo 1,3-tiazol-2-ilo, un grupo 1,3-oxazol-2-ilo, un grupo 1,3,4-oxadiazol-2-ilo, un grupo

1,3,4-tiadiazol-2-ilo, un grupo 4,5-dihidro-1,3-tiazol-2-ilo, un grupo 4,5-dihidro-1,3-oxazol-2-ilo, o un grupo 4,5-dihidro-1,3-benzotiazol-2-ilo, que pueden estar sustituidos con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes γ, de preferencia un grupo 1,3-tiazol-2-ilo, un grupo 5-metil-1,3-tiazol-2-ilo, un grupo 5-metil-1,3,4-oxadiazol-2-ilo, un grupo 4,5-dihidro-1,3-tiazol-2-ilo, un grupo 4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo 5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-etil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1R)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1S)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-4-hidroxi-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4-hidroximetil-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5R)-5-hidroximetil-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo 5-carboxil-1,3-tiazol-2-ilo, un grupo 5-dimetilaminocarbonil-1,3-tiazol-2-ilo, un grupo 5-metil-1,3,4-tiadiazol-2-ilo, o un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo, muy de preferencia un grupo 4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-etil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1R)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1S)-1-

hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4-hidroximetil-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5R)-5-hidroximetil-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo 1,3-tiazol-2-ilo, un grupo 5-carboxil-1,3-tiazol-2-ilo, un grupo 5-dimetilaminocarbonil-1,3-tiazol-2-ilo, un grupo 5-metil-1,3,4-tiadiazol-2-ilo, un grupo 5-metil-1,3,4-oxadiazol-2-ilo, un grupo 4,5-dihidro-1,3-tiazol-2-ilo, o un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo, y en particular muy preferiblemente un grupo 4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-etil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1R)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1S)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4-hidroximetil-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, o un grupo (4R,5R)-5-hidroximetil-4-metil-4,5-dihidro-1,3-oxazol-2-ilo.

En la presente invención, un "grupo fenilo que puede estar sustituido con 1 a 5 grupos seleccionados independientemente del conjunto de sustituyentes α" se refiere a un grupo fenilo o un grupo fenilo sustituido con 1 a 5 grupos seleccionados independientemente del conjunto de sustituyentes α. El grupo anteriormente mencionado es, preferiblemente, un grupo fenilo que puede estar sustituido con 1 a 5 grupos seleccionados independientemente del conjunto de sustituyentes δ, de preferencia un grupo

4-acetilfenilo, un grupo 4-(1-hidroxietil)fenilo, un grupo 4-metilsulfonilfenilo, un grupo 4-(1-azetidinil)sulfonilfenilo, un grupo 2-fluoro-4-metoxicarbonilfenilo, un grupo 4-carbamoil-2-fluorofenilo, un grupo 2-fluoro-4-metilaminocarbonilfenilo, un grupo 4-dimetilaminocarbonil-2-fluorofenilo, un grupo 4-(1-azetidinil)carbonil-2-fluorofenilo, un grupo 2-fluoro-4-(1-pirrolidinil)carbonilfenilo, un grupo 2-fluoro-4-(4-morfolinil)carbonilfenilo, un grupo 2-fluoro-4-metilaminosulfonilfenilo, un grupo 4-(1-azetidinil)sulfonil-2-fluorofenilo, un grupo 2-fluoro-4-(5-metil-1,3,4-oxadiazol-2-il)fenilo, un grupo 2-fluoro-4-(5-metil-1,3,4-tiadiazol-2-il)fenilo, un grupo 4-(1-azetidinil)carbonil-2-metilfenilo, o un grupo 4-(1-azetidinil)carbonil-2-trifluorometilfenilo, preferiblemente un grupo 4-metilsulfonilfenilo, un grupo 4-(1-azetidinil)carbonil-2-fluorofenilo, o un grupo 2-fluoro-4-(1-pirrolidinil)carbonilfenilo, de preferencia un grupo 4-metilsulfonilfenilo.

En la presente invención, un "grupo heterocíclico que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α" en R^2 se refiere al "grupo heterocíclico" anteriormente mencionado o al "grupo heterocíclico" anteriormente mencionado que está sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α. Preferiblemente, el grupo anteriormente mencionado es un grupo 2-piridilo, un grupo 3-piridilo, o un grupo 2-pirazinilo, que pueden estar sustituidos con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes δ, de preferencia un grupo 5-(1-azetidinil)carbonil-3-cloro-2-piridilo, un grupo 2-

metilsulfonil-5-piridilo, un grupo 5-(4-metil-1-piperazinil)carbonil-2-pirazinilo, un grupo 2-metilaminocarbonil-5-piridilo, un grupo 2-metilaminosulfonil-5-piridilo, o un grupo 5-metilsulfonil-2-pirazinilo, muy de preferencia un grupo 2-metilsulfonil-5-piridilo, un grupo 5-metilsulfonil-2-pirazinilo, o un grupo 5-(1-azetidinil)carbonil-3-cloro-2-piridilo.

En la presente invención, la fórmula general (I) es preferiblemente la fórmula general (Ia).

En la presente invención, A es preferiblemente un grupo representado por la fórmula =NOH o un átomo de oxígeno, de preferencia un átomo de oxígeno.

En la presente invención, R^1 es preferiblemente un grupo alquilo de C_1-C_6, un grupo alcoxi de C_1-C_6 o un grupo monoalquilamino de C_1-C_6 halogenado, de preferencia un grupo metilo o un grupo 2-cloroetilamino.

En la presente invención, el grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están unidos, que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, es preferiblemente un grupo 2-piridilo, un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo, un grupo 1,3-tiazol-2-ilo, un grupo 1,3-oxazol-2-ilo, un grupo 1,3,4-oxadiazol-2-ilo, un grupo 1,3,4-tiadiazol-2-ilo, un grupo 4,5-dihidro-1,3-tiazol-2-ilo, un grupo 4,5-dihidro-1,3-oxazol-2-ilo, o un grupo 4,5-dihidro-1,3-benzotiazol-2-ilo, que pueden estar sustituidos con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes γ, de preferencia un grupo 1,3-tiazol-2-ilo, un grupo 5-metil-1,3-tiazol-2-ilo, un grupo

5-metil-1,3,4-oxadiazol-2-ilo, un grupo 4,5-dihidro-1,3-tiazol-2-ilo, un grupo 4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo 5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-etil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1R)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1S)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-4-hidroxi-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4-hidroximetil-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5R)-5-hidroximetil-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo 5-carboxil-1,3-tiazol-2-ilo, un grupo 5-dimetilaminocarbonil-1,3-tiazol-2-ilo, un grupo 5-metil-1,3,4-tiadiazol-2-ilo, o un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo, de preferencia un grupo 4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-etil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1R)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1S)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4-hidroximetil-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5R)-5-hidroximetil-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo 1,3-tiazol-2-ilo, un grupo 5-carboxil-1,3-tiazol-2-ilo, un grupo 5-dimetilaminocarbonil-1,3-tiazol-2-

ilo, un grupo 5-metil-1,3,4-tiadiazol-2-ilo, un grupo 5-metil-1,3,4-oxadiazol-2-ilo, un grupo 4,5-dihidro-1,3-tiazol-2-ilo, o un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo, y en particular muy preferiblemente un grupo 4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-etil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1R)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1S)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4-hidroximetil-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, o un grupo (4R,5R)-5-hidroximetil-4-metil-4,5-dihidro-1,3-oxazol-2-ilo.

En la presente invención, R^2 es preferiblemente un grupo fenilo que puede estar sustituido con 1 a 5 grupos seleccionados independientemente del conjunto de sustituyentes δ, o un grupo 2-piridilo, un grupo 3-piridilo o un grupo 2-pirazinilo, que pueden estar sustituidos con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes δ, de preferencia un grupo 4-metilsulfonilfenilo, un grupo 4-(1-azetidinil)carbonil-2-fluorofenilo, un grupo 2-fluoro-4-(1-pirrolidinil)carbonilfenilo, un grupo 5-(1-azetidinil)carbonil-3-cloro-2-piridilo, un grupo 2-metilsulfonil-5-piridilo, un grupo 5-(4-metil-1-piperazinil)carbonil-2-pirazinilo, un grupo 2-metilaminocarbonil-5-piridilo, un grupo 2-metilaminosulfonil-5-piridilo, o un grupo 5-metilsulfonil-2-pirazinilo, y muy de preferencia un grupo 4-metilsulfonilfenilo, un grupo 2-metilsulfonil-5-piridilo, un grupo 5-metilsulfonil-2-pirazinilo, o un grupo 5-(1-

azetidinil)carbonil-3-cloro-2-piridilo.

En la presente invención, R^3 es preferiblemente un grupo hidroxi o un grupo metoxi.

En la presente invención, R^4 es preferiblemente un átomo de hidrógeno.

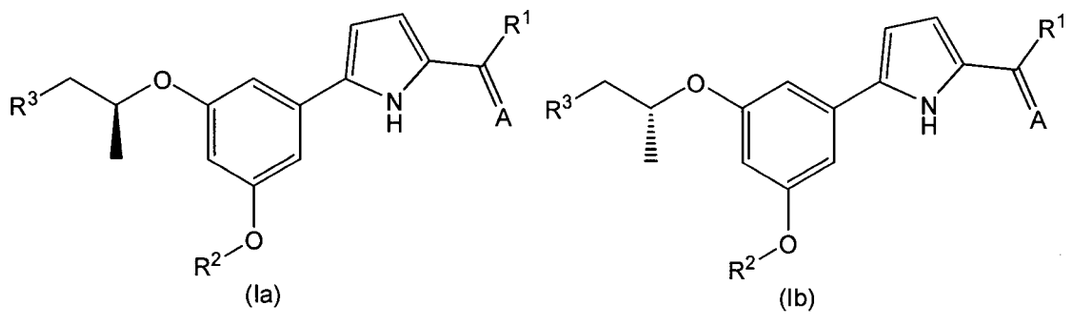
El compuesto representado por la fórmula general (I) o la sal farmacológicamente aceptable del mismo de la presente invención comprende todos sus isómeros (tales como isómeros ceto-enol, diasterómeros, isómeros ópticos, rotámeros, etc.).

El compuesto representado por la fórmula general (I) o la sal farmacológicamente aceptable del mismo de la presente invención tienen varios isómeros porque existen átomos de carbono asimétricos en la molécula. Todos estos isómeros y sus mezclas de la presente invención son representados por una sola fórmula, específicamente la fórmula general (I). Por consiguiente, la presente invención incluye todos estos isómeros y las mezclas de estos isómeros en relaciones arbitrarias.

Los estereoisómeros anteriormente mencionados se pueden obtener sintetizando el compuesto de la presente invención usando como materia prima un compuesto estereoespecífico~~ópticamente activo~~, o usando una síntesis asimétrica o técnica de inducción asimétrica, o si se desea aislando el compuesto sintetizado de la presente invención por medio de un método común de resolución o separación óptica.

El compuesto representado por la fórmula general (Ia) o su sal

farmacológicamente aceptable de la presente invención se prefieren más que un compuesto representado por la fórmula general (Ib) o su sal farmacológicamente aceptable de la presente invención.



Una "sal farmacológicamente aceptable" se refiere a una sal libre de toxicidad prominente y que se puede usar como agente farmacéutico. El compuesto representado por la fórmula general (I) de la presente invención se pueden convertir en una sal haciéndolo reaccionar con un ácido cuando el compuesto tiene un grupo básico como un grupo amino, o haciéndolo reaccionar con una base cuando tiene un grupo ácido como un grupo carboxilo.

Ejemplos de las sales basadas en un grupo básico incluyen las sales de los ácidos halogenhídricos tales como fluorhidratos, clorhidratos, bromhidratos o yodhidratos, sales de ácidos inorgánicos, tales como nitratos, percloratos, sulfatos o fosfatos; alquilsulfonatos de C_1-C_6 como metanosulfonatos, trifluorometanosulfonatos o etanosulfonatos, arilsulfonatos como bencenosulfonatos o p-toluenosulfonatos; sales de ácidos orgánicos tales como acetatos, malatos, fumaratos, succinatos, citratos, ascorbatos, tartratos, oxalatos o maleatos; y sales de aminoácidos tales como las sales de

glicina, lisina, arginina, ornitina, ácido glutámico y ácido aspártico.

Por otra parte, ejemplos de sales basadas en grupos ácidos incluyen sales de metal, tales como las sales de sodio, potasio o litio, las sales de metal alcalino, tales como las sales de calcio o magnesio, las sales de metal, tales como las sales de aluminio o hierro; las sales de amina, inorgánicas tales como las sales de amonio, u orgánicas tales como las sales de t-octilamina, dibencilamina, morfolina, glucosamina, ésteres alquílicos de fenilglicina, etilendiamina, N-metilglucamina, guanidina, dietilamina, trietilamina, diciclohexilamina, N,N'-dibenciletilendiamina, cloroprocaína, procaína, dietanolamina, N-bencilfenetilamina, piperazina, tetrametilamonio o tris(hidroximetil)aminometano; y las sales de aminoácidos, tales como las sales de glicina, lisina, arginina, ornitina, ácido glutámico y ácido aspártico.

El compuesto representado por la fórmula general (I) o una sal farmacológicamente aceptable del mismo de la presente invención se pueden convertir en hidratos incorporando moléculas de agua al dejarse en la atmósfera o por recristalización, y tales hidratos también están incluidos en las sales de la presente invención.

El compuesto representado por la fórmula general (I) o una sal farmacológicamente aceptable del mismo de la presente invención se pueden convertir en solvatos absorbiendo otro tipo de disolvente, y tales solvatos también están incluidos en las sales de la presente invención.

En la presente invención, el "síndrome metabólico" se refiere a un estado patológico basado en la resistencia a la insulina, por el cual el

riesgo de enfermedad de la arteria coronaria aumenta considerablemente debido a la acumulación de múltiples factores de riesgo para los vasos coronarios (que incluyen enfermedades del estilo de vida como hiperlipemia, diabetes, obesidad e hipertensión) (*Diabetes, Obesity and Metabolism*, 9, 2007, 246-258; *Journal of the American Medical Association*, 285, 2486-2497 (2001); *Diabet. Med.*, 15, 539-553 (1998)).

Efecto de la invención

El compuesto representado por la fórmula general (I) de la presente invención, o una sal farmacológicamente aceptable del mismo, tiene una actividad activadora de GK superior y es útil como agente farmacéutico para la prevención o tratamiento de una enfermedad seleccionada del conjunto que consiste en diabetes, deterioro de tolerancia a la glucosa, diabetes gestacional, complicaciones crónicas de la diabetes (que incluyen neuropatía periférica diabética, nefropatía diabética, retinopatía diabética y macroangiopatía diabética), y síndrome metabólico, en animales de sangre caliente (preferiblemente en mamíferos, incluyendo humanos). Además, el compuesto novedoso representado por la fórmula general (I) provisto por la presente invención, o una sal farmacológicamente aceptable del mismo, tiene una actividad activadora de GK superior y es útil como ingrediente activo de una composición farmacéutica para la prevención o tratamiento de las enfermedades anteriormente mencionadas en animales de sangre caliente. Los ejemplos preferidos de enfermedades incluyen diabetes y deterioro de

tolerancia a la glucosa. El compuesto representado por la fórmula general (I) de la presente invención, o una sal farmacológicamente aceptable del mismo, se puede usar preferiblemente como una composición farmacéutica para el tratamiento de las enfermedades anteriormente mencionadas.

DESCRIPCION DETALLADA DE LA INVENCION

El compuesto representado por la fórmula general (I) de la presente invención se puede producir de acuerdo con los métodos A-L que se describen más abajo.

No hay limitaciones particulares sobre el disolvente utilizado en las reacciones de cada paso de los siguientes métodos A-L, siempre que disuelva hasta cierto grado la materia prima inicial sin perjudicar la reacción; el disolvente se selecciona, por ejemplo, del conjunto de disolventes indicado más abajo. El conjunto de disolventes está compuesto de hidrocarburos tales como pentano, hexano, octano, éter de petróleo, ligroína o ciclohexano; amidas como formamida, N,N-dimetilformamida, N,N-dimetilacetamida, N-metil-2-pirrolidona, N-metil-2-pirrolidinona o hexametilfosfato triamida; éteres como éter dietílico, éter diisopropílico, tetrahidrofurano, dioxano, dimetoxietano o éter dimetílico de dietilenglicol; alcoholes como metanol, etanol, n-propanol, i-propanol, n-butanol, 2-butanol, 2-metil-1-propanol, t-butanol, alcohol isoamílico, dietilenglicol, glicerina, octanol, ciclohexanol o metil celosolve; sulfóxidos como sulfóxido de dimetilo; sulfonas como

sulfolano; nitrilos como acetonitrilo, propionitrilo, butironitrilo o isobutironitrilo; ésteres como formiato de etilo, acetato de etilo, acetato de propilo, acetato de butilo o carbonato de dietilo; cetonas como acetona, metil-etil-cetona, 4-metil-2-pentanona, metil-isobutil-cetona, isoforona o ciclohexanona; compuestos nitro como nitroetano o nitrobenceno; hidrocarburos halogenados como diclorometano, 1,2-dicloroetano, clorobenceno, diclorobenceno, cloroformo o tetracloruro de carbono; hidrocarburos aromáticos como benceno, tolueno o xileno; ácidos carboxílicos como ácido acético, pacido fórmico, ácido propiónico, ácido butírico o ácido trifluoroacético; aminas como N-metilmorfolina, trietilamina, tripropilamina, tributilamina, diisopropiletilamina, diciclohexilamina, N-metilpiperidina, piridina, 2,6-lutidina, 4-pirrolidinopiridina, picolina, 4-dimetilaminopiridina, 2,6-di(t-butil)-4-metilpiridina, quinolina, N,N-dimetilanilina, N,N-dietilanilina, 1,5-diazabiciclo[4.3.0]-5-noneno (DBN), 1,4-diazabiciclo[2.2.2]octano (DABCO), 1,8-diazabiciclo[5.4.0]-7-undeceno (DBU) o piperidina; agua; y disolventes combinados de los mismos.

Ejemplos de bases usadas en las reacciones de cada paso de los métodos A-L siguientes incluyen bases inorgánicas tales como carbonatos de metal alcalino como carbonato de sodio, carbonato de potasio, carbonato de litio o carbonato de cesio; carbonatos ácidos de metal alcalino tales como carbonato ácido de sodio, carbonato ácido de potasio o carbonato ácido de litio; acetatos de metal alcalino como acetato de sodio, acetato de potasio, acetato de litio o acetato de cesio; hidruros de metal alcalino como hidruro de litio, hidruro de sodio o hidruro de potasio; hidróxidos de metal alcalino como

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hidróxido de sodio, hidróxido de potasio, hidróxido de bario o hidróxido de litio; y fluoruros de metal alcalino como fluoruro de sodio o fluoruro de potasio; alcóxidos de metal alcalino como metóxido de sodio, etóxido de sodio, t-butóxido de sodio, metóxido de potasio, etóxido de potasio, t-butóxido de potasio o metóxido de litio; trialquil-silóxidos de metal alcalino como trimetilsilóxido de sodio, trimetilsilóxido de potasio o trimetilsilóxido de litio; mercaptanos de metal alcalino como tiometóxido de sodio o tioetóxido de sodio; bases orgánicas tales como N-metilmorfolina, trietilamina, tripropilamina, tributilamina, N,N-diisopropiletilamina, diciclohexilamina, N-metilpiperidina, piridina, 2,6-lutidina, 4-pirrolidinopiridina, picolina, 4-dimetilaminopiridina, 2,6-di(t-butil)-4-metilpiridina, quinolina, N,N-dimetilanilina, N,N-dietilanilina, 1,5-diazabiciclo[4.3.0]-5-noneno (DBN), 1,4-diazabiciclo[2.2.2]octano (DABCO) o 1,8-diazabiciclo[5.4.0]-7-undeceno (DBU); bases organometálicas como n-butil-litio, diisopropilamida de litio o bis(trimetilsilil)amida de litio; y aminoácidos como prolina.

Ejemplos de los agentes de condensación usados en las reacciones de cada paso de los métodos A-L siguientes incluyen hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (HATU), anhídrido cíclico del ácido 1-propanofosfónico (T3P), diciclohexilcarbodiimida (DCCD), clorhidrato de 1-etil-3-(dimetilaminopropil)carbodiimida (WSCI·HCl), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (EDCI), 1-etil-3-(3-dimetilaminopropil)-carbodiimida (EDAC), cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-

metilmorfolinio n-hidratado (DMT-MM), cloroformiato de isobutilo (IBCF), 1,1'-carbonilbis-1H-imidazol (CDI), cianofosfonato de dietilo (DEPC), fosforazidato de difenilo (DPPA), N-hidroxisuccinimida, N-hidroxi-5-norborneno-2,3-dicarboxiimida y disulfuro de dipiridilo, y estos se pueden usar en presencia de 1-hidroxibenzotriazol (HOBt) o 1-hidroxibenzotriazol monohidratado conforme sea necesario.

Ejemplos de los agentes de desmetilación usados en las reacciones de cada paso de los métodos A-L siguientes incluyen tiometóxido de sodio, tioetóxido de sodio, tiofenóxido de sodio, yodotrimetilsilano, cloruro de aluminio, bromuro de aluminio, tribromuro de boro, triyoduro de boro, yoduro de metilmagnesio y bromuro de hidrógeno.

Ejemplos de los catalizadores de paladio usados en las reacciones de cada paso de los métodos A-L siguientes incluyen catalizadores de paladio de valencia cero o catalizadores de paladio divalentes, tales como tetrakis(trifenilfosfina) paladio (0), paladio-carbón activado, acetato de paladio (II), trifluoroacetato de paladio (II), negro de paladio, bromuro de paladio (II), cloruro de paladio (II), yoduro de paladio (II), cianuro de paladio (II), nitrato de paladio (II), óxido de paladio (II), sulfato de paladio (II), diclorobis(acetonitrilo)paladio (II), diclorobis(benzonitrilo)paladio (II), dicloro(1,5-ciclooctadieno)paladio (II), acetilacetona de paladio (II), sulfuro de paladio (II), dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II), tris(dibencilidenacetona) dipaladio (0), tetrafluoroborato de tetrakis(acetonitrilo)paladio (II), y dímeros de cloruro de arilo-paladio.

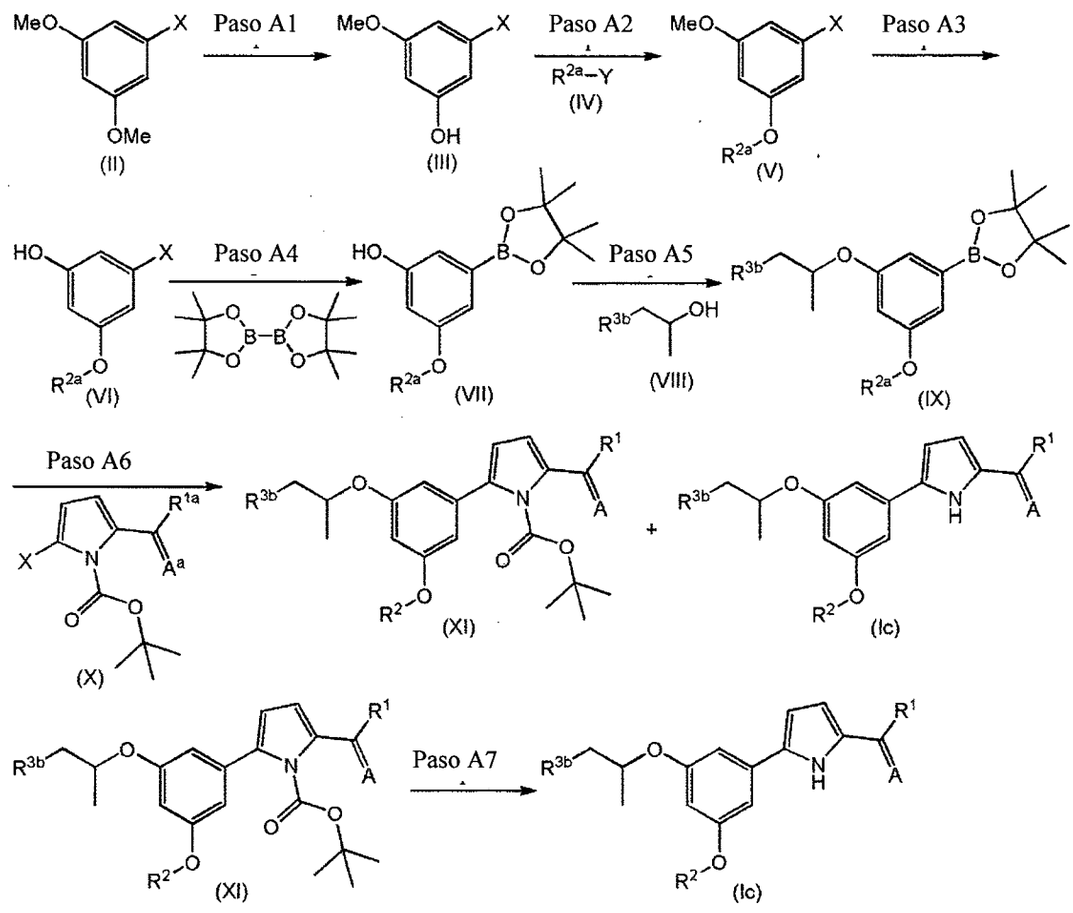
Las temperaturas de reacción de las reacciones de cada paso de los métodos A-L siguientes varían dependiendo del disolvente, la materia prima inicial, los reactivos, etcétera, mientras que los tiempos de reacción varían dependiendo del disolvente, la materia prima inicial, los reactivos, la temperatura de reacción, etcétera.

En las reacciones de cada paso de los métodos A-L siguientes, cada compuesto deseado se recoge de la mezcla de reacción de acuerdo con los métodos convencionales después de que termina la reacción. El compuesto deseado se obtiene, por ejemplo, de la siguiente manera. La mezcla de reacción se neutraliza adecuadamente, y si hay materia insoluble se quita por filtración. Después se le agrega agua y un disolvente orgánico inmiscible, tal como acetato de etilo, y la capa orgánica que contiene el compuesto deseado se separa. La capa orgánica se lava con agua o similar y después se seca sobre sulfato de magnesio anhidro, sulfato de sodio anhidro, bicarbonato de sodio anhidro o similares, y se filtra. Después se evapora el disolvente. El compuesto resultante deseado se puede aislar y purificar, si es necesario, combinando adecuadamente los métodos usuales, por ejemplo, métodos usados convenientemente para el aislamiento y purificación de compuestos orgánicos, tales como recristalización y reprecipitación, y eluyendo con un eluente adecuado por aplicación de cromatografía. El compuesto deseado insoluble en un disolvente se puede purificar lavando el producto crudo sólido resultante con un disolvente. El compuesto deseado en cada paso también se puede usar como tal para la siguiente reacción sin

purificar.

El método A es un método para producir un compuesto representado por la fórmula general (Ic) en donde R^3 es un grupo alcoxi de C_1-C_6, entre los compuestos representados por la fórmula general (I).

METODO A



En la presente invención, A, R^1 y R^2 son como se define arriba, R^{3b} representa un grupo alcoxi de C_1-C_6, X representa un átomo de halógeno

(preferiblemente un átomo de cloro, un átomo de bromo o un átomo de yodo, de preferencia un átomo de bromo), Y representa un átomo de halógeno, un grupo alquilsulfoniloxi de C_1-C_6, un grupo alcoxisulfoniloxi de C_1-C_6 o un grupo arilsulfoniloxi de C_6-C_{10} (preferiblemente un átomo de halógeno, de preferencia un átomo de flúor o un átomo de cloro, muy de preferencia un átomo de flúor), y A^a, R^{1a} y R^{2a} son grupos en donde un grupo amino, un grupo hidroxi o un grupo carboxilo contenidos como sustituyentes en los grupos A, R^1 y R^2, son un grupo amino, un grupo hidroxi o un grupo carboxilo opcionalmente protegidos, o representan los mismos grupos definidos para los grupos A, R^1 y R^2.

Paso A1

Este paso es para producir un compuesto representado por la fórmula general (III).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (II) con un agente de desmetilación en un disolvente.

El compuesto representado por la fórmula general (II) usado en este paso es un compuesto conocido, o se produce fácilmente de acuerdo con un método conocido o un método similar al mismo usando como materia prima inicial un compuesto conocido.

El disolvente usado en este paso es preferiblemente una amida, de preferencia N-metil-2-pirrolidona.

El agente de desmetilación usado en este paso es

preferiblemente tiometóxido de sodio.

La temperatura de reacción en este paso normalmente es de 50 °C a 140°C, de preferencia de 80 °C a 120°C.

El tiempo de reacción en este paso normalmente es de 0.5 horas a 12 horas, de preferencia de 1 hora a 5 horas.

Paso A2

Este paso es para producir un compuesto representado por la fórmula general (V).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (III) con un compuesto representado por la fórmula general (IV) en un disolvente y en presencia de una base.

El compuesto representado por la fórmula (IV) usado en este paso es un compuesto conocido, o se produce fácilmente de acuerdo con un método conocido o un método similar al mismo usando como materia prima inicial un compuesto conocido.

El disolvente usado en este paso es preferiblemente una amida, de preferencia N,N-dimetilformamida.

La base usada en este paso es preferiblemente un carbonato de metal alcalino, de preferencia carbonato de potasio.

La temperatura de reacción en este paso normalmente es de 50 °C a 140°C, de preferencia de 80 °C a 120°C.

El tiempo de reacción en este paso normalmente es de 12 horas a 72 horas, de preferencia de 24 horas a 48 horas.

Paso A3

Este paso es para producir un compuesto representado por la fórmula general (VI).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (V) con un agente de desmetilación en un disolvente.

El disolvente usado en este paso es preferiblemente un hidrocarburo halogenado, de preferencia diclorometano.

El agente de desmetilación usado en este paso es preferiblemente tribromuro de boro.

La temperatura de reacción en este paso normalmente es de -100 °C a 40°C, de preferencia de -78 °C a 25°C.

El tiempo de reacción en este paso normalmente es de 1 hora a 72 horas, de preferencia de 12 horas a 36 horas.

Paso A4

Este paso es para producir un compuesto representado por la fórmula general (VII).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (VI) con bis(pinacolato)diboro en un disolvente, en presencia de un catalizador de paladio y una base inorgánica.

El disolvente usado en este paso es preferiblemente una amida, de preferencia N,N-dimetilformamida.

El catalizador de paladio usado en este paso es preferiblemente

un catalizador de paladio divalente, de preferencia complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]-paladio (II)-diclorometano.

La base inorgánica usada en este paso es preferiblemente un acetato de metal alcalino, de preferencia acetato de potasio.

La temperatura de reacción en este paso normalmente es de 50 °C a 130 °C, de preferencia de 70 °C a 110 °C.

El tiempo de reacción en este paso normalmente es de 1 hora a 24 horas, de preferencia de 2 horas a 10 horas.

Paso A5

Este paso es para producir un compuesto representado por la fórmula general (IX).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (VII) con un compuesto representado por la fórmula general (VIII) en un disolvente, en presencia de trifenilfosfina y azodicarboxilato de dietilo.

El compuesto representado por la fórmula (VIII) usado en este paso y sus isómeros ópticos son compuestos conocidos, o se producen fácilmente de acuerdo con los métodos conocidos o similares usando como materia prima inicial un compuesto conocido.

El disolvente usado en este paso es preferiblemente un éter, de preferencia tetrahidrofurano.

La temperatura de reacción en este paso normalmente es de -20 °C a 40 °C, de preferencia de 0 °C a 25 °C.

El tiempo de reacción en este paso normalmente es de 0.5 horas a 72 horas, de preferencia de 1 hora a 36 horas.

Paso A6

Este paso es para producir un compuesto representado por la fórmula general (XI) y un compuesto representado por la fórmula general (Ic).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (IX) con un compuesto representado por la fórmula general (X) en un disolvente, en presencia de un catalizador de paladio y una base inorgánica, seguido por la eliminación del grupo protector del grupo amino, hidroxi o carboxilo en A^a, R^{1a} y R^{2a} según se requiera.

El disolvente usado en este paso es preferiblemente un éter, un hidrocarburo aromático, un alcohol, agua, o un disolvente combinado de los mismos, de preferencia dioxano, tolueno, etanol, agua o un disolvente combinado de los mismos, muy de preferencia un disolvente combinado de dioxano y agua o un disolvente combinado de tolueno, etanol y agua.

El catalizador de paladio usado en este paso es preferiblemente un catalizador de paladio divalente, de preferencia complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano.

La base inorgánica usada en este paso es preferiblemente un carbonato de metal alcalino, de preferencia carbonato de potasio.

La temperatura de reacción en este paso normalmente es de 25 °C a 100 °C, de preferencia de 40 °C a 70 °C.

El tiempo de reacción en este paso normalmente es de 0.5 horas

a 12 horas, de preferencia de 1 hora a 5 horas.

Paso A7

Este paso es para producir un compuesto representado por la fórmula general (Ic).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (XI) con un ácido en un disolvente.

El disolvente usado en este paso es preferiblemente un hidrocarburo halogenado, de preferencia diclorometano.

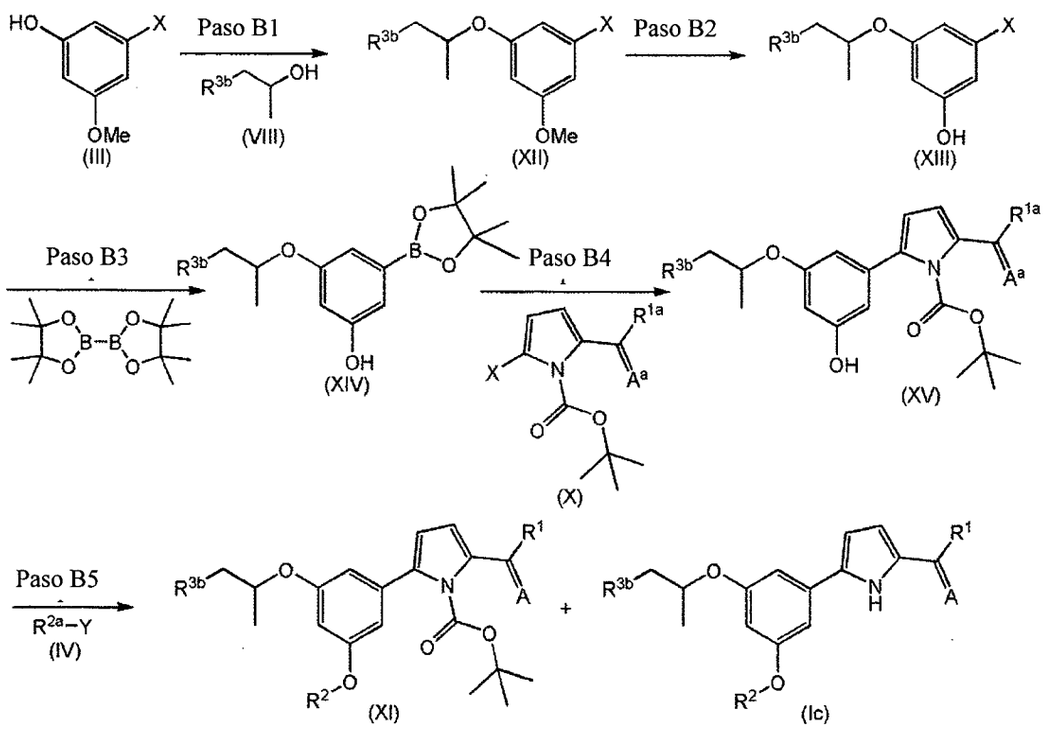
El ácido usado en este paso es, por ejemplo, un halogenuro de hidrógeno como cloruro de hidrógeno gaseoso o bromuro de hidrógeno gaseoso; un ácido mineral como ácido sulfúrico, sulfato de metilo, ácido bromhídrico o ácido clorhídrico; un ácido sulfónico orgánico como ácido metanosulfónico, ácido p-toluenosulfónico, p-toluenosulfonato de piridinio (PPTS), ácido alcanforsulfónico o ácido trifluorometanosulfónico; un ácido carboxílico como ácido acético, ácido fórmico o ácido trifluoroacético; un ácido de Lewis como cloruro de aluminio, cloruro de zinc, yoduro de zinc, tetracloruro de estaño, tricloruro de titanio, trifluoruro de boro, tribromuro de boro ~~o sulfato de metilo~~; o una resina ácido de intercambio iónico; preferiblemente un ácido carboxílico, de preferencia ácido trifluoroacético.

La temperatura de reacción en este paso normalmente es de -20 °C a 60 °C, de preferencia de 0 °C a 40 °C.

El tiempo de reacción en este paso normalmente es de 0.1 horas a 5 horas, de preferencia de 0.5 horas a 3 horas.

El método B es para producir un compuesto representado por la fórmula general (Ic) en donde R^3 es un grupo alcoxi de C_1-C_6, entre los compuestos representados por la fórmula general (I).

METODO B



En la presente invención, A, R^1, R^2, R^{3b}, A^a, R^{1a}, R^{2a}, X y Y son como se define arriba.

Paso B1

Este paso es para producir un compuesto representado por la fórmula general (XII).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (III) obtenido en el paso A1 del método A

anteriormente mencionado con un compuesto representado por la fórmula general (VIII), en un disolvente y en presencia de trifenilfosfina y azodicarboxilato de dietilo.

El disolvente usado en este paso es preferiblemente un hidrocarburo aromático, de preferencia tolueno.

La temperatura de reacción en este paso normalmente es de -20 °C a 40 °C, de preferencia de 0 °C a 25 °C.

El tiempo de reacción en este paso normalmente es de 0.1 horas a 72 horas, de preferencia de 0.5 horas a 36 horas.

Paso B2

Este paso es para producir un compuesto representado por la fórmula general (XIII).

Este paso se efectúa igual que el paso A1 del método A anteriormente mencionado haciendo reaccionar un compuesto representado por la fórmula general (XII) con un agente de desmetilación.

Paso B3

Este paso es para producir un compuesto representado por la fórmula general (XIV).

Este paso se efectúa igual que el paso A4 del método A anteriormente mencionado haciendo reaccionar un compuesto representado por la fórmula general (XIII) con bis(pinacolato)diboro en un disolvente, en presencia de un catalizador de paladio y una base inorgánica.

Paso B4

Este paso es para producir un compuesto representado por la fórmula general (XV).

Este se efectúa igual que el paso A6 del método A anteriormente mencionado haciendo reaccionar un compuesto representado por la fórmula general (XIV) con un compuesto representado por la fórmula general (X) en un disolvente, en presencia de un catalizador de paladio y una base inorgánica.

Paso B5

Este paso es para producir un compuesto representado por la fórmula general (XI) y un compuesto representado por la fórmula general (Ic).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (XV) con un compuesto representado por la fórmula general (IV) en un disolvente, en presencia de una base, seguido por eliminación del grupo protector del grupo amino, hidroxi o carboxilo en A^a, R^{1a} y R^{2a} según sea necesario.

El disolvente usado en este paso es preferiblemente un sulfóxido o una amida, de preferencia sulfóxido de dimetilo o N,N-dimetilformamida.

La base usada en este paso es preferiblemente un hidruro de metal alcalino o un carbonato de metal alcalino, de preferencia hidruro de sodio o carbonato de potasio.

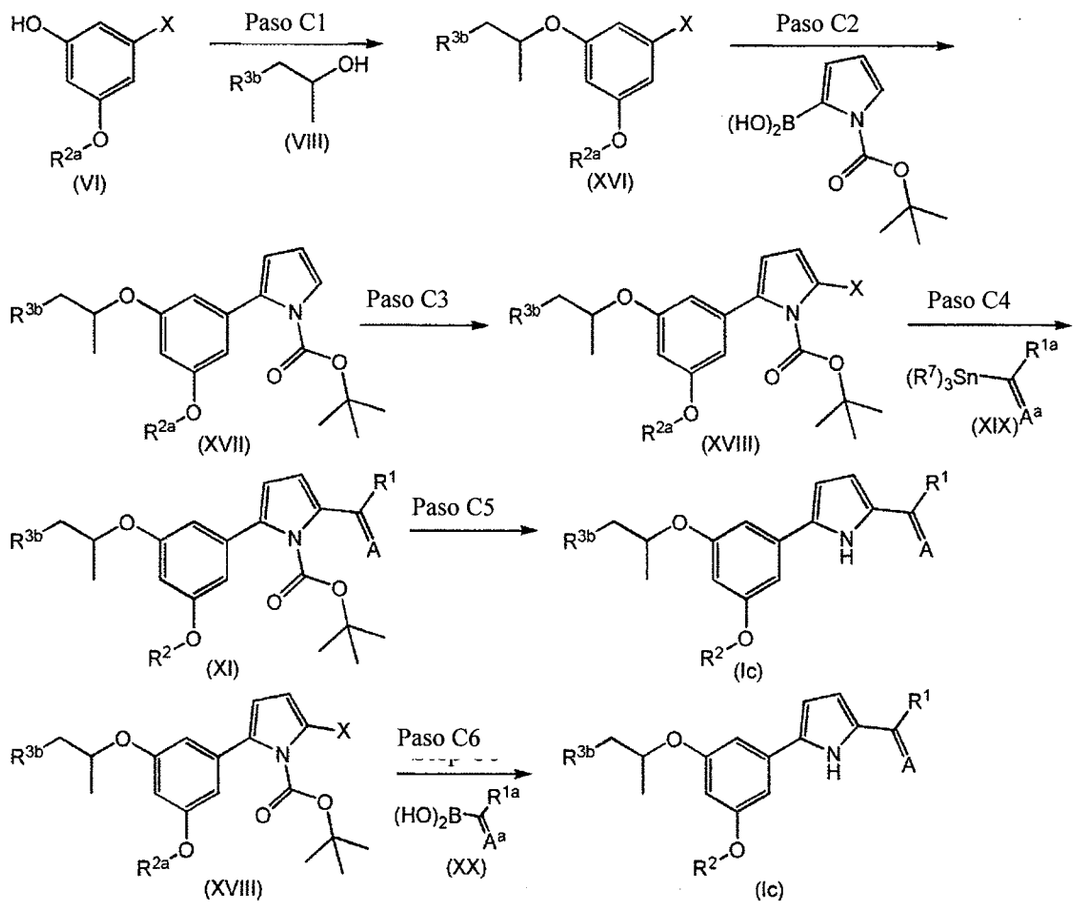
La temperatura de reacción en este paso normalmente es de 50 °C a 140°C, de preferencia de 80 °C a 120°C.

El tiempo de reacción en este paso normalmente es de 1 hora a

72 horas, de preferencia de 3 horas a 36 horas.

El método C es para producir un compuesto representado por la fórmula general (Ic) en donde R^3 es un grupo alcoxi de C_1-C_6, entre los compuestos representados por la fórmula general (I).

METODO C



En la presente invención, A, R^1, R^2, R^{3b}, A^a, R^{1a}, R^{2a} y X son como se define arriba, y R^7 representa un grupo alquilo de C_1-C_6 (preferiblemente un grupo n-butilo).

Paso C1

Este paso es para producir un compuesto representado por la fórmula general (XVI).

Este paso se efectúa igual que el paso B1 del método B anteriormente mencionado haciendo reaccionar un compuesto representado por la fórmula general (VI), obtenido en el paso A3 del método A anteriormente mencionado, con un compuesto representado por la fórmula general (VIII), en un disolvente y en presencia de trifenilfosfina y azodicarboxilato de dietilo.

Paso C2

Este paso es para producir un compuesto representado por la fórmula general (XVII).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (XVI) con ácido 1-(t-butoxicarbonil)pirrol-2-borónico en un disolvente, en presencia de un catalizador de paladio, trifenilfosfina y una base inorgánica.

El disolvente usado en este paso es preferiblemente un éter, agua o un disolvente combinado de los mismos, de preferencia dimetoxietano, agua o un disolvente combinado de los mismos, muy de preferencia un disolvente combinado de dimetoxietano y agua.

El catalizador de paladio usado en este paso es preferiblemente un catalizador de paladio divalente, de preferencia acetato de paladio (II).

La base usada en este paso es preferiblemente un carbonato de

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metal alcalino, de preferencia carbonato de potasio.

La temperatura de reacción en este paso normalmente es de 40 °C a 100°C, de preferencia de 60 °C a 90°C.

El tiempo de reacción en este paso normalmente es de 1 hora a 72 horas, de preferencia de 3 horas a 24 horas.

Paso C3

Este paso es para producir un compuesto representado por la fórmula general (XVIII).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (XVII) con un agente de halogenación en un disolvente.

El disolvente usado en este paso es preferiblemente un éter o un disolvente combinado de un éter y un alcohol, de preferencia tetrahidrofurano o un disolvente combinado de tetrahidrofurano y metanol.

El agente de halogenación usado en este paso es, por ejemplo, un ácido inorgánico como ácido clorhídrico, bromuro de hidrógeno o yoduro de hidrógeno; una molécula de halógeno como cloro, bromo o yodo; o una succinimida como N-clorosuccinimida, N-bromosuccinimida o N-yodosuccinimida; preferiblemente una succinimida, de preferencia N-bromosuccinimida.

La temperatura de reacción en este paso normalmente es de -20 °C a 40°C, de preferencia de 0 °C a 25°C.

El tiempo de reacción en este paso normalmente es de 0.5 horas

a 24 horas, de preferencia de 1 hora a 12 horas.

Paso C4

Este paso es para producir un compuesto representado por la fórmula general (XI).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (XVIII) con un compuesto representado por la fórmula general (XIX) en un disolvente, en presencia de un catalizador de paladio, seguido por la eliminación del grupo protector del grupo amino, hidroxi o carboxilo en A^a, R^{1a} y R^{2a}, conforme sea necesario.

El compuesto representado por la fórmula general (XIX) usado en este paso es un compuesto conocido, o se produce fácilmente de acuerdo con un método conocido o un método similar al mismo usando como materia prima inicial un compuesto conocido.

El disolvente usado en este paso es preferiblemente un hidrocarburo aromático, de preferencia tolueno.

El catalizador de paladio usado en este paso es preferiblemente un catalizador de paladio de valencia cero, de preferencia tetrakis(trifenilfosfina)paladio (0).

La temperatura de reacción en este paso normalmente es de 90 °C a 130°C, de preferencia de 100 °C a 120°C.

El tiempo de reacción en este paso normalmente es de 1 hora a 72 horas, de preferencia de 3 horas a 24 horas.

Paso C5

Este paso es para producir un compuesto representado por la fórmula general (Ic).

Este paso se efectúa igual que el paso A7 del método A anteriormente mencionado haciendo reaccionar un compuesto representado por la fórmula general (XI) con un ácido.

Paso C6

Este paso es para producir un compuesto representado por la fórmula general (Ic).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (XVIII) con un compuesto representado por la fórmula general (XX) en un disolvente, en presencia de un catalizador de paladio y una base inorgánica, seguido por la eliminación del grupo protector del grupo amino, hidroxi o carboxilo en A^a, R^{1a} y R^{2a}, conforme sea necesario.

El compuesto representado por la fórmula general (XX) usado en este paso es un compuesto conocido, o se produce fácilmente de acuerdo con un método conocido o un método similar al mismo usando como materia prima inicial un compuesto conocido.

El disolvente usado en este paso es preferiblemente un éter, agua, o un disolvente combinado de los mismos, de preferencia dimetoxietano, agua o un disolvente combinado de los mismos, muy de preferencia un disolvente combinado de dimetoxietano y agua.

El catalizador de paladio usado en este paso es preferiblemente un catalizador de paladio divalente, de preferencia complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano.

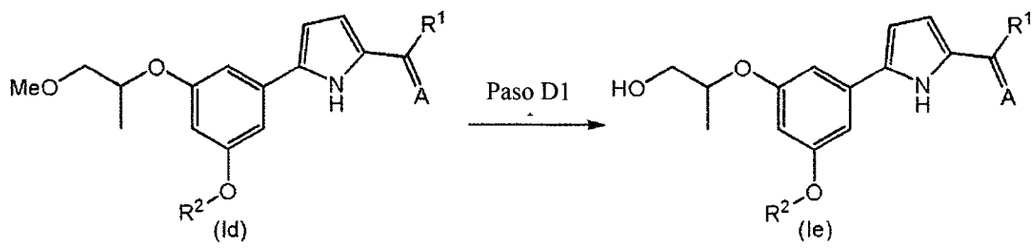
La base inorgánica usada en este paso es preferiblemente un carbonato de metal alcalino, de preferencia carbonato de potasio.

La temperatura de reacción en este paso normalmente es de 60 °C a 120°C, de preferencia de 80 °C a 100°C.

El tiempo de reacción en este paso normalmente es de 1 hora a 480 horas, de preferencia de 12 horas a 240 horas.

El método D es para producir un compuesto representado por la fórmula general (Ie) en donde R^3 es un grupo hidroxi, entre los compuestos representados por la fórmula general (I).

METODO D



En la presente invención, A, R^1 y R^2 son como se define arriba.

Paso D1

Este paso es para producir un compuesto representado por la fórmula general (Ie).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (Id) en donde R^{3b} es un grupo metoxi entre los compuestos representados por la fórmula general (Ic), obtenido en el paso A6 del método A anteriormente mencionado, el paso A7 del método A anteriormente mencionado, el paso B5 del método B anteriormente mencionado, el paso C5 del método C anteriormente mencionado, y el paso C6 del método C anteriormente mencionado, con un agente de desmetilación, en un disolvente.

El disolvente usado en este paso es preferiblemente un hidrocarburo halogenado, de preferencia diclorometano.

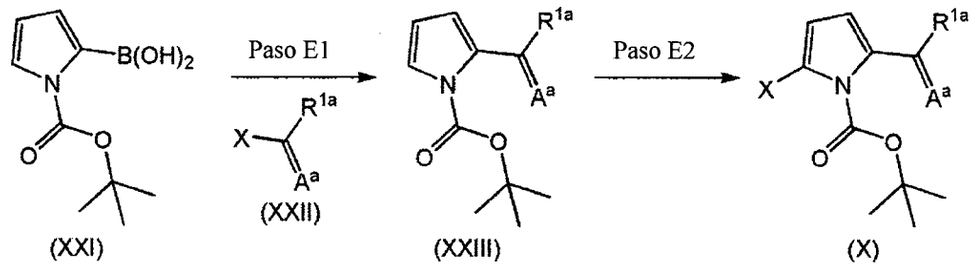
El agente de desmetilación usado en este paso es preferiblemente yodotrimetilsilano o tribromuro de boro, de preferencia tribromuro de boro.

La temperatura de reacción en este paso normalmente es de -100 °C a 40°C, de preferencia de -78 °C a 25°C.

El tiempo de reacción en este paso normalmente es de 0.05 horas a 12 horas, de preferencia de 0.1 horas a 3 horas.

El método E es para producir un compuesto representado por la fórmula general (X), usado en el paso A6 del método A anteriormente mencionado y en el paso B4 del método B anteriormente mencionado.

METODO E



En la presente invención, A^a, R^{1a} y X son como se define arriba.

Paso E1

Este paso es para producir un compuesto representado por la fórmula general (XXIII).

Este paso se efectúa igual que el paso C2 del método C anteriormente mencionado haciendo reaccionar ácido 1-(t-butoxicarbonil)pirrol-2-borónico (XXI) con un compuesto representado por la fórmula general (XXII) en un disolvente, en presencia de un catalizador de paladio, trifenilfosfina y una base inorgánica.

El ácido 1-(t-butoxicarbonil)pirrol-2-borónico (XXI) usado en este paso se produce fácilmente de acuerdo con un método conocido o similar al mismo usando como materia prima inicial un compuesto conocido.

El compuesto representado por la fórmula general (XXII) usado en este paso es un compuesto conocido, o se produce fácilmente de acuerdo con un método conocido o un método similar al mismo usando como materia prima inicial un compuesto conocido.

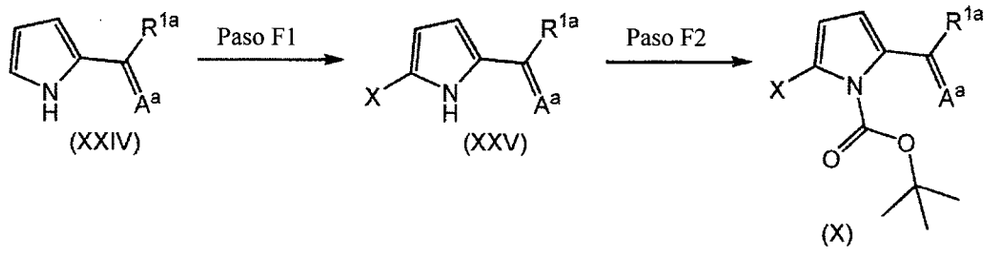
Paso E2

Este paso es para producir un compuesto representado por la fórmula general (X).

Este paso se efectúa igual que el paso C3 del método C anteriormente mencionado haciendo reaccionar un compuesto representado por la fórmula general (XXIII) con un agente de halogenación en un disolvente.

El método F es para producir un compuesto representado por la fórmula general (X), usado en el paso A6 del método A anteriormente mencionado y en el paso B4 del método B anteriormente mencionado.

METODO F



En la presente invención, A^a, R^{1a} y X son como se define arriba.

Paso F1

Este paso es para producir un compuesto representado por la fórmula general (XXV).

Este paso se efectúa igual que el paso C3 del método C haciendo reaccionar un compuesto representado por la fórmula general (XXIV) con un agente de halogenación en un disolvente.

El compuesto representado por la fórmula general (XXIV) usado

en este paso es un compuesto conocido, o se produce fácilmente de acuerdo con un método conocido o un método similar al mismo usando como materia prima inicial un compuesto conocido.

Paso F2

Este paso es para producir un compuesto representado por la fórmula general (X).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (XXV) con dicarbonato de di-t-butilo, en un disolvente y en presencia de una base.

El disolvente usado en este paso es preferiblemente un hidrocarburo halogenado, de preferencia diclorometano.

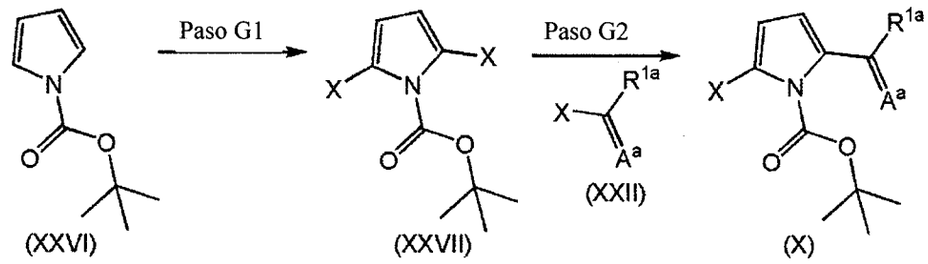
La base usada en este paso es preferiblemente una base orgánica, de preferencia trietilamina, 4-dimetilaminopiridina, o una base combinada de las mismas, de preferencia una base combinada de trietilamina y 4-dimetilaminopiridina.

La temperatura de reacción en este paso normalmente es de -20 °C a 40°C, de preferencia de 0 °C a 25°C.

El tiempo de reacción en este paso normalmente es de 0.1 horas a 12 horas, de preferencia de 0.5 horas a 3 horas.

El método G es para producir un compuesto representado por la fórmula general (X), usado en el paso A6 del método A anteriormente mencionado y en el paso B4 del método B anteriormente mencionado.

METODO G



En la presente invención, A^a, R^{1a} y X son como se define arriba.

Paso G1

Este paso es para producir un compuesto representado por la fórmula general (XXVII).

Este paso se efectúa igual que el paso C3 del método C haciendo reaccionar pirrol-1-carbonato de t-butilo (XXVI) con un agente de halogenación en un disolvente.

El pirrol-1-carbonato de t-butilo (XXVI) usado en este paso se produce fácilmente de acuerdo con un método conocido o similar al mismo usando como materia prima inicial un compuesto conocido.

Paso G2

Este paso es para producir un compuesto representado por la fórmula general (X).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (XXVII) con un compuesto representado por la fórmula general (XXII) en un disolvente y en presencia de una base.

El disolvente usado en este paso es preferiblemente un éter, de

preferencia éter dietílico.

La base usada en este paso es preferiblemente una base organometálica, de preferencia n-butil-litio.

La temperatura de reacción en este paso normalmente es de -100 °C a 40°C, de preferencia de -78 °C a 25°C.

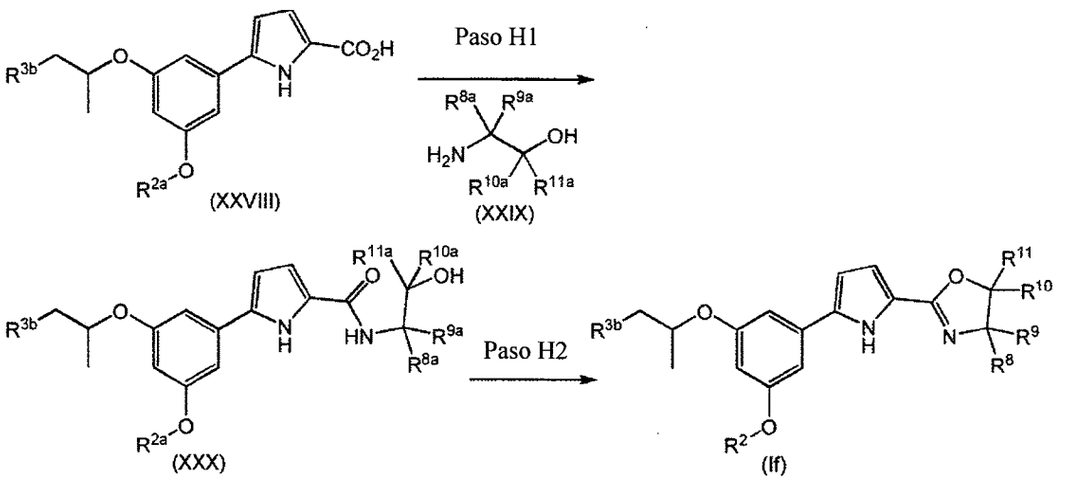
El tiempo de reacción en este paso normalmente es de 0.5 horas a 24 horas, de preferencia de 1 hora a 12 horas.

Un compuesto representado por la fórmula general (I), en donde A y R^1, junto con el átomo de carbono al que están unidos, forman un grupo heterocíclico que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, también se puede producir de acuerdo con un método que construye al último un anillo heterocíclico. Por ejemplo, los métodos H e I indican métodos en donde el grupo heterocíclico es un grupo 4,5-dihidro-1,3-oxazol-2-ilo, o un grupo 1,3,4-oxadiazol-2-ilo. Otros grupos heterocíclicos también se producen fácilmente de acuerdo con métodos similares.

El método H es para producir un compuesto representado por la fórmula general (If), en donde el grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están unidos, que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, es el grupo 4,5-dihidro-1,3-oxazol-2-ilo que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, y

R^3 es un grupo alcoxi de C_1-C_6, entre los compuestos representados por la fórmula general (I).

METODO H



En la presente invención, R^2, R^{3b} y R^{2a} son como se define arriba, R^8, R^9, R^{10} y R^{11} representan un átomo de hidrógeno o un grupo que pertenece al conjunto de sustituyentes α, y R^{8a}, R^{9a}, R^{10a} y R^{11a} son grupos en donde un grupo amino, hidroxi o carboxilo, contenidos como sustituyentes en los grupos R^8, R^9, R^{10} y R^{11}, son un grupo amino, un grupo hidroxi o un grupo carboxilo opcionalmente protegidos, o representan los mismos grupos definidos para R^8, R^9, R^{10} y R^{11}.

Paso H1

Este paso es para producir un compuesto representado por la fórmula general (XXX).

Este paso se efectúa haciendo reaccionar un compuesto

representado por la fórmula general (XXVIII) con un compuesto representado por la fórmula general (XXIX), en un disolvente y en presencia de un agente de condensación y en presencia o ausencia de una base.

El compuesto representado por la fórmula general (XXIX) usado en este paso es un compuesto conocido, o se produce fácilmente de acuerdo con un método conocido o un método similar al mismo usando como materia prima inicial un compuesto conocido.

El disolvente usado en este paso es preferiblemente un alcohol, un hidrocarburo halogenado o una amida, de preferencia metanol, diclorometano o N,N-dimetilformamida.

El agente de condensación usado en este paso es preferiblemente DMT-MM, WSCI·HCl o HATU.

La base usada en este paso es preferiblemente una base orgánica, de preferencia N-metilmorfolina, 4-dimetilaminopiridina o N,N-diisopropiletilamina.

La temperatura de reacción en este paso normalmente es de -20 °C a 60°C, de preferencia de 0 °C a 30°C.

El tiempo de reacción en este paso normalmente es de 0.5 horas a 72 horas, de preferencia de 1 hora a 24 horas.

Paso H2

Este paso es para producir un compuesto representado por la fórmula general (If).

Este paso se efectúa haciendo reaccionar un compuesto

representado por la fórmula general (XXX) con una base y anhídrido del ácido metanosulfónico o trifluoruro de bis(2-metoxietil)aminoazufre en un disolvente, seguido por la eliminación del grupo protector del grupo amino, hidroxi o carboxilo en R^{2a}, R^{8a}, R^{9a}, R^{10a} y R^{11a}.

El disolvente usado en este paso es preferiblemente un éter, de preferencia tetrahidrofurano o dimetoxietano.

En caso de usar anhídrido del ácido metanosulfónico en este paso, la base usada es preferiblemente una base orgánica, de preferencia trietilamina. En caso de usar trifluoruro de bis(2-metoxietil)aminoazufre, la base es preferiblemente un carbonato de metal alcalino, de preferencia carbonato de potasio.

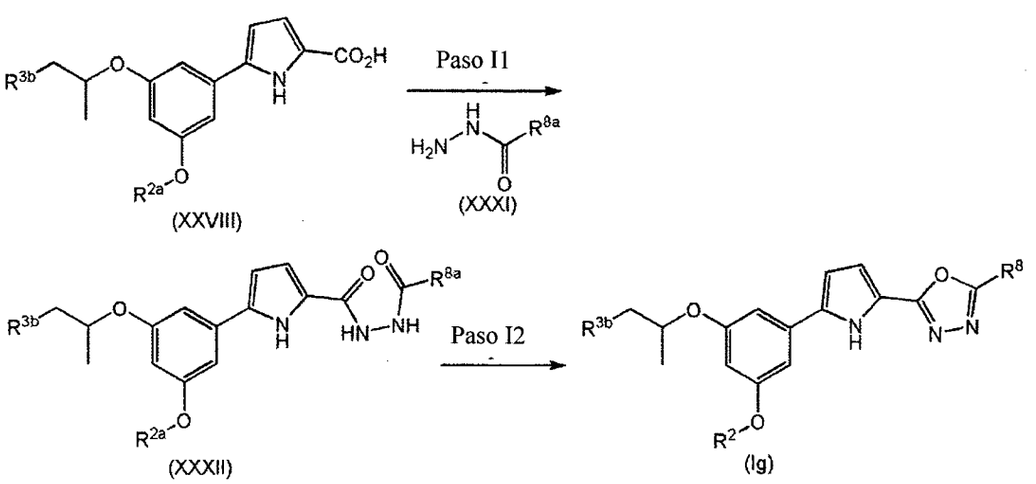
La temperatura de reacción en este paso normalmente es de -100 °C a 85°C, y en caso de usar anhídrido del ácido metanosulfónico, es preferiblemente de 10 °C a 60 °C. En caso de usar trifluoruro de bis(2-metoxietil)aminoazufre, la temperatura de reacción es preferiblemente de -78 °C a 30 °C.

El tiempo de reacción en este paso normalmente es de 0.5 horas a 72 horas, de preferencia de 1 hora a 24 horas.

El método I es para producir un compuesto representado por la fórmula general (Ig), en donde el grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están unidos, que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, es un grupo 1,3,4-oxadiazol-2-ilo que puede estar sustituido con 1 grupo

seleccionado del conjunto de sustituyentes α, y R^3 es un grupo alcoxi de C_1-C_6, entre los compuestos representados por la fórmula general (I).

METODO I



En la presente invención, R^2, R^{3b}, R^8, R^{2a} y R^{8a} son como se define arriba.

Paso I1

Este paso es para producir un compuesto representado por la fórmula general (XXXII).

Este paso se efectúa igual que el paso H1 del método H anteriormente mencionado, haciendo reaccionar un compuesto representado por la fórmula general (XXVIII) con un compuesto representado por la fórmula general (XXXI) en un disolvente, en presencia de un agente de condensación y en presencia o ausencia de una base.

El compuesto representado por la fórmula general (XXXI) usado

en este paso es un compuesto conocido, o se produce fácilmente de acuerdo con un método conocido o un método similar al mismo usando como materia prima inicial un compuesto conocido.

Paso I2

Este paso es para producir un compuesto representado por la fórmula general (Ig).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (XXXII) con cloruro de p-toluenosulfonilo y una base en un disolvente, seguido por la eliminación del grupo protector del grupo amino, hidroxi o carboxilo en R^{2a} y R^{8a} conforme sea necesario.

El disolvente usado en este paso es preferiblemente un hidrocarburo halogenado, de preferencia diclorometano.

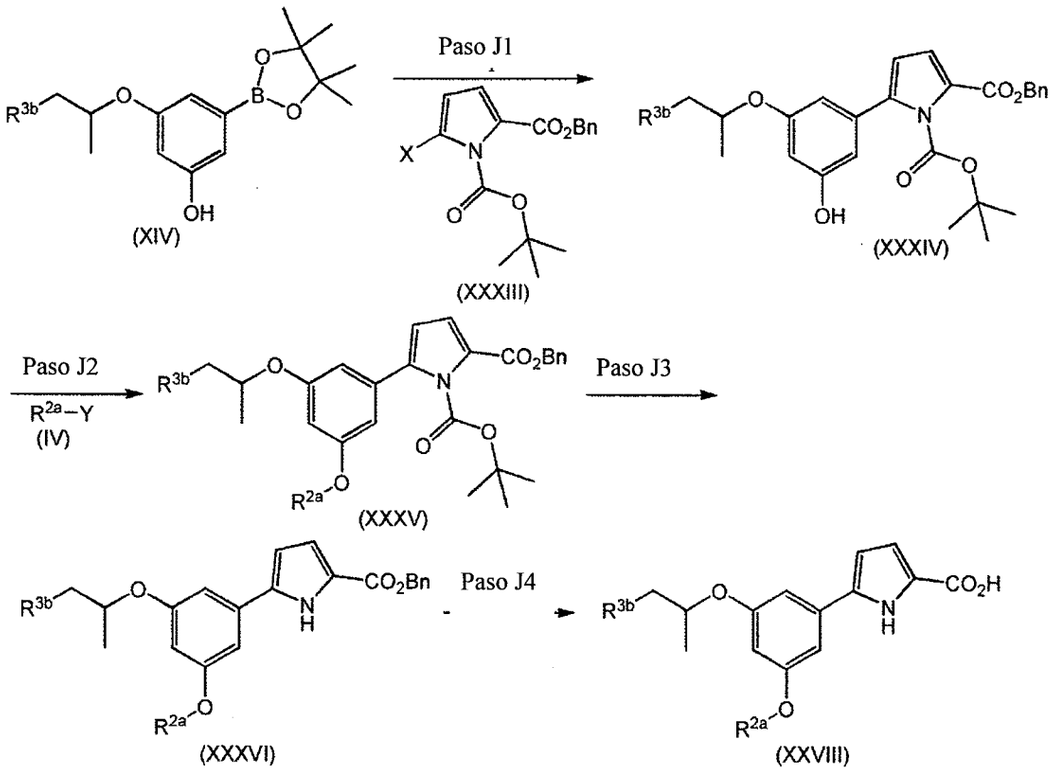
La base usada en este paso es preferiblemente una base orgánica, de preferencia trietilamina.

La temperatura de reacción en este paso normalmente es de -20 °C a 40°C, de preferencia de 0 °C a 30°C.

El tiempo de reacción en este paso normalmente es de 0.5 horas a 24 horas, de preferencia de 1 hora a 12 horas.

El método J es para producir un compuesto representado por la fórmula general (XXVIII), usado en el paso H1 del método H anteriormente mencionado, el paso I1 del método I anteriormente mencionado, y el paso L1 del método L anteriormente mencionado.

METODO J



En la presente invención, R^{2a}, R^{3b}, X y Y son como se define arriba.

Paso J1

Este paso es para producir un compuesto representado por la fórmula general (XXXIV).

Este paso se efectúa igual que el paso A6 del método A anteriormente mencionado, haciendo reaccionar un compuesto representado por la fórmula general (XIV), obtenido en el paso B3 del método B anteriormente mencionado, con un compuesto representado por la fórmula general (XXXIII), en un disolvente y en presencia de un catalizador de paladio

y una base inorgánica.

Paso J2

Este paso es para producir un compuesto representado por la fórmula general (XXXV).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (XXXIV) con un compuesto representado por la fórmula general (IV), en un disolvente y en presencia de una base.

El disolvente usado en este paso es preferiblemente una amida o un nitrilo, de preferencia N,N-dimetilformamida o acetonitrilo.

La base usada en este paso es preferiblemente un carbonato de metal alcalino, de preferencia carbonato de potasio.

La temperatura de reacción en este paso normalmente es de 50 °C a 140°C, de preferencia de 60 °C a 100°C.

El tiempo de reacción en este paso normalmente es de 1 hora a 72 horas, de preferencia de 2 horas a 24 horas.

Paso J3

Este paso es para producir un compuesto representado por la fórmula general (XXXVI).

Este paso se efectúa igual que el paso A7 del método A anteriormente mencionado, haciendo reaccionar un compuesto representado por la fórmula general (XXXV) con un ácido.

Paso J4

Este paso es para producir un compuesto representado por la

fórmula general (XXVIII).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (XXXVI) en un disolvente y bajo una atmósfera de hidrógeno, en presencia de un catalizador de paladio.

El disolvente usado en este paso es preferiblemente un éter, un alcohol o un éster, de preferencia tetrahidrofurano, metanol, etanol o acetato de etilo.

El catalizador de paladio usado en este paso es preferiblemente un catalizador de paladio de valencia cero, de preferencia paladio-carbón activado.

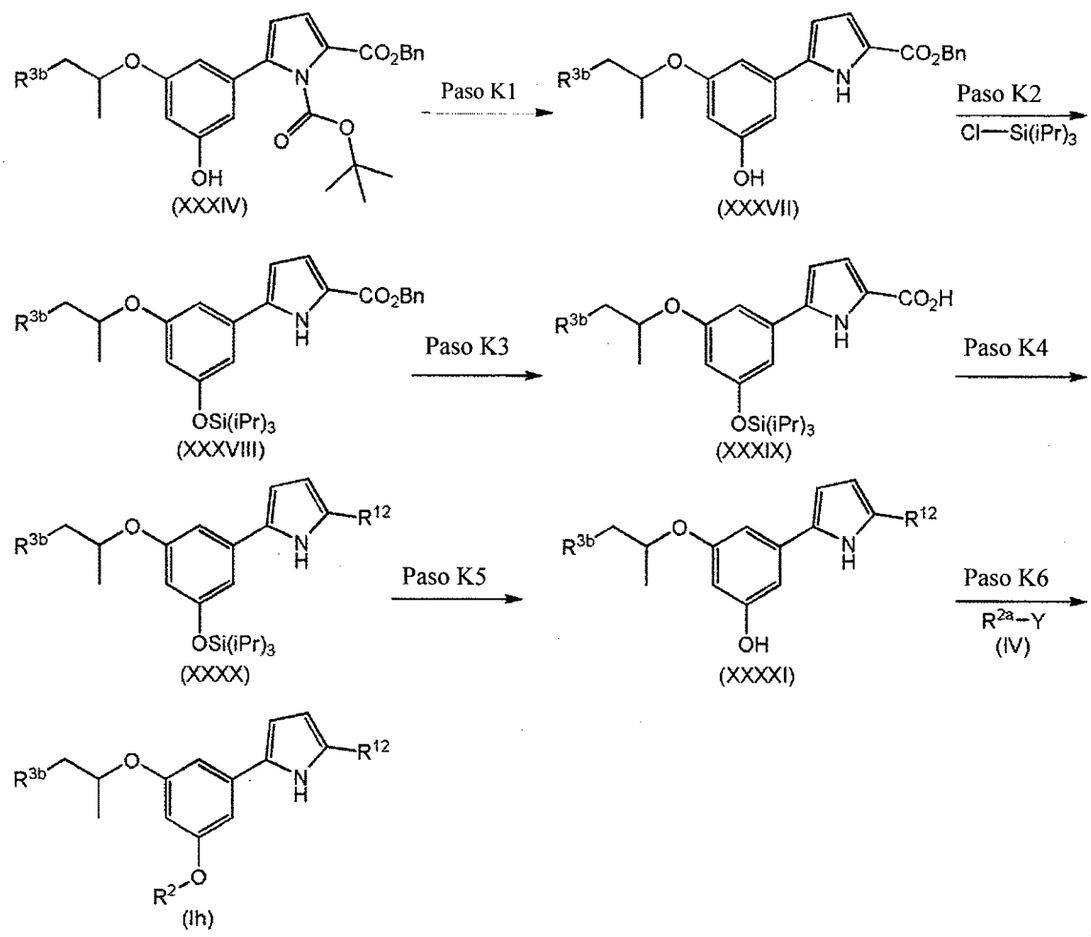
La temperatura de reacción en este paso normalmente es de -10 °C a 40°C, de preferencia de 0 °C a 30°C.

El tiempo de reacción en este paso normalmente es de 0.1 horas a 72 horas, de preferencia de 0.5 horas a 24 horas.

El método K es para producir un compuesto representado por la fórmula general (Ih), en donde el grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están unidos, que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, es un grupo 4,5-dihidro-1,3-oxazol-2-ilo que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, o un grupo 1,3,4-oxadiazol-2-ilo que puede estar sustituido con 1 grupo seleccionado del conjunto de sustituyentes α, y R^3 es un grupo alcoxi de C_1-

C_6, entre los compuestos representados por la fórmula general (I).

METODO K



En la presente invención, R^2, R^{3b}, Y y R^{2a} son como se define arriba, y R^{12} representa un grupo 4,5-dihidro-1,3-oxazol-2-ilo que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, o un grupo 1,3,4-oxadiazol-2-ilo que puede estar sustituido con 1 grupo seleccionado del conjunto de sustituyentes α.

Paso K1

Este paso es para producir un compuesto representado por la fórmula general (XXXVII).

Este paso se efectúa igual que el paso A7 del método A anteriormente mencionado, haciendo reaccionar un compuesto representado por la fórmula general (XXXIV), obtenido en el paso J1 del método J anteriormente mencionado, con un ácido en un disolvente.

Paso K2

Este paso es para producir un compuesto representado por la fórmula general (XXXVIII).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (XXXVII) con cloruro de triisopropilsililo en un disolvente y en presencia de una base.

El disolvente usado en este paso es preferiblemente un hidrocarburo halogenado, de preferencia diclorometano.

La base usada en este paso es preferiblemente una base orgánica, de preferencia trietilamina o una base mixta de trietilamina y 4-dimetilaminopiridina.

La temperatura de reacción en este paso normalmente es de -10 °C a 40°C, de preferencia de 0 °C a 30°C.

El tiempo de reacción en este paso normalmente es de 0.1 horas a 72 horas, de preferencia de 0.5 horas a 24 horas.

Paso K3

Este paso es para producir un compuesto representado por la fórmula general (XXXIX).

Este paso se efectúa igual que el paso J4 del método J haciendo reaccionar un compuesto representado por la fórmula general (XXXVIII) en un disolvente y bajo una atmósfera de hidrógeno, en presencia de un catalizador de paladio.

Paso K4

Este paso es para producir un compuesto representado por la fórmula general (XXXX).

Este paso se efectúa de acuerdo con el método H (pasos H1 y H2), o el método I (pasos I1 e I2).

Paso K5

Este paso es para producir un compuesto representado por la fórmula general (XXXXI).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (XXXX) con fluoruro de tetrabutilamonio en un disolvente.

El disolvente usado en este paso es preferiblemente un éter, de preferencia tetrahidrofurano.

La temperatura de reacción en este paso normalmente es de -10 °C a 40°C, de preferencia de 0 °C a 30°C.

El tiempo de reacción en este paso normalmente es de 0.1 horas

a 12 horas, de preferencia de 0.5 horas a 3 horas.

Paso K6

Este paso es para producir un compuesto representado por la fórmula general (Ih).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (XXXXI) con un compuesto representado por la fórmula general (IV), en un disolvente y en presencia de una base, seguido por la eliminación del grupo protector del grupo amino, hidroxi o carboxilo en R^{2a} conforme sea necesario.

El disolvente usado en este paso es preferiblemente una amida o un nitrilo, de preferencia N,N-dimetilformamida o acetonitrilo.

La base usada en este paso es preferiblemente un carbonato de metal alcalino, de preferencia carbonato de potasio o carbonato de cesio.

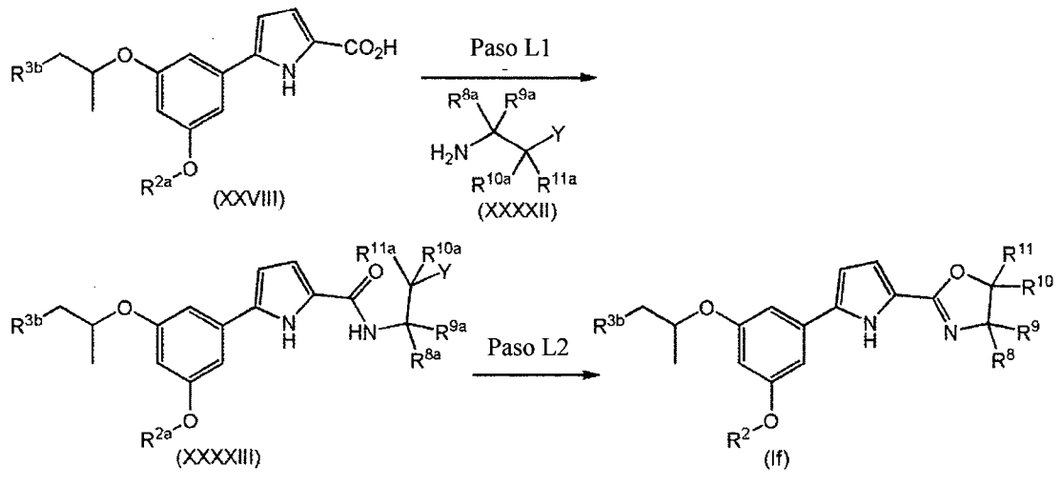
La temperatura de reacción en este paso normalmente es de 10 °C a 140°C, de preferencia de 20 °C a 120°C.

El tiempo de reacción en este paso normalmente es de 1 hora a 72 horas, de preferencia de 2 horas a 24 horas.

El método L es para producir un compuesto representado por la fórmula general (If), en donde el grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están unidos, que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, es un grupo 4,5-dihidro-1,3-oxazol-2-ilo que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α,

y R^3 es un grupo alcoxi de C_1-C_6, entre los compuestos representados por la fórmula general (I).

METODO L



En la presente invención, R^2, R^8, R^9, R^{10}, R^{11}, R^{2a}, R^{3b}, R^{8a}, R^{9a}, R^{10a}, R^{11a} y Y son como se define arriba.

Paso L1

Este paso es para producir un compuesto representado por la fórmula general (XXXXIII).

Este paso se efectúa igual que el paso H1 del método H anteriormente mencionado, haciendo reaccionar un compuesto representado por la fórmula general (XXVIII) con un compuesto representado por la fórmula general (XXXXII) en un disolvente, en presencia de un agente de condensación y una base.

El compuesto representado por la fórmula general (XXXXII)

usado en este paso es un compuesto conocido, o se produce fácilmente de acuerdo con un método conocido o un método similar al mismo usando como materia prima inicial un compuesto conocido.

Paso L2

Este paso es para producir un compuesto representado por la fórmula general (If).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (XXXXIII) con una base en un disolvente, seguido por la eliminación del grupo protector del grupo amino, hidroxi o carboxilo en R^{2a}, R^{8a}, R^{9a}, R^{10a} y R^{11a}, conforme sea necesario.

El disolvente usado en este paso es preferiblemente un éter, de preferencia tetrahidrofurano.

La base usada en este paso es preferiblemente un hidruro de metal alcalino, de preferencia hidruro de sodio.

La temperatura de reacción en este paso normalmente es de -20 °C a 40 °C, de preferencia de 0 °C a 25 °C.

El tiempo de reacción en este paso normalmente es de 0.5 horas a 48 horas, de preferencia de 1 hora a 24 horas.

En las descripciones anteriores, el grupo protector de un "grupo amino opcionalmente protegido", un "grupo hidroxi opcionalmente protegido" y un "grupo carboxilo opcionalmente protegido" en las definiciones de A^a, R^{1a}, R^{2a}, R^{8a}, R^{9a}, R^{10a} y R^{11a}, se refiere a un grupo protector susceptible de ser separado mediante un método químico como hidrogenólisis, hidrólisis,

electrólisis o fotólisis, usados comúnmente en la química orgánica sintética (véase por ejemplo T.W. Greene, *et al.*, "Protective Groups in Organic Sinthesis", 3ª edición, John Wiley & Sons, Inc. (1999)).

En las descripciones anteriores no hay limitaciones particulares sobre el "grupo protector" del "grupo hidroxi opcionalmente protegido" en las definiciones de A^a, R^{1a}, R^{2a}, R^{8a}, R^{9a}, R^{10a} y R^{11a}, siempre que sea un grupo protector de hidroxi usado en el campo de la química orgánica sintética, y los ejemplos incluyen "grupos alquilcarbonilo" tales como un grupo formilo, el "grupo alquilcarbonilo de C_2-C_7" anteriormente mencionado, grupos alquilcarbonilo halogenados como cloroacetilo, dicloroacetilo, tricloroacetilo y trifluoroacetilo, grupos alcoxialquilcarbonilo como metoxiacetilo, y grupos alquilcarbonilo insaturados como acriloilo, propioloilo, metacriloilo, crotonoilo, isocrotonoilo y (E)-2-metil-2-butenoilo; "grupos arilcarbonilo" tales como arilcarbonilo, como benzoilo, α-naftoilo y β-naftoilo, grupos arilcarbonilo halogenados como 2-bromobenzoilo y 4-clorobenzoilo, grupos aril(C_1-C_6)-carbonilo alquilados como 2,4,6-trimetilbenzoilo y 4-toluoilo, grupos aril(C_1-C_6)carbonilo alcoxilados como 4-anisoilo, grupos nitroarilcarbonilo como 4-nitrobenzoilo y 2-nitrobenzoilo, grupos arilcarbonilo de C_2-C_7 alcoxicarbonilados como 2-(metoxicarbonil)benzoilo, y grupos arilcarbonilo arilados como 4-fenilbenzoilo; "grupos alcoxicarbonilo" como el "grupo alcoxicarbonilo de C_2-C_7" anteriormente mencionado, y grupos alcoxicarbonilo de C_2-C_7 sustituidos con un halógeno o tri-alquil(C_1-C_6)sililo como 2,2,2-tricloroetoxicarbonilo y 2-trimetilsililetoxicarbonilo; "grupos tetrahidropiranilo o

tetrahidrotiopiranilo" como tetrahidropiran-2-ilo, 3-bromotetrahidropiran-2-ilo, 4-metoxitetrahidropiran-4-ilo, tetrahidrotiopiran-2-ilo y 4-metoxitetrahidrotiopiran-4-ilo; "grupos tetrahidrofuranilo o tetrahidrotiofuranilo" como tetrahidrofuran-2-ilo y tetrahidrotiofuran-2-ilo; "grupos sililo" tales como grupos como tri-alquil(C_1-C_6)sililo como trimetilsililo, trietilsililo, isopropildimetilsililo, t-butildimetilsililo, metildiisopropilsililo, metil-di-t-butilsililo y triisopropilsililo, y grupos alquil(C_1-C_6)diarilsililo y di-alquil(C_1-C_6)arilsililo como difenilmetilsililo, difenilbutilsililo, difenilisopropilsililo y fenildiisopropilsililo; "grupos alcoximetilo" tales como los grupos alcoxi(C_1-C_6)metilo como metoximetilo, 1,1-dimetil-1-metoximetilo, etoximetilo, propoximetilo, isopropoximetilo, butoximetilo y t-butoximetilo, grupos alcoxi(C_1-C_6)-alcoxi(C_1-C_6)-metilo como 2-metoxietoximetilo, y grupos alcoxi(C_1-C_6)metilo halogenados como 2,2,2-tricloroetoximetilo y bis(2-cloroetoxi)metilo; "grupos etilo sustituidos" tales como los grupos alcoxi(C_1-C_6)etilo como 1-etoxietilo y 1-(isopropoxi)etilo, y grupos etilo halogenados como 2,2,2-tricloroetilo; "grupos aralquilo" tales como los grupos alquilo de C_1-C_6 sustituidos con 1 a 3 grupos arilo como bencilo, α-naftilmetilo, β-naftilmetilo, difenilmetilo, trifenilmetilo, α-naftildifenilmetilo y 9-antrilmetilo, y grupos alquilo de C_1-C_6 sustituidos con 1 a 3 grupos arilo, en donde un anillo de arilo está sustituido con un alquilo de C_1-C_6, alcoxi de C_1-C_6, nitro, halógeno o ciano, como 4-metilbencilo, 2,4,6-trimetilbencilo, 3,4,5-trimetilbencilo, 4-metoxibencilo, 4-metoxifenildifenilmetilo, 2-nitrobencilo, 4-nitrobencilo, 4-clorobencilo, 4-bromobencilo y 4-cianobencilo; "grupos alqueniloxicarbonilo" como viniloxicarbonilo y aliloxicarbonilo; y

"grupos aralquiloxicarbonilo" en donde un anillo de arilo está sustituido opcionalmente con 1 o 2 grupos alcoxi de C_1-C_6 o nitro, como benciloxicarbonilo, 4-metoxibenciloxicarbonilo, 3,4-dimetoxibenciloxicarbonilo, 2-nitrobenciloxicarbonilo y 4-nitrobenciloxicarbonilo; de preferencia grupos alquilcarbonilo, grupos sililo o grupos aralquilo.

En las descripciones anteriores no hay limitaciones particulares sobre el "grupo protector" de un "grupo carboxilo opcionalmente protegido" en las definiciones de A^a, R^{1a}, R^{2a}, R^{8a}, R^{9a}, R^{10a} y R^{11a}, siempre que sea un grupo protector de carboxilo usado en el campo de la química orgánica sintética, y los ejemplos incluyen el "grupo alquilo de C_1-C_6" anteriormente mencionado; el "grupo alquenilo de C_2-C_6" anteriormente mencionado; el "grupo alquinilo de C_2-C_6" anteriormente mencionado; el "grupo alquilo de C_1-C_6 halogenado" anteriormente mencionado; grupos hidroxialquilo de C_1-C_6 como hidroximetilo y 2-hidroxietilo; grupos alquilcarbonil(C_2-C_7)-alquilo(C_1-C_6) como acetilmetilo; los "grupos aralquilo" anteriormente mencionados, y los "grupos sililo" anteriormente mencionados; de preferencia grupos alquilo o aralquilo de C_1-C_6.

En las descripciones anteriores, no hay limitaciones particulares sobre el "grupo protector" del "grupo amino opcionalmente protegido" en las definiciones de A^a, R^{1a}, R^{2a}, R^{8a}, R^{9a}, R^{10a} y R^{11a}, siempre que sea un grupo protector de amino usado en el campo de la química orgánica sintética, y ejemplos de los mismos incluyen grupos similares a los "grupos alquilcarbonilo", "grupos arilcarbonilo", "grupos alcoxicarbonilo", "grupos sililo",

"grupos aralquilo", "grupos alqueniloxicarbonilo" y "grupos aralquiloxicarbonilo" mencionados anteriormente como "grupos protectores de hidroxi", y "grupos metileno sustituidos que forman una base de Schiff", tales como N,N-dimetilaminometileno, bencilideno, 4-metoxibencilideno, 4-nitrobencilideno, salicilideno, 5-clorosalicilideno, difenilmetileno y (5-cloro-2-hidroxifenil)fenilmetileno; preferiblemente grupos alquilcarbonilo, grupos arilcarbonilo o grupos alcoxicarbonilo, de preferencia grupos alcoxicarbonilo.

Los pasos que requieren protección/desprotección se realizan de acuerdo con los métodos conocidos (por ejemplo, los métodos descritos en Theodora W. Greene, Peter G. M. Wuts, "Protective Groups in Organic Sinthesis", 1999, A Wiley-Interscience Publication, etc.).

El compuesto de la presente invención o su sal farmacológicamente aceptable se pueden administrar de varias maneras. Ejemplos de las vías de administración incluyen administración oral usando tabletas, cápsulas, gránulos, emulsiones, píldoras, polvos, jarabes (soluciones), etcétera; y administración parenteral usando inyecciones (administración intravenosa, intramuscular, subcutánea o intraperitoneal), infusiones de goteo, supositorios (administración rectal), etcétera. Estas composiciones farmacéuticas se preparan de acuerdo con los métodos usuales, usando los auxiliares comunes en el campo de la farmacia, tales como excipientes, aglutinantes, desintegradores, lubricantes, agentes saborizantes, auxiliares de disolución, agentes de suspensión y agentes de recubrimiento, además del principio activo.

Para usarse como tableta, los ejemplos de los vehículos que se pueden usar incluyen excipientes como lactosa, sacarosa, cloruro de sodio, glucosa, urea, almidón, carbonato de calcio, caolin, celulosa cristalina y ácido silícico; aglutinantes como agua, etanol, propanol, jarabe simple, solución de glucosa, solución de almidón, solución de gelatina, carboximetilcelulosa, goma laca, metilcelulosa, fosfato de potasio y polivinilpirrolidona; desintegradores como almidón seco, alginato de sodio, polvo de agar, polvo de laminaran, carbonato ácido de sodio, carbonato de calcio, ésteres de ácido graso de polioxietilensorbitán, laurilsulfato de sodio, monoglicérido esteárico, almidón y lactosa; inhibidores de desintegración como sacarosa, estearina, manteca de cacao y aceite hidrogenado; incrementadores de absorción como sales de amonio cuaternario y laurilsulfato de sodio; humectantes como glicerina y almidón; adsorbentes como almidón, lactosa, caolín, bentonita y ácido silícico coloidal; lubricantes como talco purificado, estearato, polvo de ácido fluobórico y polietilenglicol, etcétera. Además, si se requiere, se pueden preparar tabletas recubiertas comunes, tales como por ejemplo tabletas grageadas, tabletas con recubrimiento de gelatina, tabletas con recubrimiento entérico, tabletas con recubrimiento de película, tabletas de doble capa y tabletas de multicapa.

Para usarse como píldora, los ejemplos de los vehículos que se pueden usar incluyen excipientes tales como glucosa, lactosa, manteca de cacao, aceite vegetal hidrogenado, caolin y talco; aglutinantes como goma arábiga pulverizada, tragacanto pulverizado, gelatina y etanol;

desintegradores como laminaran, ~~y~~ agar, etcétera.

Para usarse como supositorio se puede usar una amplia gama de vehículos conocidos en este campo, por ejemplo polietilenglicol, manteca de cacao, alcoholes superiores, ésteres de alcoholes superiores, gelatina, glicéridos semisintéticos, etcétera.

Para usarse como inyección se pueden preparar soluciones, emulsiones o suspensiones. Preferiblemente, estas soluciones, emulsiones y suspensiones se esterilizan y se hacen isotónicas con la sangre. Las soluciones ~~Los disolventes~~ para producir estas soluciones, emulsiones y suspensiones no están limitados particularmente, en tanto se puedan usar como diluentes para uso medicinal, por ejemplo agua, etanol, propilenglicol, alcohol isoestearílico etoxilado, alcohol isoestearílico polioxilado, ésteres de ácido graso de polioxietilensorbitán, etcétera. En este caso se puede agregar una cantidad suficiente de cloruro de sodio, glucosa o glicerina para hacer una solución isotónica, y también se pueden agregar los auxiliares de disolución usuales, amortiguadores, agentes balsámicos, etcétera.

Además, si es necesario se pueden agregar a las composiciones farmacéuticas anteriormente mencionadas agentes colorantes, conservadores, perfumes, agentes saborizantes, edulcorantes, etcétera. Además también se pueden agregar otros fármacos.

La cantidad de compuesto contenido como principio activo en las composiciones farmacéuticas anteriormente mencionadas no está limitada particularmente, pero usualmente es de 0.5% a 70% en peso del total de la

composición farmacéutica, de preferencia de 1% a 30% en peso.

La dosis varía dependiendo de los síntomas, la edad, etcétera del paciente (un animal de sangre caliente, en particular un humano). En caso de administración oral, la dosis diaria recomendada para un adulto es de 0.1 mg como límite inferior (preferiblemente 1 mg, de preferencia 10 mg), a 2000 mg como límite superior (preferiblemente 100 mg), que se dividen en 1 a 6 dosis dependiendo de los síntomas.

EJEMPLOS

Aunque lo siguiente provee una explicación más detallada de la presente invención por medio de ejemplos y ejemplos de prueba, el alcance de la presente invención no se limita a los mismos.

La elución de cromatografía en columna indicada en los ejemplos se hizo bajo observación por medio de cromatografía en capa delgada (TLC). Para las observaciones de TLC se usó una placa de TLC de gel de sílice $60F_{254}$ de Merck; el disolvente de elución usado en la cromatografía en columna se usó como disolvente de desarrollo, y para la detección se usó un detector de UV. Para la cromatografía en columna se usó gel de sílice SK-85 (malla 230 a 400) de Merck, o gel de sílice FL100B de Fuji Silysia Chemical. Además de la cromatografía en columna común se usó un sistema de cromatografía automático (Purif-α2) y una columna desechable (Purif-pack) de Moritex. Para purificación por TLC preparativa se usó una

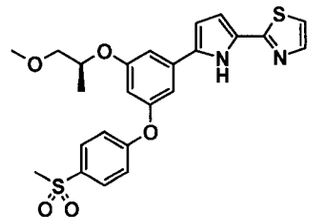
placa de gel de sílice $60F_{254}$ de Merck que tiene un grosor de 0.5 mm y mide 20 cm x 20 cm. Además, las abreviaturas usadas en los ejemplos tienen los significados que se indican: mg: miligramos, g: gramos, mL: mililitros, MHz: megaHertz, HATU: hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio, WSCI·HCl: clorhidrato de 1-etil-3-(dimetilaminopropil)carbodiimida, HOBT·H_2O: 1-hidroxibenzotriazol monohidratado.

En los siguientes ejemplos se obtuvieron espectros de resonancia magnética nuclear (llamados ^{1}H-RMN) usando como estándar tetrametilsilano, y los valores de desplazamiento químico se indican con valores δ (ppm). En los patrones de división, un singulete se indica con una "s", un doblete con una "d", un triplete con una "t", un cuarteto con una "q", un patrón amplio con "br" y un multiplete con una "m".

Se efectuó espectrometría de masa, referida como (MS), con el método de bombardeo atómico rápido (FAB), el método de ionización electrónica (EI), o el método de ionización de electroaspersión (ESI).

EJEMPLO 1

2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol



(1a) 3-Bromo-5-metoxifenol

Se disolvió 1-bromo-3,5-dimetoxibenceno (18.74 g, 86.3 mmol), disponible comercialmente, en 1-metil-2-pirrolidona (100 mL), y se le agregó tiometóxido sodio (6.74 g, 96.2 mmol), seguido por agitación a 100°C durante 3 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó ácido clorhídrico 1N (200 mL) y se extrajo con éter dietílico (500 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-25%), para producir el compuesto deseado como un sólido blanco (15.03 g, rendimiento de 86%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 3.77 (3H, s), 4.82 (1H, s), 6.33 (1H, t, J = 2.4 Hz), 6.61 (1H, t, J = 2.0 Hz), 6.66 (1H, t, J = 2.0 Hz).

(1b) 1-Bromo-3-metoxi-5-[4-(metilsulfonil)fenoxi]benceno

El 3-bromo-5-metoxifenol (13.10 g, 64.5 mmol) sintetizado en el

ejemplo (1a) y 4-fluorofenilmetilsulfona (10.45 g, 60.0 mmol), disponible comercialmente, se disolvieron en N,N-dimetilformamida (100 mL), y a esto se le agregó carbonato de potasio (25.00 g, 181 mmol), seguido por agitación a 100°C durante 36 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, el carbonato de potasio se removió por filtración en Celite; subsiguientemente se agregó a la solución ácido clorhídrico 0.1N (500 mL) y se extrajo dos veces con éter dietílico (400 mL) y acetato de etilo (100 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el sólido resultante se lavó con éter dietílico para producir el compuesto deseado como un sólido pardo pálido (18.30 g, rendimiento de 79%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 3.07 (3H, s), 3.80 (3H, s), 6.56 (1H, t, J = 2.4 Hz), 6.81 (1H, t, J = 2.0 Hz), 6.92 (1H, t, J = 2.0 Hz), 7.12 (2H, d, J = 9.0 Hz), 7.92 (2H, d, J = 9.0 Hz).

(1c) 3-Bromo-5-[4-(metilsulfonil)fenoxi]fenol

El 1-bromo-3-metoxi-5-[4-(metilsulfonil)fenoxi]benceno (18.29 g, 51.2 mmol) sintetizado en el ejemplo (1b) se disolvió en diclorometano (400 mL) y se enfrió a -78°C; se le agregó tribromuro de boro (solución 1.0M en diclorometano, 100 mL, 100 mmol) usando un embudo de goteo durante 30 minutos bajo una atmósfera de nitrógeno. La mezcla se agitó a -78°C durante 2 horas, seguido por aumento de la temperatura de forma natural y agitación a temperatura ambiente durante la noche. Se le agregó una solución acuosa

saturada de carbonato ácido de sodio bajo enfriamiento en un baño de hielo para neutralizar la solución de reacción, y se extrajo dos veces con diclorometano (500 mL) y metanol (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida para producir el compuesto deseado como un sólido amarillo pálido (16.89 g, rendimiento de 96%).

^{1}H-RMN (DMSO-D_6, 400 MHz): δ 3.19 (3H, s), 6.49 (1H, t, J = 2.1 Hz), 6.77 (1H, t, J = 2.0 Hz), 6.84 (1H, t, J = 2.0 Hz), 7.23 (2H, d, J = 8.6 Hz), 7.94 (2H, d, 9.0 Hz), 10.27 (1H, s).

(1d) 3-[4-(Metilsulfonil)fenoxi]-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenol

El 3-bromo-5-[4-(metilsulfonil)fenoxi]fenol (10.10 g, 29.4 mmol) sintetizado en el ejemplo (1c) se disolvió en N,N-dimetilformamida (100 mL) y se le agregó bis(pinacolato)diboro (11.09 g, 43.7 mmol), complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano (722 mg, 0.884 mmol) y acetato de potasio (14.92 g, 152 mmol), seguido por agitación a 90°C durante 5 horas bajo una atmósfera de nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente, se diluyó con acetato de etilo (400 mL) y el material insoluble se removió por filtración en Celite. Se agregó agua (400 mL) al filtrado para separarlo y la capa orgánica se lavó con salmuera saturada, seguido por secado sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se

purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-50%), para producir el compuesto deseado como un sólido blanco (11.88 g, rendimiento de ~100%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (12H, s), 3.06 (3H, s), 5.16 (1H, s), 6.69 (1H, t, J = 2.4 Hz), 7.06-7.12 (4H, m), 7.87 (2H, t, J = 9.0 Hz).

(1e) 2-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-4,4,5,5-tetrametil-1,3,2-dioxaborolano

El 3-[4-(metilsulfonil)fenoxi]-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenol (13.20 g, 33.8 mmol) sintetizado en el ejemplo (1d) se disolvió en tetrahidrofurano (300 mL) y se le agregó (R)-(-)-1-metoxi-2-propanol (3.70 mL, 37.8 mmol) y trifenilfosfina (9.78 g, 37.3 mmol); subsiguientemente se enfrió a 0°C. Se le agregó a gotas azodicarboxilato de dietilo (solución en tolueno al 40%, 16.2 mL, 37.2 mmol) durante 10 minutos, bajo una atmósfera de nitrógeno, y se agitó a 0°C durante 30 minutos, seguido por aumento natural de la temperatura y agitación a temperatura ambiente durante la noche. Se le agregó agua (300 mL) y acetato de etilo (300 mL) y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-40%), para producir el compuesto deseado como un aceite incoloro (11.94 g, rendimiento de 76%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J = 6.7 Hz), 1.33 (12H,

s), 3.05 (3H, s), 3.40 (3H, s), 3.48 (1H, dd, J = 4.3, 10.2 Hz), 3.57 (1H, dd, J = 5.9, 10.2 Hz), 4.58-4.62 (1H, m), 6.76 (1H, t, J = 2.4 Hz), 7.05-7.09 (3H, m), 7.24 (1H, d, J = 2.4 Hz), 7.87 (2H, d, J = 9.0 Hz).

(1f) 2-(1,3-Tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo

Se disolvió ácido 1-(t-butoxicarbonil)pirrol-2-borónico (10.06 g, 47.7 mmol), disponible comercialmente, en un disolvente mixto de 1,2-dimetoxietano (150 mL) y agua (25 mL), y se le agregó 2-bromotiazol (4.40 mL, 48.8 mmol), acetato de paladio (II) (535 mg, 2.38 mmol), trifenilfosfina (2.50 g, 9.53 mmol) y carbonato de potasio (19.50 g, 141 mmol), seguido por agitación a 90°C durante 16 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (300 mL) y acetato de etilo (400 mL), y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-20%), para producir el compuesto deseado como un aceite amarillo pálido (6.71 g, rendimiento de 56%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.42 (9H, s), 6.26 (1H, t, J = 3.4 Hz), 6.58 (1H, dd, J = 1.6, 3.5 Hz), 7.37 (1H, d, J = 3.1 Hz), 7.41 (1H, dd, J = 1.6, 3.1 Hz), 7.85 (1H, d, J = 3.1 Hz).

(1g) 2-Bromo-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo

El 2-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (6.70 g,

26.8 mmol) sintetizado en el ejemplo (1f) se disolvió en tetrahidrofurano (100 mL) y se enfrió a 0°C. Con agitación y bajo una atmósfera de nitrógeno se dividió en 5 partes N-bromosuccinimida (4.79 g, 26.9 mmol) para agregarse cada 10 minutos, seguido por más agitación a 0°C durante 2 horas. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (200 mL) y se extrajo con acetato de etilo (300 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-16%), para producir el compuesto deseado como un sólido blanco (7.55 g, rendimiento de 86%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.47 (9H, s), 6.30 (1H, d, J = 3.9 Hz), 6.52 (1H, d, J = 3.9 Hz), 7.29 (1H, d, J = 3.1 Hz), 7.79 (1H, d, J = 3.1 Hz).

(1h) 2-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo

El 2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-4,4,5,5-tetrametil-1,3,2-dioxaborolano (6.44 g, 13.9 mmol) sintetizado en el ejemplo (1e), y el 2-bromo-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (5.21 g, 15.8 mmol) sintetizado en el ejemplo (1g), se disolvieron en un disolvente mixto de 1,4-dioxano (200 mL) y agua (50 mL) y se les agregó complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano (564 mg, 0.691 mmol) y carbonato de potasio (9.67 g, 70.0 mmol), seguido por agitación a 50°C durante 3 horas bajo una atmósfera de

nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente se le agregó agua (200 mL) y se extrajo con acetato de etilo (400 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-50%), para producir el compuesto deseado como un aceite amarillo pálido (7.12 g, rendimiento de 88%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.31 (9H, s), 1.32 (3H, d, J = 6.4 Hz), 3.05 (3H, s), 3.40 (3H, s), 3.49 (1H, dd, J = 3.9, 10.3 Hz), 3.58 (1H, dd, J = 5.9, 10.3 Hz), 4.53-4.57 (1H, m), 6.27 (1H, d, J = 3.9 Hz), 6.58 (1H, d, J = 3.9 Hz), 6.65 (1H, s), 6.72 (1H, s), 6.89 (1H, s), 7.15 (2H, d, J = 8.8 Hz), 7.31 (1H, d, J = 3.4 Hz), 7.81 (1H, d, J = 3.4 Hz), 7.89 (2H, d, J = 8.8 Hz).

(1i) 2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-1,3-tiazol

El 2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (7.16 g, 12.2 mmol) sintetizado en el ejemplo (1h) se disolvió en diclorometano (15 mL) y se enfrió a 0°C. Se le agregó a gotas ácido trifluoroacético (30 mL) con agitación y bajo una atmósfera de nitrógeno. Se agitó a temperatura ambiente durante 30 minutos, seguido por más agitación a 40°C durante 30 minutos. El disolvente se removió por destilación bajo presión reducida, seguido por dilución con acetato de etilo (300 mL); se le agregó una solución acuosa saturada de

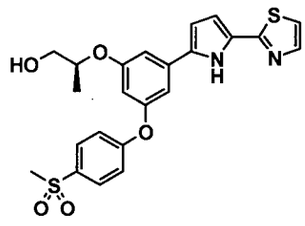
carbonato ácido de sodio (200 mL) y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-50%), para producir el compuesto deseado como un sólido amarillo pálido (5.21 g, rendimiento de 88%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 3.9, 10.2 Hz), 3.59 (1H, dd, J = 5.9, 10.2 Hz), 4.55-4.60 (1H, m), 6.53-6.56 (2H, m), 6.73 (1H, dd, J = 2.4, 3.5 Hz), 6.85 (1H, t, J = 2.0 Hz), 7.02 (1H, t, J = 2.0 Hz), 7.14 (2H, d, J = 8.6 Hz), 7.17 (1H, d, J = 3.5 Hz), 7.67 (1H, d, J = 3.5 Hz), 7.91 (2H, d, J = 8.6 Hz), 9.60 (1H, brs).

MS (ESI) m/z: 485.12291 $(M+H)^+$.

EJEMPLO 2

(2S)-2-{3-[4-(Metilsulfonil)fenoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]}fenoxi]}propan-1-ol



Bajo una atmósfera de nitrógeno, el 2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol (88.8 mg,

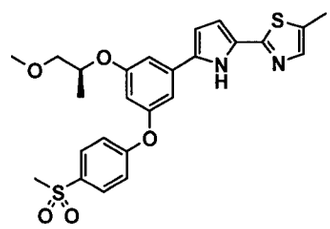
0.183 mmol) sintetizado en el ejemplo (1i) se disolvió en diclorometano (5 mL), y se le agregó una solución de tribromuro de boro/diclorometano (1.0M, 220 μL, 0.22 mmol) a -78°C. Subsiguientemente, la temperatura se regresó a la temperatura ambiente, seguido por agitación durante 30 minutos. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio, y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-50%), para producir el compuesto deseado como un sólido amarillo pálido (52.2 mg, rendimiento de 61%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.76-3.79 (2H, m), 4.56 (1H, dd, J = 10.6, 6.3 Hz), 6.52-6.55 (2H, m), 6.74 (1H, dd, J = 3.7, 2.5 Hz), 6.87 (1H, t, J = 1.8 Hz), 7.01 (1H, t, J = 1.8 Hz), 7.14 (2H, d, J = 9.0 Hz), 7.68 (1H, d, J = 3.5 Hz), 7.91 (2H, dt, J = 9.5, 2.3 Hz), 9.73 (1H, s).

MS (FAB) m/z: 471 $(M+H)^+$.

EJEMPLO 3

2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-5-metil-1,3-tiazol



(3a) 2-[1-(Triisopropilsilil)-1H-pirrol-2-il]-1,3-tiazol

El 2-(1H-pirrol-2-il)-1,3-tiazol (1.42 g, 9.45 mmol), conocido en la literatura (*European Journal of Organic Chemistry*, vol. 2000, No. 13, 2449-2458 (2000)), se disolvió en N,N-dimetilformamida (100 mL) y se enfrió a 0°C. Se le agregó hidruro de sodio (aceite al 60%, 570 mg, 14.3 mmol) y cloruro de triisopropilsililo (4.0 mL, 18.7 mmol), y se agitó a temperatura ambiente durante 30 minutos bajo una atmósfera de nitrógeno. Se le agregó agua (100 mL) y éter dietílico (100 mL) y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: hexano), para producir el compuesto deseado como un aceite amarillo pálido (2.33 g, rendimiento de 80%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.09 (18H, d, J = 7.4 Hz), 1.74 (3H, m), 6.30 (1H, t, J = 3.1 Hz), 6.78 (1H, dd, J = 1.5, 3.1 Hz), 7.04 (1H, m), 7.13 (1H, d, J = 3.1 Hz), 7.64 (1H, d, J = 3.1 Hz).

(3b) 5-Metil-2-[1-(triisopropilsilil)-1H-pirrol-2-il]-1,3-tiazol

El 2-[1-(triisopropilsilil)-1H-pirrol-2-il]-1,3-tiazol (317 mg, 1.03 mmol) sintetizado en el ejemplo (3a) se disolvió en tetrahidrofurano (10 mL) y se enfrió a -78°C. Se le agregó a gotas n-butil-litio (solución en hexano 2.64M, 0.51 mL, 1.35 mmol), seguido por agitación durante 40 minutos; subsiguientemente se le agregó yodometano (0.13 mL, 2.09 mmol) y se agitó durante 3 horas aumentando gradualmente la temperatura de -78°C a temperatura ambiente. Se le agregó agua (10 mL) y se extrajo con éter dietílico (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: hexano), para producir el compuesto deseado como un aceite incoloro (215 mg, rendimiento de 65%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.09 (18H, d, J = 7.8 Hz), 1.73 (3H, m), 2.44 (3H, s), 6.28 (1H, m), 6.68 (1H, m), 7.04 (1H, m), 7.01 (1H, m), 7.27 (1H, brs).

(3c) 5-Metil-2-(1H-pirrol-2-il)-1,3-tiazol

El 5-metil-2-[1-(triisopropilsilil)-1H-pirrol-2-il]-1,3-tiazol (215 mg, 0.67 mmol) sintetizado en el ejemplo (3b) se disolvió en tetrahidrofurano (8 mL), y se le agregó fluoruro de tetrabutilamonio (solución en tetrahidrofurano 1M, 0.87 mL, 0.87 mmol), seguido por agitación a temperatura ambiente durante 30 minutos bajo una atmósfera de nitrógeno. Se le agregó agua (10

mL) y se extrajo con éter dietílico (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 5%-30%), para producir el compuesto deseado como un sólido blanco (100 mg, rendimiento de 91%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.46 (3H, s), 6.25 (1H, m), 6.61 (1H, m), 6.87 (1H, m), 7.30 (1H, brs), 9.68 (1H, brs).

(3d) 2-(5-Bromo-1H-pirrol-2-il)-5-metil-1,3-tiazol

El 5-metil-2-(1H-pirrol-2-il)-1,3-tiazol (100 mg, 0.61 mmol) sintetizado en el ejemplo (3c) se disolvió en tetrahidrofurano (7 mL) y se enfrió a 0°C. Se le agregó N-bromosuccinimida (108 mg, 0.61 mmol) y se agitó a temperatura ambiente durante 18 horas bajo una atmósfera de nitrógeno. Se le agregó agua (10 mL) y la solución se separó con éter dietílico (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se usó como tal en la siguiente reacción.

(3e) 2-Bromo-5-(5-metil-1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo

Un producto crudo purificado del 2-(5-bromo-1H-pirrol-2-il)-5-metil-1,3-tiazol sintetizado en el ejemplo (3d), se disolvió en diclorometano (8 mL), y se le agregó dicarbonato de di-t-butilo (165 mg, 1.35 mmol), trietilamina

(0.18 mL, 1.29 mmol) y 4-dimetilaminopiridina (8.0 mg, 0.065 mmol), seguido por agitación a temperatura ambiente durante 1.5 horas bajo una atmósfera de nitrógeno. Se le agregó agua (10 mL) y se extrajo con diclorometano (10 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-20%), para producir el compuesto deseado como un aceite incoloro (172 mg, rendimiento de 84%, 2 pasos).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.48 (9H, s), 2.47 (3H, s), 6.28 (1H, d, J = 3.5 Hz), 6.45 (1H, d, J = 3.5 Hz), 7.42 (1H, m).

(3f) 2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-5-metil-1,3-tiazol

El 2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-4,4,5,5-tetrametil-1,3,2-dioxaborolano (220 mg, 0.492 mmol) sintetizado en el ejemplo (1e), y el 2-bromo-5-(5-metil-1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (598 mg, 1.49 mmol) sintetizado en el ejemplo (3e), se disolvieron en 1,4-dioxano (10 mL) y se les agregó complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano (20.0 mg, 0.024 mmol) y una solución acuosa de carbonato de sodio (3M, 0.33 mL, 0.990 mmol), seguido por agitación a 50°C durante 20 horas bajo una atmósfera de nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente, se le agregó agua (10 mL) y se extrajo con acetato de etilo (20 mL).

La capa orgánica se lavó con salmuera saturada; subsiguientemente se secó sobre sulfato de magnesio anhidro y el disolvente se removió por destilación bajo presión reducida.

El residuo resultante se disolvió en diclorometano (10 mL) y se enfrió a 0°C. Se le agregó a gotas ácido trifluoroacético (10 mL) con agitación y bajo una atmósfera de nitrógeno. Después de agitar a temperatura ambiente durante 30 minutos, el disolvente se removió por destilación bajo presión reducida, seguido por dilución con acetato de etilo (30 mL); se le agregó una solución acuosa saturada de carbonato ácido de sodio (20 mL) y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-40%), para producir el compuesto deseado como un sólido amarillo pálido (49.6 mg, rendimiento de 20%).

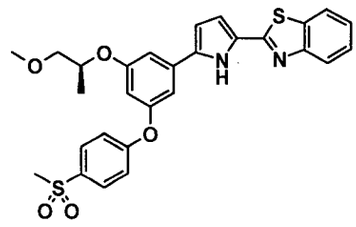
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 2.46 (3H, brs), 3.07 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 3.9, 10.2 Hz), 3.61 (1H, dd, J = 5.9, 10.2 Hz), 4.56 (1H, m), 6.50-6.54 (2H, m), 6.63 (1H, dd, J = 2.4, 3.9 Hz), 6.85 (1H, t, J = 2.0 Hz), 7.02 (1H, t, J = 2.0 Hz), 7.13 (1H, d, J = 8.6 Hz), 7.29 (1H, t, J = 2.0 Hz), 7.90 (2H, d, J = 8.6 Hz), 9.89 (1H, brs).

MS (ESI) m/z: 521.11551 $(M+Na)^+$.

557

EJEMPLO 4

2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-1,3-benzotiazol



(4a) 2-(1,3-Benzotiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo

Se disolvió ácido 1-(t-butoxicarbonil)pirrol-2-borónico (417 mg, 1.98 mmol), disponible comercialmente, en 1,2-dimetoxietano (20 mL), y se le agregó 2-cloro-1,3-benzotiazol (0.25 mL, 2.02 mmol), acetato de paladio (II) (23.0 mg, 0.102 mmol), trifenilfosfina (105 mg, 0.400 mmol) y una solución acuosa de carbonato de potasio (3M, 1.3 mL, 0.433 mmol), seguido por agitación a 100°C durante 22 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) y acetato de etilo (20 mL) y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-20%), para producir el compuesto deseado como un aceite amarillo pálido (490 mg, rendimiento de 82%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.38 (9H, s), 6.30 (1H, t, J = 3.1

Hz), 6.72 (1H, dd, J = 2.0, 3.1 Hz), 7.39 (1H, ddd, J = 1.2, 7.0, 8.0 Hz), 7.46 (1H, dd, J = 2.0, 3.1 Hz), 7.49 (1H, ddd, J = 1.2, 7.0, 8.0 Hz), 7.89 (1H, brd, J = 8.0 Hz), 8.05 (1H, dt, J = 1.2, 8.0 Hz).

(4b) 2-Bromo-5-(1,3-benzotiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo

El 2-(1,3-benzotiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (490 mg, 1.63 mmol) sintetizado en el ejemplo (4a) se disolvió en tetrahidrofurano (20 mL), y se enfrió a 0°C. Se le agregó N-bromosuccinimida (290 mg, 1.63 mmol) y se agitó a temperatura ambiente durante 14 horas bajo una atmósfera de nitrógeno. Se le agregó agua (20 mL) y se extrajo con éter dietílico (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-16%), para producir el compuesto deseado como un sólido amarillo pálido (548 mg, rendimiento de 89%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.52 (9H, s), 6.34 (1H, d, J = 3.9 Hz), 6.69 (1H, d, J = 3.9 Hz), 7.37 (1H, dt, J = 1.2, 8.0 Hz), 7.46 (1H, dt, J = 1.2, 8.0 Hz), 7.86 (1H, brd, J = 8.0 Hz), 7.93 (1H, brd, J = 8.0 Hz).

(4c) 2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-1,3-benzotiazol

El 2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-4,4,5,5-tetrametil-1,3,2-dioxaborolano (305 mg, 0.682 mmol) sintetizado

en el ejemplo (1e), y el 2-bromo-5-(1,3-benzotiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (260 mg, 0.686 mmol) sintetizado en el ejemplo (4b), se disolvieron en 1,2-dimetoxietano (20 mL) y se les agregó complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano (28 mg, 0.034 mmol) y una solución acuosa de carbonato de potasio (3M, 0.44 mL, 1.32 mmol), seguido por agitación a 50°C durante 17 horas bajo una atmósfera de nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) y se extrajo con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada; subsiguientemente se secó sobre sulfato de magnesio anhidro y el disolvente se removió por destilación bajo presión reducida.

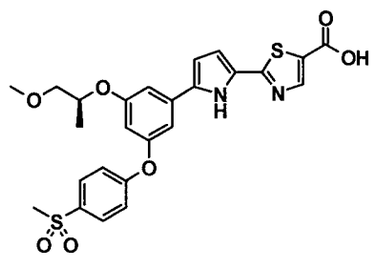
El residuo resultante se disolvió en diclorometano (10 mL) y se enfrió a 0°C. Se le agregó a gotas ácido trifluoroacético (10 mL) con agitación y bajo una atmósfera de nitrógeno. Después de agitar a temperatura ambiente durante 30 minutos, el disolvente se removió por destilación bajo presión reducida, seguido por dilución con acetato de etilo (30 mL); se le agregó una solución acuosa saturada de carbonato ácido de sodio (20 mL) y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-40%), para producir el compuesto deseado como un sólido amarillo (174 mg, rendimiento de 48%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 3.9, 10.2 Hz), 3.61 (1H, dd, J = 6.3, 10.2 Hz), 4.58 (1H, m), 6.57 (1H, t, J = 2.0 Hz), 6.60 (1H, dd, J = 2.7, 3.9 Hz), 6.88 (1H, dd, J = 2.4, 3.9 Hz), 6.92 (1H, t, J = 2.0 Hz), 7.08 (1H, t, J = 2.0 Hz), 7.13 (2H, d, J = 8.6 Hz), 7.32 (1H, dt, J = 1.2, 7.4 Hz), 7.44 (1H, brt, J = 7.4 Hz), 7.83 (1H, brd, J = 7.4 Hz), 7.91 (2H, d, J = 8.6 Hz), 10.10 (1H, brs).

MS (ESI) m/z: 535.13653 $(M+H)^+$.

EJEMPLO 5

Acido 2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol-5-carboxílico



(5a) 2-[1-(t-Butoxicarbonil)-1H-pirrol-2-il]-1,3-tiazol-5-carboxilato de etilo

Se disolvió ácido 1-(t-butoxicarbonil)pirrol-2-borónico (850 mg, 4.3 mmol) en 1,2-dimetoxietano (30 mL), y se le agregó 2-bromo-1,3-tiazol-5-carboxilato de etilo (0.50 mL, 3.35 mmol), disponible comercialmente, acetato de paladio (II) (38.0 mg, 0.169 mmol), trifenilfosfina (176 mg, 0.671 mmol) y una solución acuosa de carbonato de potasio (3M, 2.20 mL, 6.60 mmol),

seguido por agitación a 100°C durante 14 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (30 mL) y acetato de etilo (40 mL) y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-30%), para producir el compuesto deseado como un sólido amarillo (800 mg, rendimiento de 74%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.39 (3H, t, J = 7.0 Hz), 1.50 (9H, s), 4.38 (2H, q, J = 7.0 Hz), 6.28 (1H, dd, J = 3.1,3.5 Hz), 6.79 (1H, dd, J = 2.0, 3.5 Hz), 7.43 (1H, dd, J = 2.0, 3.1 Hz), 8.39 (1H, s).

(5b) 2-[5-Bromo-1-(t-butoxicarbonil)-1H-pirrol-2-il]-1,3-tiazol-5-carboxilato de etilo

El 2-[1-(t-butoxicarbonil)-1H-pirrol-2-il]-1,3-tiazol-5-carboxilato de etilo (800 mg, 2.48 mmol) sintetizado en el ejemplo (5a) se disolvió en tetrahidrofurano (30 mL) y se enfrió a 0°C. Se le agregó N-bromosuccinimida (442 mg, 2.48 mmol) con agitación y bajo una atmósfera de nitrógeno, y subsiguientemente se agitó a temperatura ambiente durante 19 horas. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (30 mL) y se extrajo con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el

residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-30%), para producir el compuesto deseado como un sólido amarillo pálido (598 mg, rendimiento de 60%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.39 (3H, t, J = 7.0 Hz), 1.50 (9H, s), 4.38 (2H, q, J = 7.0 Hz), 6.32 (1H, d, J = 3.8 Hz), 6.64 (1H, d, J = 3.8 Hz), 8.31 (1H, s).

(5c) 2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-1,3-tiazol-5-carboxilato de etilo

El 2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-4,4,5,5-tetrametil-1,3,2-dioxaborolano (666 mg, 1.49 mmol) sintetizado en el ejemplo (1e), y el 2-[5-bromo-1-(t-butoxicarbonil)-1H-pirrol-2-il]-1,3-tiazol-5-carboxilato de etilo (598 mg, 1.49 mmol) sintetizado en el ejemplo (5b), se disolvieron en un disolvente mixto de tolueno (14 mL) y etanol (6 mL) y se les agregó complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano (61.0 mg, 0.075 mmol) y una solución acuosa de carbonato de sodio (2M, 1.50 mL, 3.00 mmol), seguido por agitación a 100°C durante 19 horas bajo una atmósfera de nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente, se le agregó agua (10 mL) y se extrajo con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada; subsiguientemente se secó sobre sulfato de magnesio anhidro y el disolvente se removió por destilación bajo presión reducida.

El residuo resultante se disolvió en diclorometano (10 mL) y se

enfrió a 0°C. Se le agregó a gotas ácido trifluoroacético (10 mL) con agitación y bajo una atmósfera de nitrógeno. Después de agitar a temperatura ambiente durante 30 minutos, el disolvente se removió por destilación bajo presión reducida, seguido por dilución con acetato de etilo (30 mL); se le agregó una solución acuosa saturada de carbonato ácido de sodio (20 mL) y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-50%), para producir el compuesto deseado como un sólido amarillo pálido (505 mg, rendimiento de 61%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 1.39 (3H, t, J = 7.0 Hz), 3.07 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 4.3, 10.2 Hz), 3.61 (1H, dd, J = 6.3, 10.2 Hz), 4.37 (2H, q, J = 7.0 Hz), 4.59 (1H, m), 6.56 (1H, dd, J = 2.7, 3.9 Hz), 6.58 (1H, t, J = 2.0 Hz), 6.83 (1H, dd, J = 2.7, 3.9 Hz), 6.87 (1H, t, J = 2.0 Hz), 7.03 (1H, t, J = 2.0 Hz), 7.14 (2H, d, J = 9.0 Hz), 7.91 (2H, d, J = 9.0 Hz), 8.25 (1H, s), 9.64 (1H, brs).

MS (ESI) m/z: 557.14052 $(M+H)^+$.

(5d) Acido 2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol-5-carboxílico

El 2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-1,3-tiazol-5-carboxilato de etilo (53.5 mg, 0.096 mmol) sintetizado en el ejemplo (5c) se disolvió en etanol (4 mL). Se le agregó una

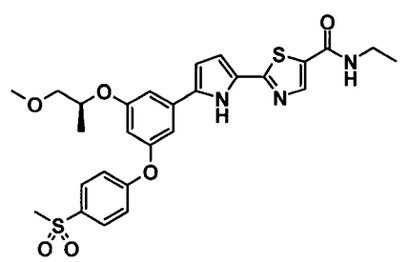
solución acuosa de hidróxido de sodio (5M, 2 mL) y se agitó a 70°C durante 30 minutos. Después de enfriar a temperatura ambiente, se le agregó ácido clorhídrico (2M, 5 mL) y acetato de etilo (10 mL), y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida para producir el compuesto deseado como un sólido amarillo pálido (52.5 mg, rendimiento de ~100%).

^{1}H-RMN (DMSO, 400 MHz): δ 1.25 (3H, d, J = 6.3 Hz), 3.19 (3H, s), 3.30 (3H, s), 3.44-3.52 (2H, m), 4.78 (1H, m), 6.56 (1H, brt, J = 2.0 Hz), 6.73 (1H, brd, J = 10.2 Hz), 7.21 (2H, d, J = 8.6 Hz), 7.27 (1H, brt, J = 2.0 Hz), 7.41 (1H, brt, J = 2.0 Hz), 7.93 (2H, d, J = 8.6 Hz), 12.0 (1H, brs).

MS (ESI) m/z: 529.11053 $(M+H)^+$.

EJEMPLO 6

N-Etil-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol-5-carboxamida



El ácido 2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol-5-carboxílico (62.8 mg, 0.119 mmol)

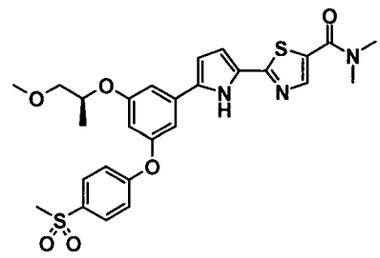
sintetizado en el ejemplo (5d) se disolvió en N,N-dimetilformamida (5 mL), y se le agregó clorhidrato de etilamina (23.3 mg, 0.286 mmol), HATU (63.8 mg, 0.168 mmol) y N,N-diisopropiletilamina (80 μL, 0.46 mmol), seguido por agitación a temperatura ambiente durante 20 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó agua (20 mL) y se extrajo con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-80%), para producir el compuesto deseado como un sólido amarillo (57.7 mg, rendimiento de 87%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.27 (3H, t, J = 7.4 Hz), 1.34 (3H, d, J = 6.3 Hz), 3.08 (3H, s), 3.43 (3H, s), 3.47-3.53 (3H, m), 3.60 (1H, dd, J = 6.3, 10.2 Hz), 4.56-4.60 (1H, m), 5.88 (1H, brs), 6.55-6.59 (2H, m), 6.80 (1H, dd, J = 2.3, 3.9 Hz), 6.86 (1H, t, J = 1.6 Hz), 7.02 (1H, t, J = 1.8 Hz), 7.14 (2H, d, J = 6.6 Hz), 7.92 (2H, d, J = 6.6 Hz), 7.98 (1H, s), 9.56 (1H, brs).

MS (ESI) m/z: 556.15812 $(M+H)^+$.

EJEMPLO 7

2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-N,N-dimetil-1,3-tiazol-5-carboxamida



El ácido 2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol-5-carboxílico (62.8 mg, 0.119 mmol) sintetizado en el ejemplo (5d) se disolvió en N,N-dimetilformamida (5 mL), y se le agregó clorhidrato de dimetilamina (27.0 mg, 0.331 mmol), HATU (68.2 mg, 0.179 mmol) y N,N-diisopropiletilamina (80 μL, 0.46 mmol), seguido por agitación a temperatura ambiente durante 20 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó agua (20 mL), y se extrajo con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 60%-90%), para producir el compuesto deseado como un sólido amarillo (59.8 mg, rendimiento de 90%).

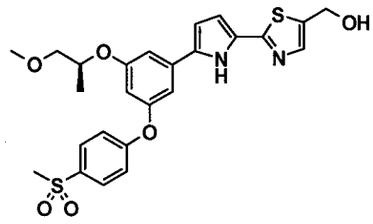
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.32 (6H, brs), 3.42 (3H, s), 3.51 (1H, dd, J = 4.3, 10.2 Hz), 3.59 (1H, dd, J

= 6.3, 10.2 Hz), 4.55-4.60 (1H, m), 6.55-6.58 (2H, m), 6.79 (1H, dd, J = 2.4, 3.9 Hz), 6.86 (1H, t, J = 1.8 Hz), 7.02 (1H, t, J = 1.8 Hz), 7.14 (2H, d, J = 9.0 Hz), 7.89 (1H, s), 7.91 (2H, d, J = 9.0 Hz), 9.52 (1H, brs).

MS (ESI) m/z: 556.15717 $(M+H)^+$.

EJEMPLO 8

[2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol-5-il]metanol



Se suspendió hidruro de litio y aluminio (22 mg, 0.580 mmol) en tetrahidrofurano (2 mL). El 2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol-5-carboxilato de etilo (106 mg, 0.190 mmol) sintetizado en el ejemplo (5c) se disolvió en tetrahidrofurano (2 mL), seguido por su adición gota a gota a 0°C bajo una atmósfera de nitrógeno. Después de agitar a 0°C durante 30 minutos, se le agregó lenta y secuencialmente, gota a gota, agua (22 μL) y una solución acuosa de hidróxido de sodio (5M, 88 μL). después de filtración a través de Celite, el disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-100%), para producir el compuesto

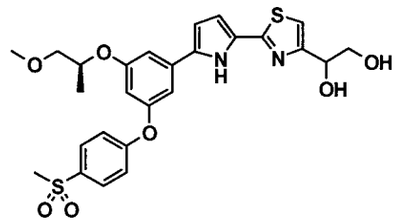
deseado como un sólido amarillo pálido (48 mg, rendimiento de 49%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.30 (3H, d, J = 6.3 Hz), 3.06 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 3.9, 10.5 Hz), 3.58 (1H, dd, J = 6.3, 10.5 Hz), 4.48 (1H, m), 4.82 (2H, brs), 6.51-6.54 (2H, m), 6.70 (1H, dd, J = 2.4, 3.9 Hz), 6.86 (1H, brt, J = 2.0 Hz), 7.00 (1H, brt, J = 2.0 Hz), 7.12 (2H, d, J = 9.0 Hz), 7.47 (1H, brs), 7.89 (2H, d, J = 9.0 Hz), 10.20 (1H, brs).

MS (ESI) m/z: 515.12920 $(M+H)^+$.

EJEMPLO 9

1-[2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol-4-il]etano-1,2-diol



(9a) (2-Bromo-1,3-tiazol-4-il)(oxo)acetato de etilo

Se disolvió (2-formamido-1,3-tiazol-4-il)(oxo)acetato de etilo (5.09 g, 22.3 mmol), disponible comercialmente, en un disolvente mixto de etanol (50 mL) y 1,4-dioxano, y se le agregó ácido sulfúrico al 30% (12 mL), seguido por agitación a 60°C durante 1 hora. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) y acetato de etilo (20 mL), y la solución se separó. El disolvente se removió por destilación bajo presión reducida y se le agregó ácido sulfúrico al 30% (40 mL) y bromuro de

potasio (9.3 g, 78.2 mmol), seguido por enfriamiento a 0°C. Se disolvió en agua (40 mL) nitrito de sodio (20.0 g, 290 mmol), seguido por su adición gota a gota durante 1 hora y agitación a 0°C durante 1 hora. La solución se separó con acetato de etilo (200 mL), la capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-20%), para producir el compuesto deseado como un aceite amarillo (3.07 g, rendimiento de 52%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.43 (3H, t, J = 7.0 Hz), 4.45 (2H, q, J = 7.0 Hz) 8.55 (1H, s).

(9b) 1-(2-Bromo-1,3-tiazol-4-il)etano-1,2-diol

El (2-bromo-1,3-tiazol-4-il)(oxo)acetato de etilo (3.07 g, 11.6 mmol) sintetizado en el ejemplo (9a) se disolvió en metanol (100 mL), y se enfrió a 0°C. Se le agregó borohidruro de sodio (1.32 g, 34.9 mmol) en pequeñas porciones y se agitó a 0°C durante 1.5 horas, seguido por agitación a temperatura ambiente durante 2 horas más. Se le agregó ácido clorhídrico diluido (1M, 100 mL) y la solución se separó con acetato de etilo (200 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-80%), para producir el compuesto deseado como un aceite amarillo (1.10

g, rendimiento de 42%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 3.87 (1H, dd, J = 5.9, 11.3 Hz), 3.97 (1H, dd, J = 3.5, 11.3 Hz), 4.89 (1H, dd, J = 3.5,5.3 Hz) 7.27 (1H, s).

(9c) 2-[4-(1,2-Dihidroxietil)-1,3-tiazol-2-il]-1H-pirrol-1-carboxilato de t-butilo

El 1-(2-bromo-1,3-tiazol-4-il)etano-1,2-diol (1.10 g, 4.91 mmol) sintetizado en el ejemplo (9b) y ácido 1-(t-butoxicarbonil)pirrol-2-borónico (1.55 g, 7.35 mmol), disponible comercialmente, se disolvieron en 1,2-dimetoxietano (40 mL) y se les agregó acetato de paladio (II) (55.0 mg, 0.245 mmol), trifenilfosfina (260 mg, 0.991 mmol) y una solución acuosa de carbonato de potasio (3M, 4.9 mL, 14.7 mmol), seguido por agitación a 100°C durante 14 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (30 mL) y acetato de etilo (40 mL), y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-100%), para producir el compuesto deseado como un aceite pardo (868 mg, rendimiento de 59%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.46 (9H, s), 3.95 (2H, m), 4.89 (1H, m), 6.25 (1H, t, J = 3.5 Hz), 6.60 (1H, dd, J = 2.0, 3.5 Hz), 7.31 (1H, brs), 7.40 (1H, dd, J = 2.0, 3.5 Hz).

(9d) 2-Bromo-5-[4-(1,2-dihidroxietil)-1,3-tiazol-2-il]-1H-pirrol-1-carboxilato de t-butilo

El 2-[4-(1,2-dihidroxietil)-1,3-tiazol-2-il]-1H-pirrol-1-carboxilato de t-butilo (868 mg, 2.80 mmol) sintetizado en el ejemplo (9c) se disolvió en tetrahidrofurano (30 mL) y se enfrió a 0°C. Se le agregó N-bromosuccinimida (498 mg, 2.80 mmol) y se agitó a temperatura ambiente durante 14 horas bajo una atmósfera de nitrógeno. Se le agregó agua (20 mL) y se extrajo con éter dietílico (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-30%), para producir el compuesto deseado como un aceite amarillo pálido (527 mg, rendimiento de 48%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.53 (9H, s), 3.92 (2H, m), 4.87 (1H, m), 6.31 (1H, d, J = 3.5 Hz), 6.54 (1H, d, J = 3.5 Hz), 7.23 (1H, brs).

(9e) 1-[2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol-4-il]etano-1,2-diol

El 2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-4,4,5,5-tetrametil-1,3,2-dioxaborolano (600 mg, 1.35 mmol) sintetizado en el ejemplo (1e), y el 2-bromo-5-[4-(1,2-dihidroxietil)-1,3-tiazol-2-il]-1H-pirrol-1-carboxilato de t-butilo (525 mg, 1.35 mmol) sintetizado en el ejemplo (9d), se disolvieron en un disolvente mixto de tolueno (30 mL) y etanol (10 mL) y se les agregó complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-

diclorometano (55 mg, 0.067 mmol) y una solución acuosa de carbonato de potasio (3M, 0.90 mL, 2.70 mmol), seguido por agitación a 100°C durante 16 horas bajo una atmósfera de nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) y se extrajo con acetato de etilo (40 mL). La capa orgánica se lavó con salmuera saturada; subsiguientemente se secó sobre sulfato de magnesio anhidro y el disolvente se removió por destilación bajo presión reducida.

El residuo resultante se disolvió en diclorometano (10 mL) y se enfrió a 0°C. Se le agregó a gotas ácido trifluoroacético (10 mL) con agitación y bajo una atmósfera de nitrógeno. Después de agitar a temperatura ambiente durante 30 minutos, el disolvente se removió por destilación bajo presión reducida, seguido por dilución con acetato de etilo (30 mL); se le agregó una solución acuosa saturada de carbonato ácido de sodio (20 mL) y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-100%), para producir el compuesto deseado como un sólido amarillo pálido (331 mg, rendimiento de 45%).

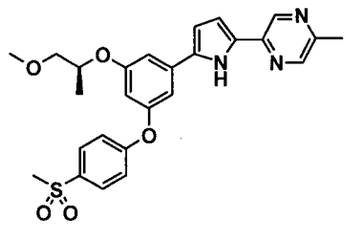
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 3.05 (3H, s), 3.40 (3H, s), 3.50 (1H, dd, J = 3.9, 10.2 Hz), 3.59 (1H, dd, J = 6.3, 10.2 Hz), 3.85-3.98 (2H, m), 4.58 (1H, m), 4.90 (1H, brs), 6.48-6.54 (2H, m), 6.67 (1H, brs), 6.89 (1H, brs), 7.07 (1H, brs), 7.12 (2H, d, J = 8.6 Hz), 7.88 (2H, d, J

= 8.6 Hz), 10.39 (1H, brs).

MS (ESI) m/z: 545.14151 $(M+H)^+$.

EJEMPLO 10

2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-5-metilpirazina



(10a) 2-(5-Metilpirazin-2-il)-1H-pirrol-1-carboxilato de t-butilo

Se disolvió 2-bromo-5-metilpirazina (260 mg, 1.50 mmol), disponible comercialmente, y ácido 1-(t-butoxicarbonil)pirrol-2-borónico (380 mg, 1.80 mmol), disponible comercialmente, en 1,2-dimetoxietano (20 mL), y se le agregó acetato de paladio (II) (17.0 mg, 0.076 mmol), trifenilfosfina (79.0 mg, 0.301 mmol) y una solución acuosa de carbonato de potasio (1.5M, 2.0 mL, 3.00 mmol), seguido por agitación a 100°C durante 19 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) y acetato de etilo (20 mL), y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución:

acetato de etilo/hexano = 5%-30%), para producir el compuesto deseado como un aceite amarillo (373 mg, rendimiento de 96%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.41 (9H, s), 2.59 (3H, s), 6.28 (1H, m), 6.48 (1H, m), 7.41 (1H, m), 8.45 (1H, brs), 8.56 (1H, brs).

(10b) 2-Bromo-5-(5-metilpirazin-2-il)-1H-pirrol-1-carboxilato de t-butilo

El 2-(5-metilpirazin-2-il)-1H-pirrol-1-carboxilato de t-butilo (373 mg, 1.44 mmol) sintetizado en el ejemplo (10a) se disolvió en tetrahidrofurano (20 mL) y se enfrió a 0°C. Se le agregó N-bromosuccinimida (256 mg, 1.44 mmol), y se agitó a temperatura ambiente durante 14 horas bajo una atmósfera de nitrógeno. Se le agregó agua (20 mL) y se extrajo con éter dietílico (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-30%), para producir el compuesto deseado como un aceite amarillo pálido (425 mg, rendimiento de 87%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.50 (9H, s), 2.57 (3H, s), 6.33 (1H, d, J = 3.5 Hz), 6.54 (1H, d, J = 3.5 Hz), 8.35 (1H, brs), 8.62 (1H, brd, J = 1.6 Hz).

(10c) 2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5-metilpirazina

El 2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-

fenil}-4,4,5,5-tetrametil-1,3,2-dioxaborolano (250 mg, 0.559 mmol) sintetizado en el ejemplo (1e), y el 2-bromo-5-(5-metilpirazin-2-il)-1H-pirrol-1-carboxilato de t-butilo (200 mg, 0.591 mmol) sintetizado en el ejemplo (10b), se disolvieron en un disolvente mixto de tolueno (20 mL) y etanol (8 mL) y se les agregó complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano (23 mg, 0.028 mmol) y una solución acuosa de carbonato de potasio (3M, 0.40 mL, 1.20 mmol), seguido por agitación a 100°C durante 7 horas bajo una atmósfera de nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) y se extrajo con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada; subsiguientemente se secó sobre sulfato de magnesio anhidro y el disolvente se removió por destilación bajo presión reducida.

El residuo resultante se disolvió en diclorometano (10 mL) y se enfrió a 0°C. Se le agregó a gotas ácido trifluoroacético (10 mL) con agitación y bajo una atmósfera de nitrógeno. Después de agitar a temperatura ambiente durante 30 minutos, el disolvente se removió por destilación bajo presión reducida, seguido por dilución con acetato de etilo (30 mL); se le agregó una solución acuosa saturada de carbonato ácido de sodio (20 mL) y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-60%), para producir el compuesto deseado

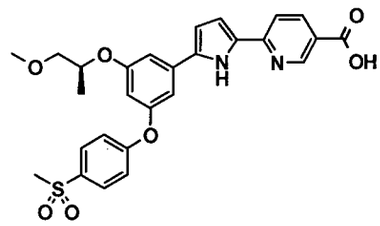
como un sólido amarillo (124 mg, rendimiento de 45%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 2.55 (3H, s), 3.07 (3H, s), 3.42 (3H, s), 3.52 (1H, dd, J = 3.9, 10.2 Hz), 3.61 (1H, dd, J = 5.9, 10.2 Hz), 4.58 (1H, m), 6.55 (1H, t, J = 2.0 Hz), 6.59 (1H, dd, J = 2.8, 3.9 Hz), 6.81 (1H, dd, J = 2.4, 3.9 Hz), 6.88 (1H, t, J = 2.0 Hz), 7.04 (1H, t, J = 2.0 Hz), 7.14 (2H, d, J = 9.0 Hz), 7.91 (2H, d, J = 9.0 Hz), 8.28 (1H, brs), 8.76 (1H, d, J = 1.6 Hz), 9.62 (1H, brs).

MS (ESI) m/z: 494.17511 $(M+H)^+$.

EJEMPLO 11

Acido 6-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il) nicotínico



(11a) 6-[1-(t-Butoxicarbonil)-1H-pirrol-2-il]nicotinato de metilo

Se disolvió 6-bromonicotinato de metilo (650 mg, 3.01 mmol), disponible comercialmente, y ácido 1-(t-butoxicarbonil)pirrol-2-borónico (960 mg, 4.34 mmol), disponible comercialmente, en 1,2-dimetoxietano (30 mL) y se les agregó acetato de paladio (II) (34.0 mg, 0.151 mmol), trifenilfosfina (158 mg, 0.602 mol) y una solución acuosa de carbonato de potasio (2M, 4.5 mL, 9.00 mmol), seguido por agitación a 100°C durante 15 horas bajo una

atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) y acetato de etilo (30 mL), y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-20%), para producir el compuesto deseado como un sólido amarillo (835 mg, rendimiento de 92%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.39 (9H, s), 3.95 (3H, s), 6.26 (1H, t, J = 3.5 Hz), 6.53 (1H, m), 7.39 (1H, m), 7.47 (1H, dd, J = 0.8, 8.2 Hz), 8.27 (1H, dd, J = 2.4, 8.2 Hz), 9.19 (1H, dd, J = 0.8, 2.4 Hz).

(11b) 6-[5-Bromo-1-(t-butitoxicarbonil)-1H-pirrol-2-il]nicotinato de metilo

El 6-[1-(t-butitoxicarbonil)-1H-pirrol-2-il]nicotinato de metilo (835 mg, 2.76 mmol) sintetizado en el ejemplo (11a) se disolvió en tetrahidrofurano (30 mL) y se enfrió a 0°C. Se le agregó N-bromosuccinimida (492 mg, 2.76 mmol), y se agitó a temperatura ambiente durante 19 horas bajo una atmósfera de nitrógeno. Se le agregó agua (30 mL) y se extrajo con éter dietílico (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-30%), para producir el compuesto deseado

como un aceite amarillo pálido (712 mg, rendimiento de 68%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.54 (9H, s), 3.94 (3H, s), 6.30 (1H, d, J = 3.5 Hz), 6.62 (1H, d, J = 3.5 Hz), 7.51 (1H, brd, J = 8.6 Hz), 8.23 (1H, dd, J = 2.0, 8.6 Hz), 9.07 (1H, m).

(11c) 6-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)nicotinato de etilo

El 2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-4,4,5,5-tetrametil-1,3,2-dioxaborolano (398 mg, 0.890 mmol) sintetizado en el ejemplo (1e), y el 6-[5-bromo-1-(t-butitoxicarbonil)-1H-pirrol-2-il]nicotinato de metilo (403 mg, 0.493 mmol) sintetizado en el ejemplo (11b), se disolvieron en un disolvente mixto de tolueno (20 mL) y etanol (8 mL) y se les agregó complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano (40 mg, 0.049 mmol) y una solución acuosa de carbonato de potasio (3M, 0.60 mL, 1.80 mmol), seguido por agitación a 100°C durante 20 horas bajo una atmósfera de nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) y se extrajo con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada; subsiguientemente se secó sobre sulfato de magnesio anhidro y el disolvente se removió por destilación bajo presión reducida.

El residuo resultante se disolvió en diclorometano (10 mL) y se enfrió a 0°C. Se le agregó a gotas ácido trifluoroacético (10 mL) con agitación y bajo una atmósfera de nitrógeno. Después de agitar a temperatura ambiente durante 30 minutos, el disolvente se removió por destilación bajo

presión reducida, seguido por dilución con acetato de etilo (30 mL); se le agregó una solución acuosa saturada de carbonato ácido de sodio (20 mL), y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-60%), para producir el compuesto deseado como un sólido amarillo (173 mg, rendimiento de 35%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 1.42 (3H, t, J = 7.0 Hz), 3.07 (3H, s), 3.42 (3H, s), 3.52 (1H, dd, J = 3.9, 10.2 Hz), 3.61 (1H, dd, J = 6.3, 10.2 Hz), 4.41 (2H, q, J = 7.0 Hz), 4.58 (1H, m), 6.55 (1H, t, J = 2.0 Hz), 6.60 (1H, dd, J = 2.0, 3.9 Hz), 6.85 (1H, dd, J = 2.0, 3.9 Hz), 7.06 (1H, t, J = 2.0 Hz), 7.14 (2H, d, J = 9.0 Hz), 7.57 (1H, dd, J = 0.8, 8.6 Hz), 7.90 (2H, d, J = 9.0 Hz), 8.21 (1H, dd, J = 2.0, 8.6 Hz), 9.06 (1H, dd, J = 0.8, 2.0 Hz), 9.94 (1H, brs), m).

MS (ESI) m/z: 551.18403 $(M+H)^+$.

(11d) Acido 6-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)nicotínico

El 6-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)nicotinato de etilo (42.0 mg, 0.076 mmol) sintetizado en el ejemplo (11c) se disolvió en etanol (4 mL). Se le agregó una solución acuosa de hidróxido de sodio (5M, 2 mL) y se agitó a 70°C durante 2 horas. Después de enfriar a temperatura ambiente , se le agregó ácido clorhídrico (2M, 5 mL) y

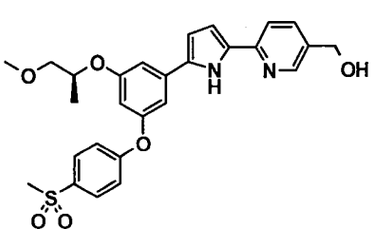
acetato de etilo (10 mL), y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida para producir el compuesto deseado como un sólido amarillo pálido (39.6 mg, rendimiento de 99%).

^{1}H-RMN (DMSO, 400 MHz): δ 1.26 (3H, d, J = 6.3 Hz), 3.20 (3H, s), 3.31 (3H, s), 3.45-3.55 (2H, m), 4.83 (1H, m), 6.58 (1H, brs), 6.80 (1H, brs), 7.01 (1H, brs), 7.22 (2H, d, J = 9.0 Hz), 7.31 (1H, brs), 7.45 (1H, brs), 7.88 (1H, d, J = 8.6 Hz), 7.93 (2H, d, J = 9.0 Hz), 8.18 (1H, J = 8.6 Hz), 9.00 (1H, s), 11.92 (1H, brs).

MS (ESI) m/z: 523.15247 $(M+H)^+$.

EJEMPLO 12

[6-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)piridin-3-il]metanol



Se suspendió hidruro de litio y aluminio (12 mg, 0.316 mmol) en tetrahidrofurano (2 mL). El 6-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)nicotinato de etilo (56.0 mg, 0.102 mmol) sintetizado en el ejemplo (11c) se disolvió en tetrahidrofurano (2 mL),

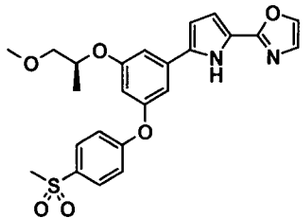
seguido por su adición gota a gota a 0°C bajo una atmósfera de nitrógeno. Después de agitar a 0°C durante 30 minutos, se le agregó lenta y secuencialmente agua (12 μL) y una solución acuosa de hidróxido de sodio (5M, 48 μL), gota a gota. Después de filtración a través de Celite, el disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-100%), para producir el compuesto deseado como un sólido amarillo pálido (33 mg, rendimiento de 64%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 3.06 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 3.9, 10.2 Hz), 3.60 (1H, dd, J = 5.9, 10.2 Hz), 4.57 (1H, m), 4.69 (2H, brs), 6.52 (1H, brt, J = 2.0 Hz), 6.57 (1H, m), 6.74 (1H, m), 6.90 (1H, brt, J = 2.0 Hz), 7.06 (1H, brt, J = 2.0 Hz), 7.13 (2H, d, J = 8.6 Hz), 7.55 (1H, brd, J = 8.2 Hz), 7.69 (1H, brd, J = 8.2 Hz), 7.89 (2H, d, J = 8.6 Hz), 8.41 (1H, brs), 10.00 (1H, brs).

MS (ESI) m/z: 509.17476 $(M+H)^+$.

EJEMPLO 13

2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-1,3-oxazol



(13a) 1-Bromo-3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]benceno

El 3-bromo-5-[4-(metilsulfonil)fenoxi]fenol (4.86 g, 14.2 mmol) sintetizado en el ejemplo (1c) se disolvió en tolueno (100 mL), y se le agregó (R)-(-)-1-metoxi-2-propanol (1.77 mL, 18.1 mmol) y trifenilfosfina (4.10 g, 15.6 mmol), seguido por enfriamiento a 0°C. Bajo una atmósfera de nitrógeno, se le agregó a gotas azodicarboxilato de dietilo (solución en tolueno al 40%, 7.75 mL, 17.1 mmol) durante 10 minutos, y se agitó a 0°C durante 30 minutos, seguido por aumento natural de la temperatura y agitación a temperatura ambiente durante la noche. Se le agregó agua (100 mL) y acetato de etilo (100 mL), y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-40%), para producir el compuesto deseado como un aceite amarillo pálido (5.06 g, rendimiento de 86%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.28 (3H, d, J = 6.3 Hz), 3.05 (3H, s), 3.37 (3H, s), 3.46 (1H, dd, J = 3.9, 10.2 Hz), 3.54 (1H, dd, J = 6.3, 10.2 Hz), 4.49 (1H, m), 6.56 (1H, d, J = 2.0 Hz), 6.77 (1H, d, J = 2.0 Hz), 6.93 (1H, d, J = 2.0 Hz), 7.10 (2H, d, J = 9.0 Hz), 7.89 (2H, d, J = 9.0 Hz).

(13b) 2-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-1-carboxilato de t-butilo

El 1-bromo-3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]benceno (2.38 g, 5.73 mmol) sintetizado en el ejemplo (13a), y ácido 1-(t-butoxicarbonil)pirrol-2-borónico (1.45 g, 6.87 mmol), se disolvieron en un disolvente mixto de 1,2-dimetoxietano (50 mL) y agua (6 mL) y se les agregó acetato de paladio (II) (40 mg, 0.178 mmol), trifenilfosfina (180 mg, 0.686 mmol) y carbonato de potasio (2.38 g, 17.2 mmol), seguido por agitación a 90°C durante 18 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (30 mL) y acetato de etilo (50 mL), y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-40%), para producir el compuesto deseado como un aceite pardo (2.71 g, rendimiento de 94%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 1.44 (9H, s), 3.05 (3H, s), 3.41 (3H, s), 3.49 (1H, dd, J = 4.3, 10.2 Hz), 3.58 (1H, dd, J =

6.3, 10.2 Hz), 4.53 (1H, m), 6.19-6.23 (2H, m), 6.61 (1H, t, J = 2.4 Hz), 6.63 (1H, dd, J = 1.6, 2.0 Hz), 6.79 (1H, dd, J = 1.6, 2.4 Hz), 7.15 (2H, d, J = 9.0 Hz), 7.31 (1H, dd, J = 2.0, 3.2 Hz), 7.88 (2H, d, J = 9.0 Hz).

(13c) 2-Bromo-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-1-carboxilato de t-butilo

El 2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-1-carboxilato de t-butilo (2.70 g, 5.38 mmol) sintetizado en el ejemplo (13b) se disolvió en tetrahidrofurano (50 mL), y se enfrió a 0°C. Después de agregar N-bromosuccinimida (960 mg, 5.38 mmol) con agitación bajo una atmósfera de nitrógeno, se agitó a temperatura ambiente durante 4 horas. Se le agregó agua (50 mL) y se extrajo con acetato de etilo (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-40%), para producir el compuesto deseado como un aceite pardo (2.93 g, rendimiento de 94%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J = 6.3 Hz), 1.42 (9H, s), 3.05 (3H, s), 3.39 (3H, s), 3.48 (1H, dd, J = 4.3, 10.2 Hz), 3.57 (1H, dd, J = 6.3, 10.2 Hz), 4.53 (1H, m), 6.21 (1H, d, J = 3.5 Hz), 6.30 (1H, d, J = 3.5 Hz), 6.57 (1H, t, J = 2.4 Hz), 6.61 (1H, d, J = 2.4 Hz), 6.75 (1H, d, J = 2.4 Hz), 7.12 (2H, d, J = 9.0 Hz), 7.89 (2H, d, J = 9.0 Hz).

(13d) 2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-1,3-oxazol

El 2-bromo-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-1-carboxilato de t-butilo (102.9 mg, 0.177 mmol) sintetizado en el ejemplo (13c) se disolvió en tolueno (5 mL), y se le agregó 2-(tri-n-butilestanil)oxazol (133.7 mg, 0.373 mmol) y tetrakis(trifenilfosfina) paladio (20.5 mg, 0.0177 mmol), seguido por calentamiento a reflujo durante 18 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) y se extrajo con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 35%-55%), para producir 2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-5-(1,3-oxazol-2-il)-1H-pirrol-1-carboxilato de t-butilo.

Este se disolvió en diclorometano (1 mL) y se le agregó ácido trifluoroacético (2 mL), seguido por agitación a temperatura ambiente durante 2 horas; subsiguientemente el disolvente se removió por destilación bajo presión reducida. El residuo se diluyó con acetato de etilo (20 mL), se lavó con una solución acuosa saturada de carbonato ácido de sodio, seguido por lavado adicional con salmuera saturada, y se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente

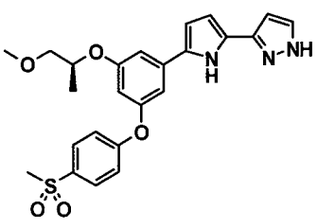
de elución: acetato de etilo/hexano = 65%), para producir el compuesto deseado como un sólido amarillo pálido (15.6 mg, rendimiento de 19%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ ppm 1.34 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 4.3, 10.2 Hz), 3.60 (1H, dd, J = 6.3, 10.2 Hz), 4.56-4.60 (1H, m), 6.55-6.57 (2H, m), 6.84-6.86 (2H, m), 7.02 (1H, t, J = 1.7 Hz), 7.13 (1H, s), 7.15 (2H, d, J = 8.6 Hz), 7.61 (1H, s), 7.91 (2H, d, J = 9.0 Hz), 9.52 (1H, brs).

MS (ESI) m/z: 469.14163 $(M+H)^+$.

EJEMPLO 14

3-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-1H-pirazol



El 2-bromo-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-1-carboxilato de t-butilo (375 mg, 0.446 mmol) sintetizado en el ejemplo (13c) y ácido 1H-pirazol-3-ilborónico (120 mg, 1.00 mmol), disponible comercialmente, se disolvió en un disolvente mixto de 1,2-dimetoxietano (20 mL) y agua (5 mL), se le agregó complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano (28 mg, 0.034 mmol) y una solución acuosa de carbonato de potasio (3M, 0.65 mL, 1.95

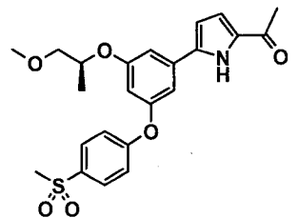
mmol), y se agitó a 100°C durante 7 días bajo una atmósfera de nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente, se le agregó agua (10 mL) y se extrajo con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-80%), para producir el compuesto deseado como un sólido amarillo pálido (106 mg, rendimiento de 35%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 3.9, 10.2 Hz), 3.60 (1H, dd, J = 6.3, 10.2 Hz), 4.57 (1H, m), 6.549-6.55 (4H, m), 6.83 (1H, brs), 7.00 (1H, brs), 7.14 (2H, d, J = 9.0 Hz), 7.57 (1H, d, J = 2.4 Hz), 7.90 (2H, d, J = 9.0 Hz), 9.30 (1H, brs).

MS (ESI) m/z: 468.15954 $(M+H)^+$.

EJEMPLO 15

1-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)etanona



(15a) 1-(5-Bromo-1H-pirrol-2-il)etanona

Se disolvió 2-acetilpirrol (2.00 g, 18.3 mmol) en un disolvente mixto de tetrahidrofurano (100 mL) y metanol (50 mL), y se le agregó N-bromosuccinimida (3.26 g, 18.3 mmol) con agitación a temperatura ambiente, bajo una atmósfera de nitrógeno. Después de agitar 1 hora, el disolvente se removió por destilación bajo presión reducida. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (200 mL), y se extrajo con acetato de etilo (300 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-20%), para producir el compuesto deseado como un sólido blanco (770 mg, rendimiento de 22%).

^{1}H-RMN ($CDCl_3$, 400 MHz): 2.40 (3H, s), 6.24 (1H, dd, J = 2.4, 4.0 Hz), 6.80 (1H, dd, J = 2.9, 4.0 Hz), 9.37 (1H, brs).

(15b) 2-Acetil-5-bromo-1H-pirrol-1-carboxilato de t-butilo

La 1-(5-bromo-1H-pirrol-2-il)etanona (770 mg, 4.1 mmol) sintetizada en el ejemplo (15a) se disolvió en diclorometano (30 mL), y se le agregó trietilamina (0.57 mL, 4.1 mmol) y 4-dimetilaminopiridina (500 mg, 4.1 mmol). Se disolvió dicarbonato de di-t-butilo (930 mg, 4.3 mmol) en diclorometano (10 mL) y la solución se le agregó, seguido por agitación a temperatura ambiente durante 3 horas bajo una atmósfera de nitrógeno. La solución de reacción se diluyó con diclorometano (200 mL), se lavó con ácido clorhídrico 1N, solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-20%), para producir el producto deseado como un sólido blanco (538 mg, rendimiento de 46%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.64 (9H, s), 2.40 (3H, s), 6.24 (1H, d, J = 3.9 Hz), 6.82 (1H, d, J = 3.9 Hz).

(15c) 1-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)etanona

El 2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-4,4,5,5-tetrametil-1,3,2-dioxaborolano (146 mg, 0.33 mmol) sintetizado en el ejemplo (1e), y el 2-acetil-5-bromo-1H-pirrol-1-carboxilato de t-butilo (141 mg, 0.49 mmol) sintetizado en el ejemplo (15b), se disolvieron en un disolvente mixto de tolueno (3 mL) y etanol (1.3 mL) y se les agregó complejo

de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano (13 mg, 0.016 mmol) y una solución acuosa de carbonato de potasio (2M, 0.41 mL, 0.83 mmol), y se agitó a 100°C durante 1.5 horas bajo una atmósfera de nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) y se extrajo con acetato de etilo (60 mL). La capa orgánica se lavó con salmuera saturada; subsiguientemente se secó sobre sulfato de magnesio anhidro y el disolvente se removió por destilación bajo presión reducida.

El residuo resultante se disolvió en diclorometano (2 mL) y se le agregó ácido trifluoroacético (1 mL, 13.0 mmol), seguido por agitación a temperatura ambiente durante 1 hora bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida, se le agregó una solución acuosa saturada de carbonato ácido de sodio (30 mL), y se extrajo con acetato de etilo (70 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-50%), para producir el compuesto deseado como un sólido amarillo pálido (95 mg, rendimiento de 66%).

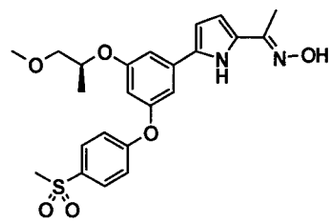
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz,), 2.44 (3H, s), 3.07 (3H, s), 3.41 (3H, s), 3.51 (1H, dd, J = 4.0, 10.2 Hz), 3.59 (1H, dd, J = 6.2, 10.2 Hz), 4.56-4.59 (1H, m), 6.53 (1H, dd, J = 2.9, 3.5 Hz), 6.62 (1H, t, J = 2.0 Hz), 6.86 (1H, t, J = 1.6 Hz), 6.93 (1H, dd, J = 2.5, 3.9 Hz), 7.02 (1H, s),

7.14 (2H, d, J = 8.9 Hz), 7.91 (2H, d, J = 8.8 Hz), 9.64 (1H, brs).

MS (ESI) m/z: 444.14808 $(M+H)^+$.

EJEMPLO 16

Oxima de (1E)-1-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)etanona



La 1-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)etanona (117 mg, 0.26 mmol) sintetizada en el ejemplo (15c) se disolvió en metanol (6 mL), y se le agregó clorhidrato de hidroxilamina (37 mg, 0.53 mmol) y acetato de sodio (26 mg, 0.32 mmol), seguido por calentamiento a reflujo durante 6 horas bajo una atmósfera de nitrógeno. La solución de reacción se diluyó con diclorometano (60 mL), se lavó con agua y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-50%), para producir el producto deseado como un sólido blanco (50 mg, rendimiento de 41%).

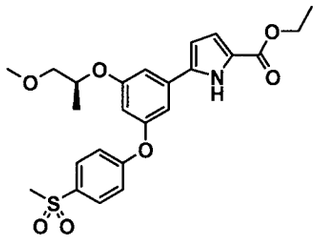
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.2 Hz), 2.19 (3H,

s), 3.06 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 4.1,10.2 Hz), 3.58 (1H, dd, J = 6.1, 10.2 Hz), 4.52-4.57 (1H, m), 6.47 (2H, d, J = 2.7 Hz), 6.53 (1H, t, J = 2.0 Hz), 6.79 (1H, t, J = 1.5 Hz), 6.89 (1H, brs), 6.95 (1H, t, J = 1.8 Hz), 7.13 (2H, d, J = 8.8 Hz), 7.90 (2H, d, J = 8.8 Hz), 9.03 (1H, brs)

MS (ESI) m/z: 459.15898 $(M+H)^+$.

EJEMPLO 17

5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxilato de etilo



(17a) 5-Bromo-1H-pirrol-2-carboxilato de etilo

Se disolvió 1H-pirrol-2-carboxilato de etilo (5.10 g, 30.7 mmol), disponible comercialmente, en un disolvente mixto de tetrahidrofurano (120 mL) y metanol (60 mL), y se enfrió a 0°C. Se le agregó N-bromosuccinimida (6.52 g, 30.7 mmol), y se agitó a temperatura ambiente durante 18 horas bajo una atmósfera de nitrógeno. Se le agregó agua (150 mL) y acetato de etilo (200 mL) y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente

de elución: acetato de etilo/hexano = 5%-30%), para producir el compuesto deseado como un sólido blanco (3.20 g, rendimiento de 40%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.36 (3H, t, J = 7.1 Hz), 4.32 (2H, q, J = 7.1 Hz), 6.21 (1H, dd, J = 2.7, 3.9 Hz), 6.82 (1H, dd, J = 2.7, 3.9 Hz), 9.21 (1H, brs).

(17b) 5-Bromo-1H-pirrol-1,2-dicarboxilato de 1-t-butilo-2-etilo

El 5-bromo-1H-pirrol-2-carboxilato de etilo (3.20 g, 14.7 mmol) sintetizado en el ejemplo (17a) se disolvió en diclorometano (100 mL), se le agregó dicarbonato de di-t-butilo (3.85 g, 17.6 mmol), trietilamina (~~2.70~~4.10 mL, 19.4 mmol) y 4-dimetilaminopiridina (180 mg, 1.47 mmol), y se agitó a temperatura ambiente durante 1 hora bajo una atmósfera de nitrógeno. Se le agregó agua (100 mL) y se extrajo con diclorometano (100 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-20%), para producir el compuesto deseado como un aceite incoloro (4.37 g, rendimiento de 94%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, t, J = 7.0 Hz), 1.63 (9H, s), 4.30 (2H, q, J = 7.0 Hz), 6.23 (1H, d, J = 3.9 Hz), 6.83 (1H, d, J = 3.9 Hz).

(17c) 5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-1,2-dicarboxilato de 1-t-butilo-2-etilo

El 2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-

fenil}-4,4,5,5-tetrametil-1,3,2-dioxaborolano (8.73 g, 18.9 mmol) sintetizado en el ejemplo (1e), y el 5-bromo-1H-pirrol-1,2-dicarboxilato de 1-t-butilo-2-etilo (8.37 g, 26.3 mmol) sintetizado en el ejemplo (17b), se disolvieron en un disolvente mixto de tolueno (180 mL) y etanol (77 mL), y se le agregó complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano (770 mg, 0.94 mmol) y una solución acuosa de carbonato de potasio (2M, 23.7 mL, 47.2 mmol), y se agitó a 100°C durante 1 hora bajo una atmósfera de nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente, se le agregó agua (200 mL) y se extrajo con acetato de etilo (400 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-50%), para producir el compuesto deseado como un aceite amarillo pálido (9.44 g, rendimiento de 84%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J = 6.3 Hz), 1.35 (3H, t, J = 7.0 Hz), 1.46 (9H, s), 3.05 (3H, s), 3.39 (3H, s), 3.48 (1H, dd, J = 4.3, 10.2 Hz), 3.57 (1H, dd, J = 5.9, 10.2 Hz), 4.32 (2H, q, J = 7.0 Hz), 4.53 (1H, m), 6.22 (1H, d, J = 3.9 Hz), 6.65 (1H, m), 6.73 (1H, m), 6.88 (1H, m), 6.89 (1H, d, J = 3.9 Hz), 7.12 (1H, d, J = . 9.0 Hz), 7.89 (2H, d, J = 9.0 Hz).

(17d) 5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-carboxilato de etilo

El 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-

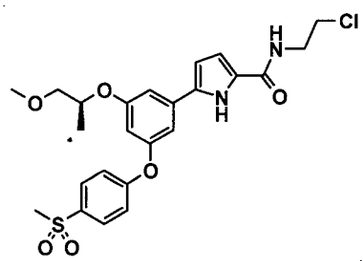
fenil}-1H-pirrol-1,2-dicarboxilato de 1-t-butilo-2-etilo (9.44 g, 16.5 mmol) sintetizado en el ejemplo (17c) se disolvió en diclorometano (90 mL) y se enfrió a 0°C. Se le agregó a gotas ácido trifluoroacético (45 mL) con agitación y bajo una atmósfera de nitrógeno, y se agitó a temperatura ambiente durante 1 hora. El disolvente se removió por destilación bajo presión reducida, seguido por dilución con acetato de etilo (300 mL); se le agregó una solución acuosa saturada de carbonato ácido de sodio (200 mL) y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-50%), para producir el compuesto deseado como un sólido amarillo pálido (6.34 g, rendimiento de 81%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 1.37 (2H, t, J = 7.0 Hz), 3.07 (3H, s), 3.41 (3H, s), 3.51 (1H, dd, J = 3.9, 10.2 Hz), 3.60 (1H, dd, J = 6.3, 10.2 Hz), 4.34 (2H, q, J = 7.0 Hz), 4.58 (1H, m), 6.51 (1H, dd, J = 2.5, 4.0 Hz), 6.58 (1H, m), 6.86 (1H, m), 6.93 (1H, dd, J = 2.5, 4.0 Hz), 7.01 (1H, m), 7.13 (2H, d, J = 8.8 Hz), 7.91 (2H, d, J = 8.8 Hz), 9.41 (1H, brs).

MS (ESI) m/z: 474.16048 $(M+H)^+$.

EJEMPLO 18

N-(2-Cloroetil)-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida



(18a) Acido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-carboxílico

El 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-carboxilato de etilo (4.36 g, 9.2 mmol) sintetizado en el ejemplo (17d) se disolvió en etanol (100 mL), y se le agregó una solución acuosa de hidróxido de sodio 4N (23 mL, 92 mmol), seguido por calentamiento a reflujo durante 1 hora bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó ácido clorhídrico 2N (45 mL) para neutralizarla, y el disolvente se removió por destilación bajo presión reducida. La solución se acidificó con ácido clorhídrico 1N y se extrajo con acetato de etilo (300 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida para producir el producto deseado como un sólido blanco (4.06 g, rendimiento de 99%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz,), 3.07 (3H,

s), 3.46 (3H, s), 3.55 (1H, dd, J = 4.2, 10.4 Hz), 3.66 (1H, dd, J = 6.3, 10.5 Hz), 4.70-4.75 (1H, m), 6.53 (1H, dd, J = 2.6, 3.9 Hz), 6.59 (1H, t, J = 2.0 Hz), 6.91 (1H, t, J = 1.6 Hz,), 7.04 (1H, dd, J = 2.3, 3.9 Hz), 7.25 (1H, m), 7.14 (2H, d, J = 8.9 Hz), 7.91 (2H, d, J = 8.8 Hz), 10.13 (1H, brs).

(18b) N-(2-Cloroetil)-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-carboxílico (150 mg, 0.34 mmol) sintetizado en el ejemplo (18a), clorhidrato de 2-cloroetilamina (78 mg, 0.68 mmol) y 4-dimetilaminopiridina (41 mg, 0.34 mmol), se disolvieron en diclorometano (15 mL) y se les agregó WSCI·HCl (71 mg, 0.37 mmol) a temperatura ambiente, y se agitó durante 2 horas bajo una atmósfera de nitrógeno. La solución de reacción se diluyó con diclorometano (150 mL), se lavó con ácido clorhídrico 1N, solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-60%), para producir el producto deseado como un sólido blanco (105 mg, rendimiento de 62%).

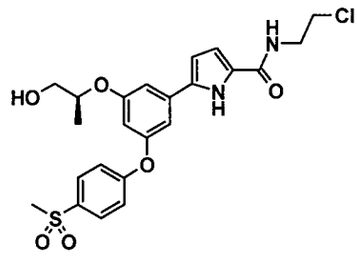
^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 4.0, 10.3 Hz), 3.59 (1H, dd, J = 6.1,10.4 Hz), 3.70 (2H, t, J = 5.4 Hz), 3.77 (2H, t, J = 5.4 Hz), 4.55-4.59 (1H, m), 6.26-6.29 (1H, brm), 6.50 (1H, dd, J = 2.9, 3.9 Hz), 6.58 (1H, t, J = 2.2 Hz), 6.63 (1H, dd,

J = 2.5, 3.8 Hz), 6.83 (1H, t, J = 1.7 Hz), 6.99 (1H, t, J = 2.0 Hz), 7.14 (2H, d, J = 8.8 Hz), 7.91 (2H, d, J = 8.8 Hz), 9.52 (1H, brs).

MS (ESI) m/z: 507.13566 $(M+H)^+$.

EJEMPLO 19

N-(2-Cloroetil)-5-{3-[(1S)-2-hidroxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida



La N-(2-cloroetil)-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida (88 mg, 0.17 mmol) sintetizada en el ejemplo (18b) se disolvió en diclorometano (5 mL) y se enfrió a -78°C, y se le agregó una solución de tribromuro de boro en diclorometano 1.0 mol/L (0.19 mL, 0.19 mmol) bajo una atmósfera de nitrógeno. La temperatura se aumentó naturalmente y la solución se agitó a temperatura ambiente durante 30 minutos; subsiguientemente se le agregó una solución acuosa saturada de carbonato ácido de sodio para neutralizar la solución de reacción y se extrajo con diclorometano (60 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo

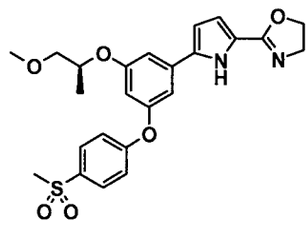
resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-80%), para producir el producto deseado como un sólido blanco (55 mg, rendimiento de 64%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.31 (3H, d, J = 6.3 Hz), 2.1 (1H, brm), 3.08 (3H, s), 3.70 (2H, t, J = 5.2 Hz), 3.76-3.80 (4H, m), 4.52-4.56 (1H, m), 6.27-6.30 (1H, brm), 6.50 (1H, dd, J = 2.9, 3.8 Hz), 6.57 (1H, t, J = 2.1 Hz), 6.64 (1H, dd, J = 2.3, 3.9 Hz), 6.85 (1H, t, J = 1.7 Hz), 6.98 (1H, t, J = 1.8 Hz), 7.14 (2H, d, J = 8.8 Hz), 7.91 (2H, d, J = 8.8 Hz), 9.56 (1H, brs).

MS (FAB) m/z: 493 $(M+H)^+$.

EJEMPLO 20

2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol



La N-(2-cloroetil)-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida (177 mg, 0.349 mmol) sintetizada en el ejemplo (18b) se disolvió en tetrahidrofurano (5 mL) y se enfrió a 0°C. Se le agregó hidruro de sodio (40 mg, 0.917 mmol) y la temperatura se elevó a temperatura ambiente, seguido por agitación durante 19 horas. Después de que la solución de reacción se enfrió a 0°C, se le

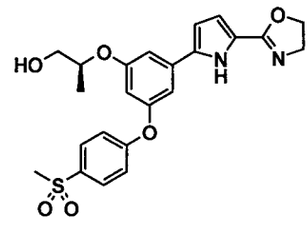
agregó agua (5 mL) y se extrajo con acetato de etilo (10 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-100%), para producir el compuesto deseado como un sólido blanco (118 mg, rendimiento de 72%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 3.9, 10.2 Hz), 3.59 (1H, dd, J = 6.3, 10.2 Hz), 3.98 (2H, t, J = 9.4 Hz), 4.40 (2H, t, J = 9.4 Hz), 4.56 (1H, m), 6.50 (1H, d, J = 3.9 Hz), 6.56 (1H, brt, J = 2.0 Hz), 6.75 (1H, d, J = 3.9 Hz), 6.83 (1H, brt, J = 2.0 Hz), 7.00 (1H, brt, J = 2.0 Hz), 7.13 (2H, d, J = 9.0 Hz), 7.90 (2H, d, J = 9.0 Hz).

MS (ESI) m/z: 471.16050 $(M+H)^+$.

EJEMPLO 21

(2S)-2-{3-[5-(4,5-Dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[4-(metilsulfonil)fenoxi]fenoxi}propan-1-ol



El 2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-

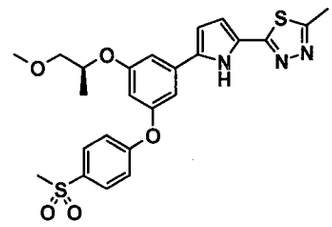
fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol (3.17 g, 6.74 mmol) sintetizado en el ejemplo 20 se disolvió en diclorometano (100 mL) y se enfrió a -78°C; se le agregó una solución de tribromuro de boro en diclorometano 1.0 mol/l (7.07 mL, 7.07 mmol) bajo una atmósfera de nitrógeno. La temperatura se elevó naturalmente, seguido por agitación a temperatura ambiente durante 30 minutos; subsiguientemente se le agregó una solución acuosa saturada de carbonato ácido de sodio para neutralizar la solución de reacción, y se extrajo con diclorometano (200 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se lavó con acetato de etilo (100 mL) y etanol (50 mL), para producir el producto deseado como un sólido blanco (1.96 g, rendimiento de 64%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.29 (3H, d, J = 6.3 Hz), 3.06 (3H, s), 3.79 (2H, d, J = 5.9 Hz), 4.00 (2H, t, J = 9.3 Hz), 4.42 (2H, t, J = 9.4 Hz), 4.58-4.63 (1H, m), 6.40 (1H, t, J = 2.2 Hz), 6.47 (1H, d, J = 3.9 Hz), 6.75 (1H, d, J = 3.8 Hz), 6.79 (1H, t, J = 1.7 Hz), 6.94 (1H, t, J = 1.8 Hz), 7.09 (2H, d, J = 8.8 Hz), 7.88 (2H, d, J = 8.8 Hz).

MS (ESI) m/z: 457.14357 $(M+H)^+$.

EJEMPLO 22

2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-5-metil-1,3,4-tiadiazol



(22a) N'-Acetil-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carbohidrazida

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-carboxílico (114.5 mg, 0.257 mmol) sintetizado en el ejemplo (18a) se disolvió en N,N-dimetilformamida (4 mL), y se le agregó acetohidrazida (39.4 mg, 0.531 mmol), HATU (150.1 mg, 0.395 mol) y N,N-diisopropiletilamina (70 μL, 0.40 mmol), y se agitó a temperatura ambiente durante 20 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó agua (20 mL) y se extrajo con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-100%), para producir el compuesto deseado como un sólido blanco (73.0 mg, rendimiento de 57%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.29 (3H, d, J = 6.3 Hz), 1.99 (3H,

s), 3.06 (3H, s), 3.40 (3H, s), 3.49 (1H, dd, J = 3.9, 10.2 Hz), 3.57 (1H, dd, J = 6.3, 10.2 Hz), 4.58-4.63 (1H, m), 6.46 (1H, dd, J = 2.7, 3.9 Hz), 6.53 (1H, s), 6.78 (1H, dd, J = 2.4, 3.9 Hz), 6.86 (1H, s), 7.10 (2H, d, J = 9.0 Hz), 7.13 (1H, s), 7.88 (2H, d, J = 8.6 Hz), 8.63 (1H, brs), 9.08 (1H, brs), 10.20 (1H, brs).

MS (ESI) m/z: 524.14725 $(M+Na)^+$.

(22b) 2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5-metil-1,3,4-tiadiazol

La N'-acetil-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-carbohidrazida (58.1 mg, 0.116 mmol) sintetizada en el ejemplo (22a) se disolvió en tolueno (4 mL), se le agregó 2,4-disulfuro de 2,4-bis-(4-metoxifenil)-1,3-ditia-2,4-difosfoetano (63.5 mg, 0.157 mmol) y piridina (20 μL, 0.25 mmol), y se agitó a 90°C durante 5 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) a la solución de reacción, y se extrajo con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 40%-80%), para producir el compuesto deseado como un sólido amarillo pálido (50.6 mg, rendimiento de 87%).

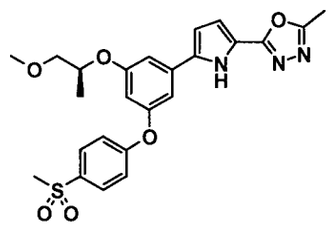
^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.34 (3H, d, J = 6.4 Hz), 2.77 (3H, s), 3.07 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 4.4, 10.3 Hz), 3.60 (1H, dd, J = 6.4, 10.3 Hz), 4.57-4.61 (1H, m), 6.55 (1H, t, J = 3.4 Hz), 6.58 (1H, t, J = 1.9

Hz), 6.67 (1H, dd, J = 2.4, 3.9 Hz), 6.87 (1H, t, J = 1.7 Hz), 7.03 (1H, s), 7.14 (2H, d, J = 8.8 Hz), 7.91 (2H, d, J = 8.8 Hz), 9.74 (1H, brs).

MS (ESI) m/z: 500.12981 $(M+H)^+$.

EJEMPLO 23)

2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-5-metil-1,3,4-oxadiazol



La N'-acetil-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-carbohidrazida (86.5 mg, 0.172 mmol) sintetizada en el ejemplo (22a) se disolvió en acetonitrilo (5 mL), y se le agregó hidróxido de (metoxicarbonilsulfamoil)trietilamonio (60.7 mg, 0.258 mmol) y trietilamina (36 μL, 0.26 mmol), y se agitó a 80°C durante 3 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) a la solución de reacción, y se extrajo con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-75%), para producir el compuesto deseado como un

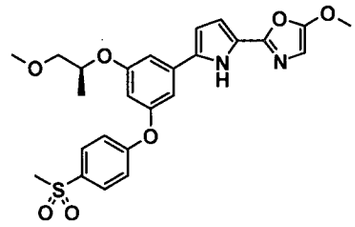
sólido blanco (49.1 mg, rendimiento de 59%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 2.58 (3H, s), 3.08 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 3.9, 10.2 Hz), 3.60 (1H, dd, J = 6.3, 10.2 Hz), 4.55-4.61 (1H, m), 6.57-6.60 (2H, m), 6.85-6.87 (2H, m), 7.02 (1H, s), 7.14 (2H, d, J = 8.6 Hz), 7.91 (2H, d, J = 8.6 Hz), 9.65 (1H, brs).

MS (ESI) m/z: 484.15505 $(M+H)^+$.

EJEMPLO 24

5-Metoxi-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-1,3-oxazol



(24a) N-[(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)carbonil]glicinato de metilo

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-carboxílico (275 mg, 0.617 mmol) sintetizado en el ejemplo (18a) se disolvió en diclorometano (10 mL), y se le agregó clorhidrato del éster metílico de glicina (120 mg, 0.956 mmol), WSCI·HCl (180 mg, 0.939 mmol) y 4-dimetilaminopiridina (150 mg, 1.23 mmol), seguido por agitación a temperatura ambiente durante 2 horas bajo una atmósfera de nitrógeno. Se le agregó ácido clorhídrico 1N (10 mL) y la solución se separó con diclorometano

(15 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-60%), para producir el producto deseado como un sólido blanco (270 mg, rendimiento de 85%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 3.9, 10.2 Hz), 3.59 (1H, dd, J = 6.3, 10.2 Hz), 3.78 (3H, s), 4.56 (1H, m), 6.48 (1H, brt, J = 3.9 Hz), 6.54-6.58 (2H, m), 6.69 (1H, dd, J = 2.4, 3.9 Hz), 6.89 (1H, t, J = 2.0 Hz), 7.02 (1H, t, J = 2.0 Hz), 7.12 (2H, d, J = 8.6 Hz), 7.89 (2H, d, J = 8.9 Hz), 10.11 (1H, brs).

(24b) 5-Metoxi-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-1,3-oxazol

El N-[(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)carbonil]glicinato de metilo (270 mg, 0.523 mmol) sintetizado en el ejemplo (24a) se disolvió en acetonitrilo (10 mL), y se le agregó trifenilfosfina (410 mg, 1.56 mmol), trietilamina (0.22 mL, 1.58 mmol) y tetracloruro de carbono (0.33 mL, 3.42 mmol), seguido por agitación a temperatura ambiente durante 15 horas bajo una atmósfera de nitrógeno. Se le agregó agua (10 mL) y la solución se separó con acetato de etilo (15 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en

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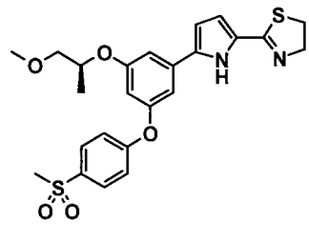
columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-40%), para producir el producto deseado como un sólido anaranjado (162 mg, rendimiento de 62%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 3.9, 10.2 Hz), 3.59 (1H, dd, J = 6.3, 10.2 Hz), 3.92 (3H, s), 4.55 (1H, m), 6.08 (1H, s), 6.51-6.55 (2H, m), 6.70 (1H, dd, J = 2.4, 3.9 Hz), 6.83 (1H, t, J = 2.0 Hz), 6.99 (1H, t, J = 2.0 Hz), 7.12 (2H, d, J = 9.0 Hz), 7.90 (2H, d, J = 9.0 Hz), 9.77 (1H, brs).

MS (ESI) m/z: 499.15601 $(M+H)^+$.

EJEMPLO 25

2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-tiazol



(25a) 2-(Tritiltio)etanoamina

Se disolvió ácido clorhídrico 2-aminoetanotiol (5.16 g, 45.4 mmol) en diclorometano (80 mL), y se le agregó ácido trifluoroacético (7.0 mL, 90.8 mmol) y cloruro de trifenilmetilo (13.29 g, 47.7 mmol), seguido por agitación a temperatura ambiente durante 1 hora. Se le agregó una solución acuosa de hidróxido de sodio 1N (150 mL) y se extrajo con diclorometano (500 mL). La

capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y al residuo resultante se le agregó metanol (100 mL); el subproducto depositado se removió por filtración. Se le agregó ácido clorhídrico 1N (300 mL) para hacer ácida la solución, y el depósito se filtró. Después de que el subproducto se lavó con diclorometano (50 mL) para removerlo, la solución se hizo alcalina con una solución acuosa de hidróxido de sodio 1N, y se extrajo con diclorometano (600 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida para producir el producto deseado como un sólido blanco (8.77 g, rendimiento de 60%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.33 (2H, t, J = 6.6 Hz), 2.59 (2H, t, J = 6.6 Hz), 7.19-7.23 (3H, m), 7.26-7.30 (6H, m), 7.41-7.44 (6H, m).

(25b) 5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-N-[2-(tritiltio)etil]-1H-pirrol-2-carboxamida

Al ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxílico (940 mg, 2.1 mmol) sintetizado en el ejemplo (18a), se le agregó la 2-(tritiltio)etanoamina (1.01 g, 3.17 mmol) sintetizada en el ejemplo (25a) y 4-dimetilaminopiridina (13 mg, 0.1 mmol), seguido por disolución en diclorometano (50 mL); subsiguientemente se le agregó WSCI·HCl (445 mg, 2.3 mmol) a temperatura ambiente y se agitó durante 1 hora bajo una atmósfera de nitrógeno. La

solución de reacción se diluyó con diclorometano (150 mL), se lavó con ácido clorhídrico 1N, solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-55%), para producir el producto deseado como un sólido blanco (1.08 g, rendimiento de 69%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 2.50 (2H, t, J = 6.5 Hz), 3.07 (3H, s), 3.27 (2H, dt, J = 5.9, 6.2 Hz), 3.42 (3H, s), 3.51 (1H, dd, J = 4.0, 10.4 Hz), 3.59 (1H, dd, J = 5.9, 10.4 Hz), 4.55-4.59 (1H, m), 5.99 (1H, brm), 6.48 (1H, dd, J = 2.8, 3.9 Hz), 6.53 (1H, dd, J = 2.5, 3.9 Hz), 6.57 (1H, t, J = 2.3 Hz), 6.81 (1H, t, J = 2.2 Hz), 6.98 (1H, t, J = 2.1 Hz), 7.14 (2H, d, J = 8.9 Hz), 7.19-7.30 (9H, m), 7.42 (6H, dd, J = 1.6, 7.3 Hz), 7.91 (2H, d, J = 8.9 Hz), 9.41 (1H, brs).

(25c) 2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-tiazol

Se disolvió óxido de trifenilfosfina (2.41 g, 8.7 mmol) en diclorometano (20 mL) y se le agregó lentamente, gota a gota, anhídrido trifluorometanosulfónico (0.73 mL, 4.3 mmol), a 0°C. Después de agitar 10 minutos se le agregó una solución de 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-N-[2-(tritiltio)etil]-1H-pirrol-2-carboxamida, sintetizada en el ejemplo (25b), en diclorometano (15 mL). Después de que la solución de reacción se agitó a temperatura ambiente durante 30 minutos, el disolvente

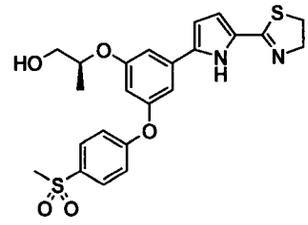
se removió por destilación bajo presión reducida, se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con acetato de etilo (200 mL). La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-80%), para producir el producto deseado como un sólido blanco (636 mg, rendimiento de 90%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.39 (2H, t, J = 8.4 Hz), 3.41 (3H, s), 3.50 (1H, dd, J = 3.9, 10.3 Hz), 3.59 (1H, dd, J = 5.9, 10.3 Hz), 4.33 (2H, t, J = 8.7 Hz), 4.55-4.59 (1H, m), 6.50 (1H, d, J = 3.9 Hz), 6.56 (1H, t, J = 2.5 Hz), 6.64 (1H, d, J = 3.9 Hz), 6.83 (1H, t, J = 2.0 Hz), 7.00 (1H, t, J = 2.4 Hz), 7.13 (2H, d, J = 8.8 Hz), 7.90 (2H, d, J = 8.8 Hz).

MS (ESI) m/z: 487.13595 $(M+H)^+$.

EJEMPLO 26

(2S)-2-{3-[5-(4,5-Dihidro-1,3-tiazol-2-il)-1H-pirrol-2-il]-5-[4-(metilsulfonil)fenoxi]fenoxi}propan-1-ol



El 2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-tiazol (88 mg, 0.18 mmol) sintetizado en el ejemplo (25c), se disolvió en diclorometano (5 mL) y se enfrió a -78°C; se le agregó una solución de tribromuro de boro en diclorometano 1.0 mol/l (0.22 mL, 0.22 mmol) bajo una atmósfera de nitrógeno. Después de que la temperatura se elevó naturalmente y la solución se agitó a temperatura ambiente durante 1 hora, subsiguientemente se le agregó una solución acuosa saturada de carbonato ácido de sodio para neutralizar la solución de reacción, seguido por extracción con diclorometano (60 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 40%-100%), para producir el producto deseado como un sólido amarillo pálido (46 mg, rendimiento de 54%).

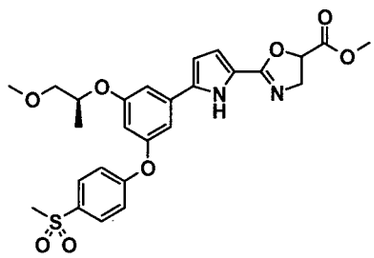
^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.29 (3H, d, J = 6.4 Hz), 3.27 (3H,

s), 3.40 (2H, t, J = 8.1 Hz), 3.76-3.78 (2H, m), 4.33 (2H, t, J = 8.2 Hz), 4.55-4.59 (1H, m), 6.47 (1H, d, J = 2.4 Hz), 6.49 (1H, d, J = 3.7 Hz), 6.65 (1H, d, J = 3.7 Hz), 6.82 (1H, s), 6.96 (1H, s), 7.11 (2H, d, J = 8.7 Hz), 7.90 (2H, d, J = 8.7 Hz).

MS (ESI) m/z: 473.12049 $(M+H)^+$.

EJEMPLO 27

2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol-5-carboxilato de metilo



(27a) 2-Hidroxi-3-{[(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)carbonil]amino}propanoato de metilo

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-carboxílico (420 mg, 0.943 mmol) sintetizado en el ejemplo (18a) se disolvió en diclorometano (10 mL), y se le agregó clorhidrato del éster metílico de DL-isoserina (300 mg, 1.93 mmol), WSCI·HCl (270 mg, 1.41 mmol) y 4-dimetilaminopiridina (230 mg, 1.88 mmol), seguido por agitación a temperatura ambiente durante 1.5 horas bajo una atmósfera de nitrógeno. Se le agregó ácido clorhídrico 1N (10 mL) y la solución se separó

con diclorometano (15 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-80%), para producir el producto deseado como un sólido blanco (400 mg, rendimiento de 78%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 3.9, 10.2 Hz), 3.60 (1H, dd, J = 6.3, 10.2 Hz), 3.72-3.85 (2H, m), 3.80 (3H, s), 4.38 (1H, brt, J = 4.7 Hz), 4.58 (1H, m), 6.43 (1H, brs), 6.47 (1H, m), 6.56 (1H, t, J = 2.0 Hz), 6.63 (1H, dd, J = 2.4, 3.9 Hz), 6.86 (1H, t, J = 2.0 Hz), 7.01 (1H, t, J = 2.0 Hz), 7.12 (2H, d, J = 9.0 Hz), 7.90 (2H, d, J = 9.0 Hz), 9.85 (1H, brs).

(27b) 2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol-5-carboxilato de metilo

El 2-hidroxi-3-{[(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)carbonil]amino}propanoato de metilo (686 mg, 1.26 mmol) sintetizado en el ejemplo (27a) se disolvió en tetrahidrofurano (15 mL), y se le agregó anhídrido metanosulfónico (330 mg, 1.89 mmol) y trietilamina (0.53 mL, 3.80 mmol), seguido por agitación a temperatura ambiente durante 19 horas bajo una atmósfera de nitrógeno. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (10 mL), y la solución se separó con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de

magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-70%), para producir el producto deseado como un sólido blanco (586 mg, rendimiento de 88%).

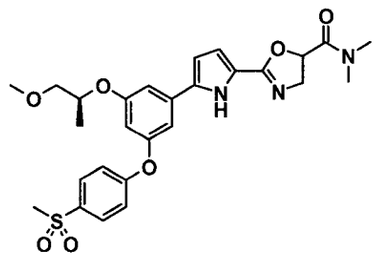
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 3.9, 10.2 Hz), 3.60 (1H, dd, J = 6.3, 10.2 Hz), 4.10 (1H, dd, J = 7.0, 14.5 Hz), 4.30 (1H, dd, J = 10.6, 14.5 Hz), 4.56 (1H, m), 5.07 (1H, dd, J = 7.0, 10.6 Hz), 6.52 (1H, d, J = 3.9 Hz), 6.57 (1H, t, J = 2.0 Hz), 6.83 (1H, t, J = 2.0 Hz), 6.86 (1H, d, J = 3.9 Hz), 7.00 (1H, t, J = 2.0 Hz), 7.14 (2H, d, J = 9.0 Hz), 7.90 (2H, d, J = 9.0 Hz), 9.66 (1H, brs).

MS (ESI) m/z: 529.16412 $(M+H)^+$.

615

EJEMPLO 28

2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-N,N-dimetil-4,5-dihidro-1,3-oxazol-5-carboxamida



(28a) Acido 2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol-5-carboxílico

El 2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol-5-carboxilato de metilo (60.5 mg, 0.114 mmol) sintetizado en el ejemplo (27b) se disolvió en etanol (4 mL). Se le agregó una solución acuosa de hidróxido de sodio (5M, 2 mL) y se agitó a 70°C durante 2.5 horas. Después de enfriar a temperatura ambiente, se le agregó ácido clorhídrico (2M, 5 mL) y acetato de etilo (10 mL) y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida para producir el compuesto deseado como un sólido amarillo pálido (69.3 mg, rendimiento de ~100%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.42 (3H, s), 3.55-3.63 (2H, m), 4.28-4.44 (2H, m), 4.78 (1H, m), 5.49 (1H, brs), 6.60-6.68 (2H, m), 7.10 (1H, brs), 7.14 (2H, d, J = 8.3 Hz), 7.26 (1H, m),

7.39 (1H, brd, J = 8.3 Hz), 7.89 (2H, d, J = 8.3 Hz), 13.10 (1H, brs).

MS (ESI) m/z: 515.14638 $(M+H)^+$.

(28b) 2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-N,N-dimetil-4,5-dihidro-1,3-oxazol-5-carboxamida

El ácido 2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol-5-carboxílico (154 mg, 0.299 mmol) sintetizado en el ejemplo (28a) se disolvió en diclorometano (10 mL), y se le agregó clorhidrato de dimetilamina (75.0 mg, 0.920 mmol), WSCI·HCl (115 mg, 0.600 mmol) y 4-dimetilaminopiridina (110 mg, 0.900 mmol), seguido por agitación a temperatura ambiente durante 2 días bajo una atmósfera de nitrógeno. Se le agregó agua (10 mL) y la solución se separó con diclorometano (15 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 70%-100%), para producir el producto deseado como un sólido blanco (107 mg, rendimiento de 66%).

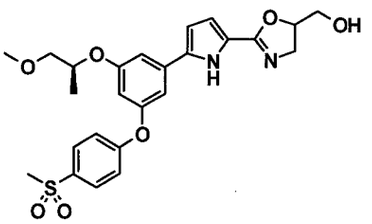
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.02 (3H, s), 3.07 (3H, s), 3.15 (3H, s), 3.42 (3H, s), 3.50 (1H, dd, J = 3.9, 10.2 Hz), 3.60 (1H, dd, J = 5.9, 10.2 Hz), 4.19 (1H, ddd, J = 1.2, 10.2, 14.1 Hz), 4.33 (1H, brdd, J = 7.8, 14.1 Hz), 4.57 (1H, m), 5.27 (1H, dd, J = 7.8, 10.2 Hz), 6.50 (1H, d, J = 3.9 Hz), 6.56 (1H, d, J = 2.0 Hz), 6.78 (1H, d, J = 3.9 Hz), 6.83 (1H, t, J = 2.0 Hz), 7.01 (1H, d, J = 2.0 Hz), 7.13 (2H, d, J = 8.6 Hz), 7.90 (2H, d, J =

8.9 Hz), 9.80 (1H, brs).

MS (ESI) m/z: 542.19865 $(M+H)^+$.

EJEMPLO 29

[2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol-5-il]metanol



Se suspendió hidruro de litio y aluminio (17.0 mg, 0.448 mmol) en tetrahidrofurano (2 mL). El 2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol-5-carboxilato de metilo (77.0 mg, 0.146 mmol) sintetizado en el ejemplo (27b) se disolvió en tetrahidrofurano (2 mL), seguido por su adición a gotas a 0°C y bajo una atmósfera de nitrógeno. Después de agitar a 0°C durante 30 minutos, se le agregó secuencialmente agua (17 μL) y una solución acuosa de hidróxido de sodio (5M, 68 μL) lentamente, gota a gota. Después de filtración a través de Celite, el disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-100%), para producir el compuesto deseado como un sólido blanco (54.1 mg, rendimiento de 74%).

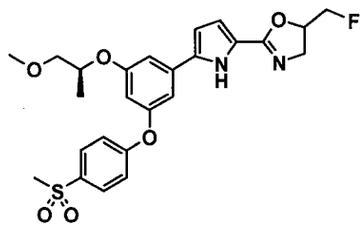
^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.29-1.33 (3H, m), 3.06 (3H, s),

3.41 (3H, s), 3.49 (1H, m), 3.58 (1H, m), 3.63-3.76 (2H, m), 3.83 (1H, m), 3.97 (1H, m), 4.59 (1H, m), 4.76 (1H, m), 6.46 (1H, m), 6.54 (1H, brs), 6.72 (1H, m), 6.69 (1H, brs), 7.05 (1H, m), 7.13 (2H, d, J = 8.8 Hz), 7.89 (2H, d, J = 8.8 Hz).

MS (ESI) m/z: 501.17097 $(M+H)^+$.

EJEMPLO 30

5-(Fluorometil)-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol



El [2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol-5-il]metanol (100 mg, 0.20 mmol) sintetizado en el ejemplo 29 se disolvió en diclorometano (5 mL), y se le agregó trifluoruro de bis(2-metoxietil)aminoazufre (81 μL, 0.44 mmol) a 0°C. Después de agitar a temperatura ambiente durante 6 horas, se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con diclorometano (60 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de

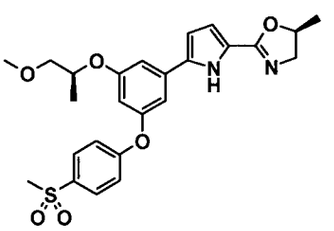
etilo/hexano = 80%-100%), para producir el producto deseado como un sólido blanco (61 mg, rendimiento de 61%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 4.1,10.3 Hz), 3.59 (1H, dd, J = 6.3, 10.3 Hz), 3.82 (1H, dd, J = 7.4, 14.5 Hz), 4.10 (1H, ddd, J = 1.4, 10.1, 14.6 Hz), 4.49 (1H, ddd, J = 5.5, 10.5, 37.9 Hz), 4.54-4.58 (1H, m), 4.62 (1H, ddd, J = 3.0, 10.6, 33.3 Hz), 4.85-4.96 (1H, m), 6.51 (1H, d, J = 3.9 Hz), 6.57 (1H, t, J = 2.1 Hz), 6.80 (1H, d, J = 3.6 Hz), 6.81 (1H, t, J = 1.9 Hz), 6.98 (1H, t, J = 1.8 Hz), 7.13 (2H, d, J = 8.9 Hz), 7.91 (2H, d, J = 8.9 Hz)

MS (ESI) m/z: 503.16398 $(M+H)^+$.

EJEMPLO 31

(5S)-2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol



(31a) N-[(2R)-2-Hidroxipropil]-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-carboxílico (204 mg, 0.458 mmol) sintetizado en el ejemplo (18a) se disolvió en diclorometano (10 mL), y se le agregó (R)-(-)-1-

amino-2-propanol (72.0μ mL, 0.914 mmol), WSCI·HCl (130 mg, 0.678 mmol) y 4-dimetilaminopiridina (115 mg, 0.941 mmol), seguido por agitación a temperatura ambiente durante 18 horas bajo una atmósfera de nitrógeno. Se le agregó ácido clorhídrico 1N (10 mL) y la solución se separó con diclorometano (15 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 60%-100%), para producir el producto deseado como un sólido blanco (191 mg, rendimiento de 83%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.21 (3H, d, J = 6.3 Hz), 1.31 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.24 (3H, s), 3.41 (3H, s), 3.51 (1H, dd, J = 3.9, 10.2 Hz), 3.57 (1H, m), 3.59 (1H, dd, J = 6.3, 10.2 Hz), 3.98 (1H, m), 4.56 (1H, m), 6.47 (1H, dd, J = 2.7, 3.9 Hz), 6.50 (1H, brs), 6.55 (1H, t, J = 2.0 Hz), 6.64 (1H, dd, J = 2.4, 3.9 Hz), 6.87 (1H, t, J = 2.0 Hz), 7.00 (1H, t, J = 2.0 Hz), 7.12 (2H, d, J = 9.0 Hz), 7.89 (2H, d, J = 9.0 Hz), 10.09 (1H, brs).

(31b) (5S)-2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol

La N-[(2R)-2-hidroxipropil]-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida (191 mg, 0.380 mmol) sintetizada en el ejemplo (31a) se disolvió en tetrahidrofurano (10 mL), y se le agregó ácido metanosulfónico anhidro (100 mg, 0.574 mmol) y trietilamina (0.16 mL, 1.15 mmol), seguido por agitación a temperatura ambiente durante

18 horas bajo una atmósfera de nitrógeno. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (10 mL) y la solución se separó con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-70%), para producir el producto deseado como un sólido blanco (136 mg, rendimiento de 74%).

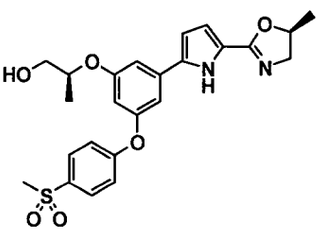
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 1.42 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 4.3, 10.2 Hz), 3.52 (1H, dd, J = 7.4, 14.1 Hz), 3.59 (1H, dd, J = 6.3, 10.2 Hz), 4.06 (1H, dd, J = 9.4, 14.1 Hz), 4.57 (1H, m), 4.82 (1H, m), 6.50 (1H, d, J = 3.9 Hz), 6.55 (1H, t, J = 2.0 Hz), 6.75 (1H, d, J = 3.9 Hz), 6.83 (1H, t, J = 2.0 Hz), 7.00 (1H, t, J = 2.0 Hz), 7.13 (2H, d, J = 9.0 Hz), 7.90 (2H, d, J = 9.0 Hz).

MS (ESI) m/z: 485.17394 $(M+H)^+$.

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EJEMPLO 32

(2S)-2-(3-{5-[(5S)-5-Metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[4-(metilsulfonil)fenoxi]fenoxi)propan-1-ol



El (5S)-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol (280 mg, 0.58 mmol) sintetizado en el ejemplo(31b) se disolvió en diclorometano (10 mL) y se enfrió a -78°C; se le agregó una solución de tribromuro de boro en diclorometano 1.0 mol/l (0.61 mL, 0.61 mmol) bajo una atmósfera de nitrógeno. Después de que la temperatura se elevó naturalmente y la solución se agitó a temperatura ambiente durante 30 minutos, se le agregó una solución acuosa saturada de carbonato ácido de sodio para neutralizar la solución de reacción, seguido por extracción con diclorometano (60 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo), para producir el producto deseado como un sólido blanco (222 mg, rendimiento de 82%).

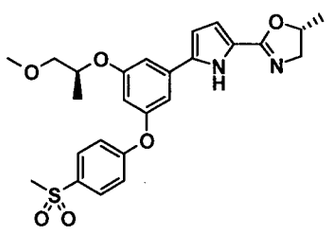
^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.28 (3H, d, J = 6.3 Hz), 1.43 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.55 (1H, dd, J = 7.3, 13.9 Hz), 3.79 (2H, d, J = 5.4

Hz), 4.09 (1H, dd, J = 9.2, 14.0 Hz), 4.60-4.64 (1H, m), 4.81-4.87 (1H, m), 6.36 (1H, t, J = 2.3 Hz), 6.46 (1H, d, J = 3.9 Hz), 6.75 (1H, d, J = 3.9 Hz), 6.91 (1H, t, J = 1.9 Hz), 7.08 (2H, d, J = 8.9 Hz), 7.88 (2H, d, J = 8.9 Hz).

MS (ESI) m/z: 471.15892 $(M+H)^+$.

EJEMPLO 33

(5R)-2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol



(33a) N-[(2S)-2-Hidroxipropil]-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-carboxílico (305 mg, 0.685 mmol) sintetizado en el ejemplo (18a) se disolvió en diclorometano (10 mL), y se le agregó (S)-(+)-1-amino-2-propanol (110μ mL, 1.40 mmol), WSCI·HCl (200 mg, 1.04 mmol) y 4-dimetilaminopiridina (170 mg, 1.39 mmol), seguido por agitación a temperatura ambiente durante 16 horas bajo una atmósfera de nitrógeno. Se le agregó ácido clorhídrico 1N (10 mL) y la solución se separó con diclorometano (15 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por

destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 60%-100%), para producir el producto deseado como un sólido blanco (285 mg, rendimiento de 83%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.24 (3H, d, J = 6.3 Hz), 1.33 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.28 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 3.9, 10.2 Hz), 3.56-3.65 (2H, m), 4.01 (1H, m), 4.58 (1H, m), 6.35 (1H, brt, J = 5.5 Hz), 6.49 (1H, dd, J = 2.7, 3.9 Hz), 6.57 (1H, t, J = 2.0 Hz), 6.62 (1H, dd, J = 2.4, 3.9 Hz), 6.84 (1H, t, J = 2.0 Hz), 7.00 (1H, t, J = 2.0 Hz), 7.13 (2H, d, J = 8.6 Hz), 7.90 (2H, d, J = 8.6 Hz), 9.66 (1H, brs).

(33b) (5R)-2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol

La N-[(2S)-2-hidroxipropil]-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida (285 mg, 0.567 mmol) sintetizada en el ejemplo (33a) se disolvió en tetrahidrofurano (10 mL), y se le agregó ácido metanosulfónico anhidro (130 mg, 0.746 mmol) y trietilamina (0.24 mL, 1.72 mmol), seguido por agitación a temperatura ambiente durante 21 horas bajo una atmósfera de nitrógeno. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (10 mL) y la solución se separó con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución:

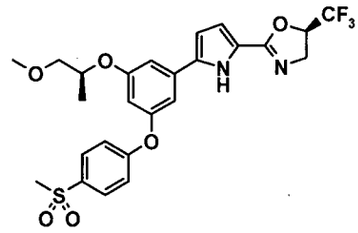
acetato de etilo/hexano = 30%-70%), para producir el producto deseado como un sólido blanco (155 mg, rendimiento de 56%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J = 6.3 Hz), 1.41 (3H, d, J = 6.3 Hz), 3.06 (3H, s), 3.40 (3H, s), 3.50 (1H, dd, J = 3.9, 10.2 Hz), 3.51 (1H, dd, J = 8.2, 14.1 Hz), 3.58 (1H, dd, J = 5.9, 10.2 Hz), 4.04 (1H, dd, J = 9.4, 14.1 Hz), 4.56 (1H, m), 4.80 (1H, m), 6.50 (1H, d, J = 3.9 Hz), 6.55 (1H, t, J = 2.0 Hz), 6.74 (1H, d, J = 3.9 Hz), 6.84 (1H, t, J = 2.0 Hz), 7.00 (1H, t, J = 2.0 Hz), 7.12 (2H, d, J = 9.0 Hz), 7.89 (2H, d, J = 9.0 Hz).

MS (ESI) m/z: 485.17398 $(M+H)^+$.

EJEMPLO 34

(5R)-2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-5-(trifluorometil)-4,5-dihidro-1,3-oxazol



(34a) 5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-N-[(2S)-3,3,3-trifluoro-2-hidroxipropil]-1H-pirrol-2-carboxamida

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-carboxílico (408 mg, 0.94 mmol) sintetizado en el ejemplo (18a), (2S)-3-amino-1,1,1-trifluoro-2-propanol (177 mg, 1.37 mmol) y 4-dimetilaminopiridina (224 mg, 1.87 mmol), se disolvieron en diclorometano

(20 mL) y se les agregó WSCI·HCl (193 mg, 1.01 mmol) a temperatura ambiente, seguido por agitación durante 2 horas bajo una atmósfera de nitrógeno. La solución de reacción se diluyó con diclorometano (200 mL), se lavó con ácido clorhídrico 1N, solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-70%), para producir el producto deseado como una sustancia amorfa blanca (339 mg, rendimiento de 67%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.31 (3H, d, J = 6.3 Hz), 3.08 (3H, s), 3.42 (3H, s), 3.52 (1H, dd, J = 3.9, 10.3 Hz), 3.60 (1H, dd, J = 6.2, 10.2 Hz), 3.58-3.65 (1H, m), 3.85 (1H, ddd, J = 2.7, 6.6, 14.9 Hz), 4.08-4.15 (1H, brm), 4.53-4.60 (1H, m), 4.74 (1H, d, J = 5.5 Hz), 6.37 (1H, t, J = 6.1 Hz), 6.50 (1H, dd, J = 3.0, 4.0 Hz), 6.58 (1H, t, J = 2.2 Hz), 6.67 (1H, dd, J = 2.7, 4.0 Hz), 6.84 (1H, t, J = 1.7 Hz), 6.99 (1H, t, J = 2.0 Hz), 7.13 (2H, d, J = 8.9 Hz), 7.91 (2H, d, J = 8.9 Hz), 9.82 (1H, brs).

(34b) (5R)-2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5-(trifluorometil)-4,5-dihidro-1,3-oxazol

La 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-N-[(2S)-3,3,3-trifluoro-2-hidroxipropil]-1H-pirrol-2-carboxamida (339 mg, 0.61 mmol) sintetizada en el ejemplo (34a) se disolvió en tetrahidrofurano (10 mL), y se le agregó trietilamina (0.51 mL, 3.66 mmol) y ácido metanosulfónico

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anhidro (296 mg, 1.71 mmol) a 0°C, seguido por calentamiento a 120°C durante 30 horas. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con acetato de etilo (60 mL). Después de lavar con salmuera saturada, se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-50%), para producir el producto deseado como un sólido blanco (328 mg, rendimiento de 84%).

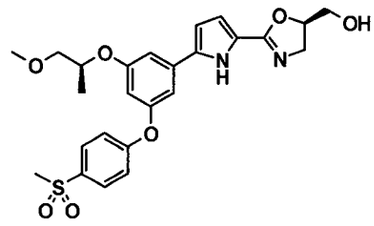
^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.08 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 3.9, 10.4 Hz), 3.59 (1H, dd, J = 6.3, 10.1 Hz), 4.15 (1H, dd, J = 6.5, 15.4 Hz), 4.22 (1H, dd, 10.0, 15.4 Hz), 4.55-4.59 (1H, m), 4.88-4.92 (1H, m), 6.52 (1H, dd, J = 2.4,4.0 Hz), 6.58 (1H, t, J = 2.2 Hz), 6.82 (1H, t, J = 1.8 Hz), 6.84 (1H, dd, J = 2.3, 3.9 Hz), 6.98 (1H, t, J = 2.0 Hz), 7.13 (2H, d, J = 8.8 Hz), 7.91 (2H, d, J = 8.8 Hz), 9.25 (1H, brs).

MS (ESI) m/z: 539.14603 $(M+H)^+$.

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EJEMPLO 35

[(5R)-2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol-5-il]metanol



(35a) N-[(2S)-2,3-Dihidroxipropil]-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxílico (338 mg, 0.759 mmol) sintetizado en el ejemplo (18a) se disolvió en diclorometano (10 mL), y se le agregó (S)-(-)-3-amino-1,2-propanodiol (105 mg, 1.15 mmol), WSCI·HCl (220 mg, 1.15 mmol) y 4-dimetilaminopiridina (185 mg, 1.51 mmol), seguido por agitación a temperatura ambiente durante 3 días bajo una atmósfera de nitrógeno. Se le agregó ácido clorhídrico 1N (10 mL) y la solución se separó con diclorometano (15 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 70%-100%), para producir el producto deseado como un sólido blanco (265 mg, rendimiento de 68%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.07 (3H,

s), 3.42 (3H, s), 3.51 (1H, dd, J = 3.9, 10.2 Hz), 3.553-3.64 (4H, m), 3.85 (1H, m), 4.57 (1H, m), 6.38 (1H, m), 6.50 (1H, dd, J = 2.7, 3.9 Hz), 6.58 (1H, t, J = 2.0 Hz), 6.64 (1H, dd, J = 2.4, 3.9 Hz), 6.84 (1H, t, J = 2.0 Hz), 7.00 (1H, t, J = 2.0 Hz), 7.13 (2H, d, J = 9.0 Hz), 7.91 (2H, d, J = 9.0 Hz), 9.59 (1H, brs).

(35b) N-{(2S)-2-Hidroxi-3-[(triisopropilsilil)oxi]propil}-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida

La N-[(2S)-2,3-dihidroxipropil]-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida (265 mg, 0.514 mmol) sintetizada en el ejemplo (35a) se disolvió en diclorometano (10 mL), y se le agregó cloruro de triisopropilsililo (0.12 mL, 0.691 mmol), trietilamina (0.21 mL, 1.51 ~~m~~mol) y 4-dimetilaminopiridina (6.0 mg, 0.049 mmol), seguido por agitación a temperatura ambiente durante 24 horas bajo una atmósfera de nitrógeno. Se le agregó agua (10 mL) y la solución se separó con diclorometano (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-50%), para producir el producto deseado como un sólido blanco (177 mg, rendimiento de 51%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.04-1.13 (21H, m), 1.32 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.21 (1H, d, J = 4.3 Hz), 3.38 (1H, m), 3.42 (3H, s), 3.51 (1H, dd, J = 3.9, 10.2 Hz), 3.60 (1H, dd, J = 6.3, 10.2 Hz), 3.67 (1H, dd, J = 6.3, 9.8 Hz), 3.73 (1H, m), 3.76 (1H, dd, J = 5.0, 9.8 Hz), 3.86 (1H, m), 4.58

(1H, m), 6.43 (1H, brt, J = 5.9 Hz), 6.48 (1H, dd, J = 2.8, 3.9 Hz), 6.56 (1H, t, J = 2.0 Hz), 6.61 (1H, dd, J = 2.4, 3.9 Hz), 6.85 (1H, t, J = 2.0 Hz), 7.00 (1H, t, J = 2.0 Hz), 7.13 (2H, d, J = 8.6 Hz), 7.90 (2H, d, J = 8.6 Hz), 9.80 (1H, brs).

(35c) (5S)-2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5-{[(triisopropilsilil)oxi]metil}-4,5-dihidro-1,3-oxazol

La N-{(2S)-2-hidroxi-3-[(triisopropilsilil)oxi]propil}-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida (177 mg, 0.262 mmol) sintetizada en el ejemplo (35b) se disolvió en tetrahidrofurano (10 mL), y se le agregó ácido metanosulfónico anhidro (70.0 mg, 0.402 mmol) y trietilamina (0.22 mL, 1.58 mmol), seguido por agitación a 70°C durante 3 días bajo una atmósfera de nitrógeno. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (10 mL) y la solución se separó con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-60%), para producir el producto deseado como un aceite amarillo (180 mg, rendimiento de ~100%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.02-1.10 (21H, m), 1.33 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 4.3, 10.2 Hz), 3.59 (1H, dd, J = 6.3, 10.2 Hz), 3.82-3.90 (3H, m), 4.00 (1H, dd, J = 9.8, 14.1 Hz), 4.58 (1H, m), 4.75 (1H, m), 6.49 (1H, d, J = 3.9 Hz), 6.55 (1H, t, J = 2.0 Hz), 6.73 (1H, d, J = 3.9 Hz), 6.83 (1H, t, J = 2.0 Hz), 7.00 (1H, t, J = 2.0 Hz), 7.13 (2H,

d, J = 9.0 Hz), 7.90 (2H, d, J = 9.0 Hz), 9.59 (1H, brs).

(35d) [(5R)-2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol-5-il]metanol

El (5S)-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5-{[(triisopropilsilil)oxi]metil}-4,5-dihidro-1,3-oxazol (180 mg, 0.262 mmol) sintetizado en el ejemplo (35c) se disolvió en tetrahidrofurano (10 mL), y se le agregó fluoruro de tetrabutilamonio (solución en tetrahidrofurano 1M, 0.53 mL, 0.53 mmol), seguido por agitación a temperatura ambiente durante 30 minutos bajo una atmósfera de nitrógeno. Se le agregó agua (10 mL) y se extrajo con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 60%-100%), para producir el compuesto deseado como un sólido blanco (103 mg, rendimiento de 79%).

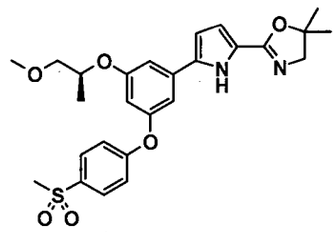
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.27 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.42 (3H, s), 3.49 (1H, dd, J = 3.9, 10.2 Hz), 3.58 (1H, dd, J = 6.3, 10.2 Hz), 3.67 (1H, dd, J = 5.1, 12.5 Hz), 3.74 (1H, dd, J = 7.4, 14.5 Hz), 3.84 (1H, dd, J = 3.1, 12.5 Hz), 4.00 (1H, dd, J = 9.8, 14.5 Hz), 4.54 (1H, m), 4.78 (1H, m), 6.46 (1H, d, J = 3.9 Hz), 6.55 (1H, t, J = 2.0 Hz), 6.71 (1H, d, J = 3.9 Hz), 6.85 (1H, t, J = 2.0 Hz), 6.98 (1H, t, J = 2.0 Hz), 7.14 (2H, d, J = 8.6 Hz), 7.90 (2H, d, J = 9.0 Hz), 9.59 (1H, brs).

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MS (ESI) m/z: 501.16898 $(M+H)^+$.

EJEMPLO 36

2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-5,5-dimetil-4,5-dihidro-1,3-oxazol



(36a) N-(2-Hidroxi-2-metilpropil)-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-carboxílico (300 mg, 0.673 mmol) sintetizado en el ejemplo (18a) se disolvió en diclorometano (10 mL), y se le agregó 1-amino-2-metil-2-propanol (150 mg, 1.68 mmol), WSCI·HCl (185 mg, 0.965 mmol) y 4-dimetilaminopiridina (165 mg, 1.35 mmol), seguido por agitación a temperatura ambiente durante 17 horas, bajo una atmósfera de nitrógeno. Se le agregó ácido clorhídrico 1N (10 mL) y la solución se separó con diclorometano (15 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de

etilo/hexano = 60%-100%), para producir el producto deseado como un sólido blanco (307 mg, rendimiento de 88%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.26 (6H, s), 1.32 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.41 (3H, s), 3.41 (2H, m), 3.51 (1H, dd, J = 3.9, 10.2 Hz), 3.59 (1H, dd, J = 6.3, 10.2 Hz), 4.58 (1H, m), 4.46 (1H, brs), 6.48 (1H, dd, J = 2.7, 3.9 Hz), 6.56 (1H, t, J = 2.0 Hz), 6.65 (1H, dd, J = 2.4, 3.9 Hz), 6.86 (1H, t, J = 2.0 Hz), 7.00 (1H, t, J = 2.0 Hz), 7.12 (2H, d, J = 9.0 Hz), 7.90 (2H, d, J = 9.0 Hz), 9.86 (1H, brs).

(36b) 2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5,5-dimetil-4,5-dihidro-1,3-oxazol

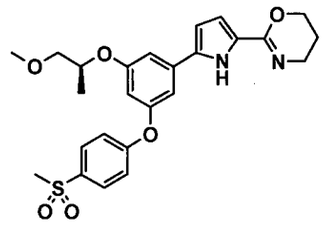
La N-(2-hidroxi-2-metilpropil)-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida (307 mg, 0.594 mmol) sintetizada en el ejemplo (36a) se disolvió en tetrahidrofurano (10 mL), y se le agregó ácido metanosulfónico anhidro (160 mg, 0.918 mmol) y trietilamina (0.25 mL, 1.79 ~~m~~mol), seguido por agitación a temperatura ambiente durante 4 días bajo una atmósfera de nitrógeno. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (10 mL) y la solución se separó con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-70%), para producir el producto deseado como un sólido blanco (187 mg, rendimiento de 63%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 1.47 (6H, s), 3.07 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 3.9, 10.2 Hz), 3.59 (1H, dd, J = 6.3, 10.2 Hz), 3.69 (1H, s), 4.57 (1H, m), 6.50 (1H, d, J = 3.9 Hz), 6.55 (1H, t, J = 2.0 Hz), 6.74 (1H, d, J = 3.9 Hz), 6.83 (1H, t, J = 2.0 Hz), 7.00 (1H, t, J = 2.0 Hz), 7.13 (2H, d, J = 9.0 Hz), 7.90 (2H, d, J = 9.0 Hz).

MS (ESI) m/z: 499.18990 $(M+H)^+$.

EJEMPLO 37

2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-5,6-dihidro-4H-1,3-oxazina



(37a) N-(3-Hidroxipropil)-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-carboxílico (250 mg, 0.561 mmol) sintetizado en el ejemplo (18a) se disolvió en diclorometano (10 mL), y se le agregó 3-amino-1-propanol (90.0 µL, 1.18 mmol), WSCI·HCl (165 mg, 0.861 mmol) y 4-dimetilaminopiridina (140 mg, 1.15 mmol), seguido por agitación a temperatura ambiente durante 16 horas bajo una atmósfera de nitrógeno. Se le agregó ácido clorhídrico 1N (10 mL) y la solución se separó con diclorometano (15

mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 60%-100%), para producir el producto deseado como un sólido blanco (216 mg, rendimiento de 77%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 1.78 (2H, m), 3.07 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 3.9, 10.2 Hz), 3.56-3.62 (3H, m), 3.71 (2H, m), 4.58 (1H, m), 6.32 (1H, brs), 6.49 (1H, dd, J = 2.7, 3.9 Hz), 6.56-6.60 (2H, m), 6.84 (1H, t, J = 2.0 Hz), 6.99 (1H, t, J = 2.0 Hz), 7.13 (2H, d, J = 9.0 Hz), 7.91 (2H, d, J = 9.0 Hz), 9.63 (1H, brs).

(37b) 2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5,6-dihidro-4H-1,3-oxazina

La N-(3-hidroxipropil)-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida (216 mg, 0.430 mmol) sintetizada en el ejemplo (37a) se disolvió en tetrahidrofurano (10 mL), y se le agregó ácido metanosulfónico anhidro (115 mg, 0.660 mmol) y trietilamina (0.18 mL, 1.29 ~~m~~mol), seguido por agitación a temperatura ambiente durante 4 días, y a 80°C durante 17 horas, bajo una atmósfera de nitrógeno. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (10 mL), y la solución se separó con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión

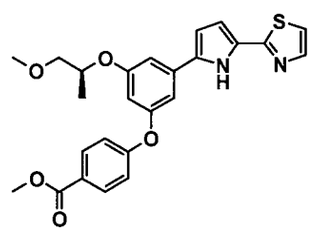
reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-90%), para producir el producto deseado como un sólido pardusco pálido (150 mg, rendimiento de 72%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 1.98 (2H, m), 3.06 (3H, s), 3.41 (3H, s), 3.48-3.54 (3H, m), 3.59 (1H, dd, J = 6.3, 10.2 Hz), 4.32 (2H, brt, J = 5.5 Hz), 4.56 (1H, m), 6.46 (1H, d, J = 3.9 Hz), 6.53 (1H, t, J = 2.0 Hz), 6.62 (1H, d, J = 3.9 Hz), 6.82 (1H, t, J = 2.0 Hz), 6.99 (1H, t, J = 2.0 Hz), 7.12 (2H, d, J = 9.0 Hz), 7.89 (2H, d, J = 9.0 Hz).

MS (ESI) m/z: 485.17572 $(M+H)^+$.

EJEMPLO 38

4-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzoato de metilo



(38a) 1-Bromo-3-metoxi-5-[(1S)-2-metoxi-1-metiletoxi]benceno

El 3-bromo-5-metoxifenol (7.60 g, 37.4 mmol) sintetizado en el ejemplo (1a) se disolvió en tolueno (100 mL), y se le agregó R-(-)-1-metoxi-2-propanol (4.40 mL, 44.9 mmol) y trifenilfosfina (13.8 g, 52.6 mmol), seguido por la adición, gota a gota, de azodicarboxilato de dietilo (solución en tolueno

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2.2 mol/l, 24 mL, 52.8 mmol) a 0°C, y agitación a temperatura ambiente durante 1.5 horas, bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida, se le agregó éter dietílico (100 mL) y el depósito se filtró para removerlo. El licor madre se destiló bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-20%), para producir el compuesto deseado como un líquido incoloro (9.22 g, rendimiento de 89%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.30 (3H, d, J = 6.3 Hz), 3.40 (3H, s), 3.47 (1H, dd, J = 10.6, 4.3 Hz), 3.55 (1H, dd, J = 10.4, 6.1 Hz), 3.76 (3H, s), 4.46-4.52 (1H, m), 6.42 (1H, t, J = 2.2 Hz), 6.65 (1H, dd, J = 2.3, 1.6 Hz), 6.69 (1H, t, J = 2.0 Hz).

MS (EI) m/z: 274 $(M)^+$.

(38b) 3-Bromo-5-[(1S)-2-metoxi-1-metiletoxi]fenol

El 1-bromo-3-metoxi-5-[(1S)-2-metoxi-1-metiletoxi]benceno (9.21 g, 33.5 mmol) sintetizado en el ejemplo (38a) se disolvió en 1-metil-2-pirrolidona (100 mL), y se le agregó tiometóxido de sodio (2.75 g, 37.3 mmol), seguido por agitación a 130°C durante 3 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó ácido clorhídrico 2N (500 mL) y se extrajo con éter dietílico (300 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en

columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-25%), para producir el compuesto deseado como un líquido incoloro (8.30 g, rendimiento de 95%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.29 (3H, d, J = 6.3 Hz), 3.41 (3H, s), 3.46 (1H, dd, J = 10.2, 4.3 Hz), 3.55 (1H, dd, J = 10.6, 5.9 Hz), 4.45-4.51 (1H, m), 4.96 (1H, br s), 6.36 (1H, t, J = 2.0 Hz), 6.59 (1H, t, J = 2.0 Hz), 6.68 (1H, t, J = 2.0 Hz).

MS (EI) m/z: 260 $(M)^+$.

(38c) 3-[(1S)-2-Metoxi-1-metiletoxi]-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenol

El 3-bromo-5-[(1S)-2-metoxi-1-metiletoxi]fenol (8.30 g, 31.8 mmol) sintetizado en el ejemplo (38b) se disolvió en N,N-dimetilformamida (100 mL), y se le agregó bis(pinacolato)diboro (10.50 g, 41.3 mmol), complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano (810 mg, 0.992 mmol) y acetato de potasio (15.50 g, 158 mmol), seguido por agitación a 90°C durante 3 horas bajo una atmósfera de nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente, se le agregó agua (500 mL) y se extrajo con éter dietílico (300 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-30%), para producir el compuesto deseado como un aceite pardusco (8.75 g, rendimiento

de 89%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.26 (3H, d, J = 4.1 Hz), 1.33 (12H, s), 3.41 (1H, s), 3.47 (1H, dd, J = 10.2, 4.7 Hz), 3.57 (1H, dd, J = 10.6, 5.9 Hz), 4.52-4.58 (1H, m), 4.80 (1H, brs), 6.55 (1H, t, J = 2.4 Hz), 6.83 (1H, d, J = 2.4 Hz), 6.95 (1H, d, J = 2.4 Hz).

MS (FAB) m/z: 309 $(M+H)^+$.

(38d) 2-{3-Hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo

El 3-[(1S)-2-metoxi-1-metiletoxi]-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenol (3.30 g, 10.7 mmol) sintetizado en el ejemplo (38c), y el 2-bromo-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (4.10 g, 12.5 mmol) sintetizado en el ejemplo (1g), se disolvieron en un disolvente mixto de 1,4-dioxano (100 mL) y agua (25 mL) y se les agregó complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano (400 mg, 0.490 mmol) y carbonato de potasio (7.20 g, 52.1 mmol), seguido por agitación a 50°C durante 4 horas bajo una atmósfera de nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente, se le agregó agua (200 mL) y se extrajo con acetato de etilo (400 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 25%-40%), para producir el compuesto deseado como un aceite amarillo pálido (3.72 g,

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rendimiento de 81%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.24-1.29 (12H, m), 3.40 (3H, s), 3.47 (1H, dd, J = 4.4, 10.3 Hz), 3.57 (1H, dd, J = 5.9, 10.3 Hz), 4.48-4.54 (1H, m), 5.74 (1H, brs), 6.19 (1H, brs), 6.39-6.44 (2H, brs), 6.55 (1H, brs), 6.60 (1H, d, J = 3.9 Hz), 7.31 (1H, d, J = 3.0 Hz), 7.81 (1H, d, J = 3.4 Hz).

(38e) 2-{3-[4-(Metoxicarbonil)fenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo

El 2-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (117 mg, 0.272 mmol) sintetizado en el ejemplo (38d) se disolvió en diclorometano (20 mL), y se le agregó ácido 4-metoxicarbonilfenil-borónico (100 mg, 0.556 mmol), acetato de cobre (II) (80 mg, 0.440 mmol), trietilamina (0.20 mL, 1.435 mmol) y tamices moleculares de 4A (100 mg), seguido por agitación a temperatura ambiente durante 3 días bajo una atmósfera de nitrógeno. El depósito de esta solución de reacción se filtró por Celite. Este licor madre se destiló bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 15%-25%), para producir el compuesto deseado como un aceite amarillo (70 mg, rendimiento de 46%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (12H, m), 3.40 (3H, s), 3.48 (1H, dd, J = 10.2, 4.3 Hz), 3.57 (1H, dd, J = 10.2, 5.9 Hz), 3.90 (3H, s), 4.48-4.58 (1H, m), 6.25 (1H, d, J = 3.5 Hz), 6.58 (1H, d, J = 3.5 Hz), 6.63 (1H, t, J = 2.4 Hz), 6.70 (1H, dd, J = 2.4, 1.2 Hz), 6.84 (1H, dd, J = 2.4, 1.6 Hz), 7.04 (2H, d, J = 9.0 Hz), 7.33 (1H, d, J = 3.1 Hz), 7.80 (1H, d, J = 3.5 Hz), 8.00 (2H, d, J

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= 9.0 Hz).

(38f) 4-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi} benzoato de metilo

El 2-{3-[4-(metoxicarbonil)fenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (70 mg, 0.124 mmol) sintetizado en el ejemplo (38e), se disolvió en diclorometano (1.0 mL). Se le agregó a gotas ácido trifluoroacético (2.0 mL) con agitación y bajo una atmósfera de nitrógeno; se agitó a temperatura ambiente durante 2 horas. El disolvente se removió por destilación bajo presión reducida, seguido por dilución con acetato de etilo (30 mL); se le agregó una solución acuosa saturada de carbonato ácido de sodio (20 mL) y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-50%), para producir el compuesto deseado como un líquido amarillo pálido (65 mg, rendimiento de ~100%).

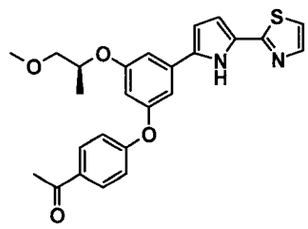
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.42 (3H, s), 3.52 (1H, dd, J = 3.9, 10.2 Hz), 3.60 (1H, dd, J = 5.9, 10.2 Hz), 3.91 (3H, s), 4.60-4.70 (1H, m), 6.56-6.59 (2H, m), 6.86 (1H, brs), 6.93 (1H, brs), 7.05 (2H, d, J = 9.0 Hz), 7.15 (1H, brs), 7.70 (1H, brs), 8.02 (2H, d, J = 9.0 Hz).

MS (ESI) m/z: 465.19025 $(M+H)^+$.

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EJEMPLO 39

1-(4-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}fenil)etanona



(39a) 2-{3-(4-Acetilfenoxi)-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo

El 2-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (92 mg, 0.214 mmol) sintetizado en el ejemplo (38d) se disolvió en diclorometano (10 mL), y se le agregó ácido 4-acetilfenilborónico (70 mg, 0.427 mmol), acetato de cobre (II) (60 mg, 0.330 mmol), trietilamina (0.15 mL, 1.08 mmol) y tamices moleculares de 4A (90 mg), seguido por agitación a temperatura ambiente durante 1 día bajo una atmósfera de nitrógeno. El depósito de esta solución de reacción se filtró por Celite. Este licor madre se destiló bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 15%-25%), para producir el compuesto deseado como un aceite amarillo (73 mg, rendimiento de 62%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (12H, m), 2.57 (3H, s), 3.40 (3H, s), 3.48 (1H, dd, J = 10.2, 4.3 Hz), 3.57 (1H, dd, J = 10.2, 5.9 Hz), 4.53-4.54 (1H, m), 6.26 (1H, d, J = 3.9 Hz), 6.59 (1H, d, J = 3.5 Hz), 6.63 (1H, t, J =

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2.3 Hz), 6.71 (1H, t, J = 1.8 Hz), 6.85 (1H, dd, J = 2.2, 1.4 Hz), 7.06 (2H, dt, J = 9.4, 2.4 Hz), 7.30 (1H, d, J = 3.1 Hz), 7.80 (1H, d, J = 3.1 Hz), 7.94 (2H, dt, J = 9.4, 2.4 Hz).

(39b) 1-(4-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}fenil)etanona

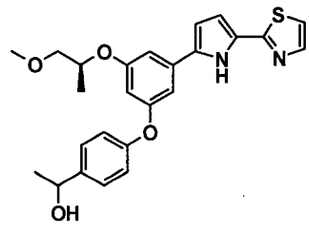
El 2-{3-(4-acetilfenoxi)-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (73 mg, 0.133 mmol) sintetizado en el ejemplo (39a) se disolvió en diclorometano (1.0 mL). Se le agregó a gotas ácido trifluoroacético (2.0 mL) con agitación y bajo una atmósfera de nitrógeno, y se agitó a temperatura ambiente durante 2.5 horas. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-40%), para producir el compuesto deseado como un líquido amarillo pálido (56 mg, rendimiento de 94%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 2.59 (3H, s), 3.42 (3H, s), 3.52 (1H, dd, J = 10.3, 3.9 Hz), 3.59 (1H, dd, J = 10.3, 5.9 Hz), 4.61-4.68 (1H, m), 6.54-6.59 (2H, m), 6.82 (1H, d, J = 2.9 Hz), 6.91 (1H, s), 7.06-7.11 (3H, br m), 7.18-7.20 (1H, br m), 7.68-7.70 (1H, br m), 7.96 (2H, d, J = 8.8 Hz), 10.51 (1H, br s).

MS (ESI) m/z: 449.15388 $(M+H)^+$.

EJEMPLO 40

1-(4-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}fenil)etanol



La 1-(4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}fenil)etanona (30 mg, 0.067 mmol) sintetizada en el ejemplo (39b) se disolvió en un disolvente mixto de tetrahidrofurano (3.0 mL) y metanol (1.0 mL), y se le agregó borohidruro de sodio (10 mg, 0.264 mmol), seguido por agitación a temperatura ambiente durante 3 horas bajo una atmósfera de nitrógeno. A esta solución de reacción, se le agregó una solución acuosa saturada de cloruro de amonio (10 mL) y se extrajo con acetato de etilo (10 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 40%-60%), para producir el compuesto deseado como un sólido blanco (27.5 mg, rendimiento de 91%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 1.53 (3H, d, J = 6.3 Hz), 3.42 (3H, s), 3.49 (1H, dd, J = 9.4, 5.1 Hz), 3.59 (1H, dd, J = 10.2, 5.9 Hz), 4.52-4.59 (1H, m), 4.92 (1H, q, J = 6.3 Hz), 6.47-6.52 (2H, m),

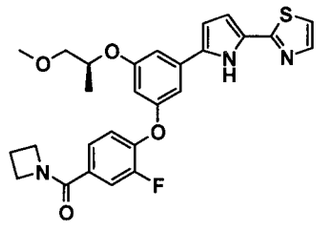
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6.72 (1H, t, J = 2.7 Hz), 6.92 (1H, s), 7.04 (2H, d, J = 8.2 Hz), 7.16 (1H, d, J = 3.1 Hz), 7.37 (2H, d, J = 9.0 Hz), 7.67 (1H, d, J = 3.1 Hz), 9.72 (1H, br s).

MS (ESI) m/z: 451.16915 $(M+H)^+$.

EJEMPLO 41

2-(5-{3-[4-(Azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol



(41a) 1-(3,4-Difluorobenzoil)azetidina

Se disolvió ácido 3,4-difluorobenzoico (3.00 g, 19.0 mmol), disponible comercialmente, en diclorometano (50 mL), y se le agregó N,N-dimetilformamida (0.10 mL), seguido por la adición a gotas de cloruro de oxalilo (1.98 mL, 22.8 mmol) y agitación a temperatura ambiente durante la noche, bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se disolvió en diclorometano (100 mL) y se le agregó clorhidrato de azetidina (2.27 g, 24.2 mmol) y trietilamina (6.60 mL, 47.4 mmol), seguido por agitación a temperatura ambiente durante 4.5 horas bajo una atmósfera de nitrógeno. Se le agregó ácido clorhídrico 0.5N (100 mL) y se extrajo con diclorometano (100 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se

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secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 40%-50%), para producir el compuesto deseado como un líquido incoloro (600 mg, rendimiento de 16%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.37 (2H, m), 4.23 (2H, t, J = 7.4 Hz), 4.32 (2H, t, J = 7.4 Hz), 7.20 (1H, m), 7.40 (1H, m), 7.50 (1H, m).

(41b) 2-(5-{3-[4-(Azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol

El 2-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (70 mg, 0.163 mmol) sintetizado en el ejemplo (38d), y la 1-(3,4-difluorobenzoil)azetidina (68 mg, 0.345 mmol) sintetizada en el ejemplo (41a), se disolvieron en sulfóxido de dimetilo (3.0 mL) y se les agregó hidruro de sodio (60%, 25 mg, 0.63 mmol), seguido por agitación a 100°C durante 5 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó ácido clorhídrico 2N (30 mL) y se extrajo con éter dietílico (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 60%-80%), para producir el compuesto deseado como un sólido amarillo (54 mg, rendimiento de 65%).

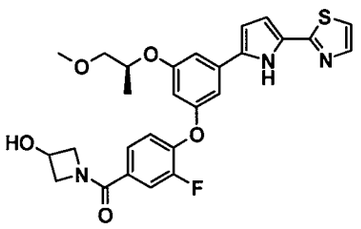
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^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 2.38 (2H, m), 3.41 (3H, s), 3.50 (1H, dd, J = 3.9, 10.2 Hz), 3.58 (1H, dd, J = 6.3, 10.2 Hz), 4.20-4.26 (2H, brs), 4.33-4.40 (2H, brs), 4,57 (1H, m), 6.49-6.52 (2H, m), 6.71 (1H, dd, J = 2.4, 3.9 Hz), 6.82 (1H, dd, J = 1.6, 2.4 Hz), 6.94 (1H, dd, J = 1.6, 2.4 Hz), 7.07 (1H, t, J = 8.2 Hz), 7.16 (1H, d, J = 3.5 Hz), 7.40 (1H, ddd, J = 1.2, 2.4, 8.6 Hz), 7.52 (1H, dd, J = 2.0, 11.0 Hz), 7.68 (1H, d, J = 3.2 Hz), 9.62 (1H, brs).

MS (ESI) m/z: 508.17094 $(M+H)^+$.

EJEMPLO 42

1-(3-Fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzoil)azetidin-3-ol



(42a) 1-(3,4-Difluorobenzoil)-3-(tetrahidro-2H-piran-2-iloxi)-azetidina

Se disolvió ácido 3,4-difluorobenzoico (1.00 g, 6.33 mmol), disponible comercialmente, en metanol (10 mL), y se le agregó clorhidrato de 3-hidroxiazetidina (830 mg, 7.58 mmol), cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio n-hidratado (2.10 g, 7.59 mmol) y N-metilmorfolina (0.85 mL, 2.83 mmol), seguido por agitación a temperatura

ambiente durante 2.5 horas bajo una atmósfera de nitrógeno. El material insoluble se removió por filtración en Celite y el disolvente se removió por destilación bajo presión reducida. El residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-70%).

El compuesto resultante se disolvió en diclorometano (20 mL) y se le agregó 3,4-dihidro-2H-pirano (1.00 mL, 11.1 mmol) y p-toluenosulfonato de piridinio (250 mg, 0.99 mmol), seguido por agitación a temperatura ambiente durante la noche bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó trietilamina (0.5 mL), el disolvente se removió por destilación bajo presión reducida, y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 35%-50%), para producir el compuesto deseado como un líquido incoloro (2.24 g, rendimiento de ~100%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.48-1.65 (4H, br m), 1.68-1.89 (2H, br m), 3.46-3.55 (2H, br m), 3.83-3.88 (2H, br m), 4.02-4.47 (2H, br m), 4.55-4.66 (2H, br m), 7.18-7.21 (1H, m), 7.38-7.42 (1H, m), 7.47-7.52 (1H, m).

(42b) 2-(5-{3-(2-Fluoro-4-{[3-(tetrahidro-2H-piran-2-iloxi)azetidin-1-il]carbonil}fenoxi)-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol

El 2-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (150 mg, 0.348 mmol) sintetizado en el ejemplo (38d), y la 1-(3,4-difluorobenzoil)-3-(tetrahidro-2H-piran-2-iloxi)azetidina (220 mg, 0.740 mmol) sintetizada en el ejemplo (42a), se

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disolvieron en sulfóxido de dimetilo (5.0 mL) y se les agregó hidruro de sodio (60%, 70 mg, 1.75 mmol), seguido por agitación a 100°C durante 1.5 horas, bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó salmuera saturada (30 mL) y se extrajo con acetato de etilo (30 mL). Subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 65%-85%), para producir el compuesto deseado como un sólido blanco (158 mg, rendimiento de 75%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 1.48-1.90 (6H, m), 3.41 (3H, s), 3.46-3.55 (2H, m), 3.50 (1H, dd, J = 10.2, 4.3 Hz), 3.59 (1H, dd, J = 10.4, 6.1 Hz), 3.80-3.89 (2H, m), 4.40-4.64 (4H, m), 6.51-6.52 (2H, m), 6.72 (1H, dd, J = 3.5, 2.7 Hz), 6.82 (1H, br s), 6.94 (1H, br s), 7.06 (1H, t, J = 8.4 Hz), 7.17 (1H, d, J = 3.5 Hz), 7.34-7.44 (1H, m), 7.52 (1H, dd, J = 10.0, 5.0 Hz), 7.68 (1H, d, J = 3.1 Hz), 9.52 (1H, br s).

MS (ESI) m/z: 608.22267 $(M+H)^+$.

(42c) 1-(3-Fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzoil)azetidin-3-ol

El 2-(5-{3-(2-fluoro-4-{[3-(tetrahidro-2H-piran-2-iloxi)azetidin-1-il]carbonil}fenoxi)-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol (110 mg, 0.181 mmol) sintetizado en el ejemplo (42b) se disolvió en metanol (10 mL), y se le agregó ácido 10-alcanforsulfónico (20 mg, 0.086 mmol),

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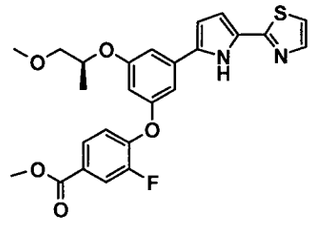
seguido por agitación a temperatura ambiente durante la noche bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó trietilamina (0.1 mL) y el disolvente se removió por destilación bajo presión reducida. El residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 90%-100%), para producir el compuesto deseado como un sólido amarillo (62 mg, rendimiento de 65%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 2.28 (1H, br s), 3.41 (3H, s), 3.50 (1H, dd, J = 10.4, 4.1 Hz), 3.59 (1H, dd, J = 10.2, 5.9 Hz), 4.08 (1H, br s), 4.23 (1H, br s), 4.45-4.58 (2H, m), 4.52-4.60 (1H, m), 4.71-4.80 (2H, m), 6.50-6.53 (2H, m), 6.73 (1H, dd, J = 3.5, 2.7 Hz), 6.83 (1H, t, J = 1.8 Hz), 6.95-6.97 (1H, m), 7.06 (1H, t, J = 8.2 Hz), 7.17 (1H, d, J = 3.1 Hz), 7.37-7.40 (1H, m), 7.50-7.53 (1H, m), 7.68 (1H, d, J = 3.1 Hz), 9.61 (1H, br s).

MS (ESI) m/z: 524.16841 $(M+H)^+$.

EJEMPLO 43

3-Fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzoato de metilo



El 2-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-

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il)-1H-pirrol-1-carboxilato de t-butilo (485 mg, 1.127 mmol) sintetizado en el ejemplo (38d), y 3,4-difluorobenzoato de metilo (540 mg, 3.137 mmol), disponible comercialmente, se disolvieron en sulfóxido de dimetilo (10 mL) y se les agregó hidruro de sodio (60%, 180 mg, 4.50 mmol), seguido por agitación a 100°C durante 2.5 horas, bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (50 mL) y se extrajo con éter dietílico (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-30%), para producir el compuesto deseado como un sólido blanco (97 mg, rendimiento de 18%).

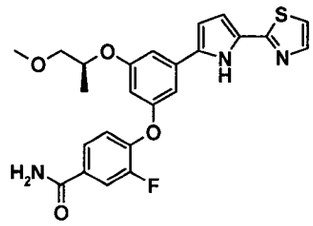
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J = 6.3 Hz), 3.39 (3H, s), 3.48 (1H, dd, J = 10.2, 3.9 Hz), 3.57 (1H, dd, J = 10.2, 5.9 Hz), 3.91 (3H, s), 4.51-4.59 (1H, m), 6.49-6.52 (2H, m), 6.71 (1H, dd, J = 3.9, 2.3 Hz), 6.82-6.85 (1H, br m), 6.98 (1H, br s), 7.05 (1H, t, J = 8.2 Hz), 7.15 (1H, d, J = 3.1 Hz), 7.66 (1H, d, J = 3.1 Hz), 7.78 (1H, d, J = 9.8 Hz), 7.85 (1H, dd, J = 11.1, 2.2 Hz), 9.78-9.87 (1H, m).

MS (ESI) m/z: 483.13782 $(M+H)^+$.

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EJEMPLO 44

3-Fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzamida



(44a) Acido 3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzoico

El 3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzoato de metilo (611 mg, 1.42 mmol) sintetizado en el ejemplo 43 se disolvió en metanol (18 mL), y se le agregó agua (3 mL) e hidróxido de litio monohidratado (298 mg, 7.10 mmol), seguido por agitación a 60°C durante 4 horas, bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó agua (50 mL) y se extrajo dos veces con acetato de etilo (40 mL), seguido por secado sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-75%), para producir el compuesto deseado como un sólido blanco (519 mg, rendimiento de 88%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.38 (3H, d, J = 6.3 Hz), 3.45 (3H, s), 3.55 (1H, dd, J = 10.2, 4.3 Hz), 3.64 (1H, dd, J = 10.2, 5.9 Hz), 4.60-4.67 (1H, m), 6.63 (1H, dd, J = 3.9, 2.7 Hz), 6.74 (1H, t, J = 2.2 Hz), 6.84 (1H, dd, J

= 3.9, 2.3 Hz), 6.99 (1H, t, J = 8.2 Hz), 7.16-7.14 (2H, m), 7.41 (1H, t, J = 1.8 Hz), 7.55 (1H, dt, J = 8.6, 1.0 Hz), 7.61 (1H, d, J = 3.1 Hz), 7.72 (1H, dd, J = 10.6, 2.0 Hz), 11.85 (1H, s).

(44b) 3-Fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzamida

El ácido 3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzoico (40.0 mg, 0.163 mmol) sintetizado en el ejemplo (44a) se disolvió en diclorometano (5 mL), y se le agregó una solución acuosa de amoniaco al 28% (0.50 mL), WSCI·HCl (19.6 mg, 0.102 mmol) y HOBt·H_2O (13.1 mg, 0.086 mmol), seguido por agitación a temperatura ambiente durante 7 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó agua (10 mL) y se extrajo con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-75%), para producir el compuesto deseado como un sólido blanco (11.3 mg, rendimiento de 28%).

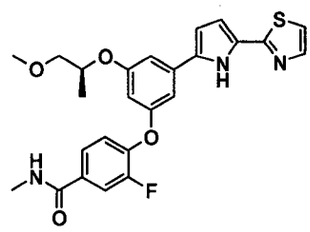
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.42 (3H, s), 3.51 (1H, dd, J = 10.3, 5.4 Hz), 3.59 (1H, dd, J = 10.3, 5.9 Hz), 4.54-4.61 (1H, m), 6.51-6.54 (2H, m), 6.73 (1H, dd, J = 3.4, 2.4 Hz), 6.84 (1H, s), 6.97 (1H, s), 7.09 (1H, t, J = 8.1 Hz), 7.18 (1H, d, J = 2.9 Hz), 7.53 (1H, d, J = 8.8 Hz), 7.67-7.73 (2H, m), 9.60 (1H, br s).

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MS (ESI) m/z: 468.13800 $(M+H)^+$.

EJEMPLO 45

3-Fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-N-metilbenzamida



El ácido 3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzoico (40.0 mg, 0.163 mmol) sintetizado en el ejemplo (44a) se disolvió en tetrahidrofurano (5 mL), y se le agregó clorhidrato de metilamina (17.3 mg, 0.256 mmol), HATU (64.5 mg, 0.170 mmol) y N,N-diisopropiletilamina (89 μL, 0.51 mmol), seguido por agitación a temperatura ambiente durante 4 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó salmuera saturada (15 mL) y se extrajo dos veces con acetato de etilo (15 mL), seguido por secado sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-55%), para producir el compuesto deseado como un sólido amarillo pálido (41 mg, rendimiento de ~100%).

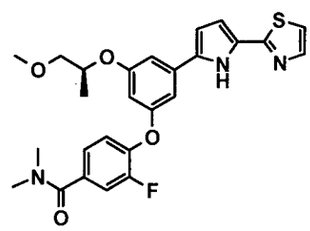
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 3.03 (3H, d, J = 4.7 Hz), 3.41 (3H, s), 3.50 (1H, dd, J = 10.2, 3.9 Hz), 3.58 (1H, dd, J =

10.2, 6.3 Hz), 4.52-4.60 (1H, m), 6.49-6.53 (2H, m), 6.72 (1H, dd, J = 3.9, 2.3 Hz), 6.79 (1H, t, J = 2.0 Hz), 6.94 (1H, t, J = 2.0 Hz), 7.08 (1H, t, J = 8.0 Hz), 7.17 (1H, d, J = 3.5 Hz), 7.47 (1H, d, J = 8.6 Hz), 7.65 (1H, dd, J = 10.9, 2.0 Hz), 7.68 (1H, d, J = 3.9 Hz), 9.48 (1H, br s).

MS (ESI) m/z: 482.15436 $(M+H)^+$.

EJEMPLO 46

3-Fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-N,N-dimetilbenzamida



El ácido 3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzoico (40.0 mg, 0.163 mmol) sintetizado en el ejemplo (44a) se disolvió en tetrahidrofurano (5 mL), y se le agregó clorhidrato de dimetilamina (20.1 mg, 0.246 mmol), HATU (64.5 mg, 0.170 mmol) y N,N-diisopropiletilamina (89 μL, 0.51 mmol), seguido por agitación a temperatura ambiente durante 4 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó salmuera saturada (15 mL) y se extrajo dos veces con acetato de etilo (15 mL), seguido por secado sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente

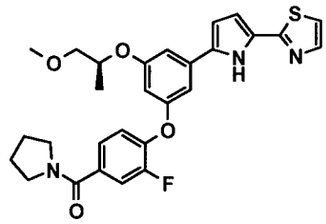
de elución: acetato de etilo/hexano = 0%-75%), para producir el compuesto deseado como un sólido amarillo pálido (45 mg, rendimiento de 99%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 3.02-3.14 (6H, br m), 3.41 (3H, s), 3.50 (1H, dd, J = 10.2, 3.9 Hz), 3.58 (1H, dd, J = 10.2, 5.9 Hz), 4.52-4.61 (1H, m), 6.49-6.54 (2H, m), 6.73 (1H, dd, J = 3.7, 1.9 Hz), 6.85 (1H, t, J = 1.6 Hz), 6.95 (1H, t, J = 1.6 Hz), 7.08 (1H, t, J = 8.0 Hz), 7.16-7.20 (2H, m), 7.29 (1H, dd, J = 10.8, 1.8 Hz), 7.68 (1H, d, J = 3.1 Hz), 9.65 (1H, br s).

MS (ESI) m/z: 496.17025 $(M+H)^+$.

EJEMPLO 47

2-(5-{3-[2-Fluoro-4-(pirrolidin-1-ilcarbonil)fenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol



El ácido 3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzoico (40.0 mg, 0.085 mmol) sintetizado en el ejemplo (44a) se disolvió en tetrahidrofurano (5 mL), y se le agregó pirrolidina (21 μL, 0.26 mmol), HATU (64.9 mg, 0.171 mmol) y N,N-diisopropiletilamina (89 μL, 0.51 mmol), seguido por agitación a temperatura ambiente durante 20 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó

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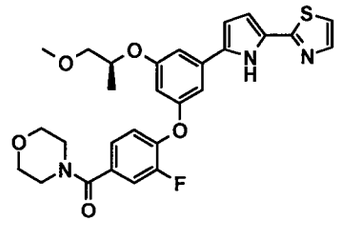
salmuera saturada (15 mL) y se extrajo dos veces con acetato de etilo (15 mL), seguido por secado sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-75%), para producir el compuesto deseado como un sólido blanco (32 mg, rendimiento de 72%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.29 (3H, d, J =.6.3 Hz), 1.84-1.98 (4H, m), 3.38 (3H, s), 3.41-3.49 (3H, m), 3.55 (1H, dd, J = 10.2, 5.9 Hz), 3.61 (2H, t, J = 6.8 Hz), 4.48-4.56 (1H, m), 6.46-6.49 (2H, m), 6.68 (1H, dd, J = 3.9, 2.7 Hz), 6.78 (1H, t, J = 1.8 Hz), 6.89 (1H, t, J = 2.0 Hz), 7.04 (1H, t, J = 8.2 Hz), 7.13 (1H, d, J = 3.1 Hz), 7.25-7.29 (1H, m), 7.38 (1H, dd, J = 10.9, 2.0 Hz), 7.64 (1H, d, J = 3.5 Hz), 9.51 (1H, br s).

MS (ESI) m/z: 522.18695 $(M+H)^+$.

EJEMPLO 48

4-(3-Fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzoil)morfolina



El ácido 3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzoico (49.0 mg, 0.105 mmol) sintetizado en el

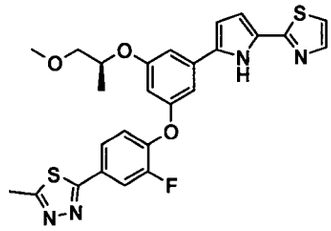
ejemplo (44a) se disolvió en tetrahidrofurano (5 mL), y se le agregó morfolina (22 μL, 0.26 mmol), HATU (64.5 mg, 0.170 mmol) y N,N-diisopropiletilamina (89 μL, 0.51 mmol), seguido por agitación a temperatura ambiente durante 4 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó salmuera saturada (15 mL) y se extrajo dos veces con acetato de etilo (15 mL), seguido por secado sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-75%), para producir el compuesto deseado como un sólido amarillo pálido (39 mg, rendimiento de 70%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.42 (3H, s), 3.51 (1H, dd, J = 10.2, 4.3 Hz), 3.59 (1H, dd, J = 10.2, 5.9 Hz), 3.72 (8H, br s), 4.52-4.61 (1H, m), 6.49-6.54 (2H, m), 6.72 (1H, dd, J = 3.7, 2.5 Hz), 6.82 (1H, t, J = 1.8 Hz), 6.93 (1H, t, J = 1.8 Hz), 7.09 (1H, t, J = 8.2 Hz), 7.16-7.19 (2H, m), 7.30 (1H, dd, J = 10.6, 2.0 Hz), 7.69 (1H, d, J = 3.1 Hz), 9.45 (1H, br s).

MS (ESI) m/z: 538.18048 $(M+H)^+$.

EJEMPLO 49

2-(3-Fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}fenil)-5-metil-1,3,4-tiadiazol



(49a) N'-Acetil-3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzohidrazida

El ácido 3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzoico (84 mg, 0.179 mmol) sintetizado en el ejemplo (44a) se disolvió en diclorometano (5.0 mL), y se le agregó acetohidrazida (40 mg, 0.540 mmol), HATU (200 mg, 0.526 mmol) y N,N-diisopropiletilamina (0.15 mL, 0.861 mmol), seguido por agitación a temperatura ambiente durante la noche, bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo), para producir el compuesto deseado como un sólido blanco (110 mg, rendimiento de ~100%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.44 (3/2H, d, J = 6.3 Hz), 1.49 (3/2H, d, J = 6.3 Hz), 2.05 (3H, s), 3.46 (3H, s), 3.55 (1H, dd, J = 10.8, 4.1 Hz), 3.65 (1H, dd, J = 10.0, 6.1 Hz), 4.58-4.69 (1H, m), 6.69 (1H, d, J = 2.3 Hz), 6.73 (1H, s), 6.77 (1H, d, J = 2.7 Hz), 7.12 (1H, br s), 7.16 (1H, br s), 7.29 (1H,

br s), 7.34 (1H, br s), 7.37 (1H, br s), 7.45 (1H, d, J = 8.2 Hz), 7.62 (1H, br s), 11.51 (1H, br s), 11.79 (1H, br s), 12.56 (1H, br s).

MS (ESI) m/z: 547.14358 $(M+Na)^+$.

(49b) 2-(3-Fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}fenil)-5-metil-1,3,4-tiadiazol

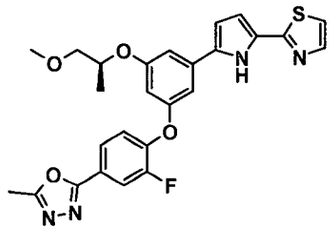
La N'-acetil-3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzohidrazida (40 mg, 0.076 mmol) sintetizada en el ejemplo (49a) se disolvió un disolvente mixto de tolueno (4.0 mL) y acetonitrilo (2.0 mL), y se le agregó 2,4-disulfuro de 2,4-bis-(4-metoxifenil)-1,3-ditia-2,4-difosfoetano (45 mg, 0.111 mmol) y piridina (0.03 mL, 0.372 mmol), seguido por agitación a 100°C durante 4 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, el disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 60%-80%), para producir el compuesto deseado como un sólido amarillo (28 mg, rendimiento de 70%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 2.83 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 10.3, 4.4 Hz), 3.60 (1H, dd, J = 10.3, 5.9 Hz), 4.57-4.63 (1H, m), 6.54-6.54 (2H, m), 6.77 (1H, s), 6.87 (1H, s), 7.00 (1H, s), 7.14-7.17 (2H, m), 7.64 (1H, dd, J = 8.3, 1.0 Hz), 7.68 (1H, d, J = 3.4 Hz), 7.84 (1H, dd, J = 11.2, 2.0 Hz), 10.01 (1H, br s).

MS (ESI) m/z: 523.12785 $(M+H)^+$.

EJEMPLO 50

2-(3-Fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}fenil)-5-metil-1,3,4-oxadiazol



La N'-acetil-3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzohidrazida (45 mg, 0.086 mmol) sintetizada en el ejemplo (49a) se disolvió en acetonitrilo (3.0 mL), y se le agregó hidróxido de (metoxicarbonilsulfamoil)trietilamonio (50 mg, 0.210 mmol) y trietilamina (0.05 mL, 0.359 mmol), seguido por agitación a 100°C durante 1 día bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 80%-100%), para producir el compuesto deseado como un líquido incoloro (26 mg, rendimiento de 60%).

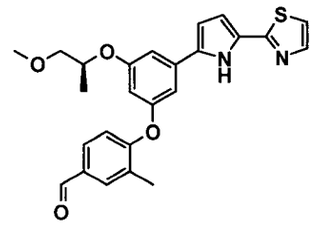
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 2.63 (3H, s), 3.42 (3H, s), 3.50 (1H, dd, J = 10.2, 4.3 Hz), 3.60 (1H, dd, J = 10.2, 5.9 Hz), 4.54-4.62 (1H, m), 6.50-6.55 (2H, m), 6.72 (1H, dd, J = 3.5, 2.0 Hz), 6.86 (1H, s), 6.99 (1H, s), 7.12-7.19 (2H, m), 7.67 (1H, d, J = 3.1 Hz), 7.78 (1H, d, J = 9.0 Hz), 7.87 (1H, dd, J = 10.8, 1.4 Hz), 9.94 (1H, br s).

MS (ESI) m/z: 507.14909 $(M+H)^+$.

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EJEMPLO 51

4-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-3-metilbenzaldehído



El 2-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (150 mg, 0.348 mmol) sintetizado en el ejemplo (38d), y 4-fluoro-3-metilbenzaldehído (0.14 mL, 1.148 mmol), disponible comercialmente, se disolvieron en sulfóxido de dimetilo (5.0 mL) y se les agregó hidruro de sodio (60%, 40 mg, 1.00 mmol), seguido por agitación a 100°C durante 4 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó una solución acuosa saturada de cloruro de amonio (30 mL), y se extrajo con éter dietílico (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 25%-30%), para producir el compuesto deseado como un sólido amarillo (84 mg, rendimiento de 54%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 2.39 (3H, s), 3.42 (3H, s), 3.50 (1H, dd, J = 10.2, 3.9 Hz), 3.60 (1H, dd, J = 10.4, 6.1 Hz),

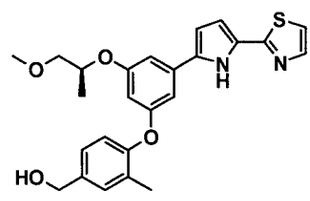
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4.55-4.64 (1H, m), 6.50 (1H, t, J = 2.2 Hz), 6.53 (1H, dd, J = 3.7, 2.9 Hz), 6.74 (1H, t, J = 2.5 Hz), 6.83 (1H, t, J = 2.0 Hz), 6.96 (1H, d, J = 8.2 Hz), 7.00-7.02 (1H, m), 7.17 (1H, d, J = 3.1 Hz), 7.65 (1H, d, J = 2.3 Hz), 7.68 (1H, d, J = 3.1 Hz), 7.81 (1H, d, J = 1.2 Hz), 9.90 (1H, br s), 9.92 (1H, s).

MS (ESI) m/z: 449.15343 $(M+H)^+$.

EJEMPLO 52

(4-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-3-metilfenil)metanol



El 4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-3-metilbenzaldehído (32 mg, 0.071 mmol) sintetizado en el ejemplo 51 se disolvió en metanol (3.0 mL), y se le agregó borohidruro de sodio (5 mg, 0.132 mmol), seguido por agitación a 0°C durante 4 horas bajo una atmósfera de nitrógeno. La solución de reacción se llevó a temperatura ambiente, se le agregó una solución acuosa saturada de cloruro de amonio (10 mL) y se extrajo con acetato de etilo (10 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente

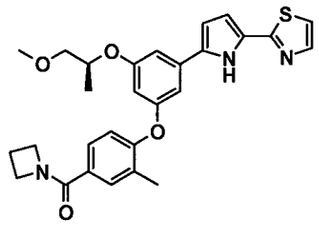
de elución: acetato de etilo/hexano = 50%-75%), para producir el compuesto deseado como un sólido blanco (26 mg, rendimiento de 81%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 2.26 (3H, s), 3.41 (3H, s), 3.49 (1H, dd, J = 10.2, 4.3 Hz), 3.58 (1H, dd, J = 10.2, 5.9 Hz), 4.51-4.60 (1H, m), 4.67 (2H, br s), 6.40 (1H, t, J = 2.2 Hz), 6.49 (1H, dd, J = 3.5, 2.7 Hz), 6.70-6.72 (2H, m), 6.86 (1H, dd, J = 3.5, 1.6 Hz), 6.96 (1H, d, J = 8.2 Hz), 7.15 (1H, d, J = 3.5 Hz), 7.19 (1H, dd, J = 8.2, 2.0 Hz), 7.28 (1H, d, J = 2.3 Hz), 7.66 (1H, d, J = 3.5 Hz), 9.72 (1H, br s).

MS (ESI) m/z: 451.16757 $(M+H)^+$.

EJEMPLO 53

2-(5-{3-[4-(Azetidin-1-ilcarbonil)-2-metilfenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol



(53a) Acido 4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-3-metilbenzoico

El 4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-3-metilbenzaldehído (50 mg, 0.11 mmol) sintetizado en el ejemplo 51 se disolvió en un disolvente mixto de t-butanol (5.0 mL) y agua (2.0 mL), y se le agregó 2-metil-2-buteno (0.15 mL, 1.42 mmol) y fosfato diácido de sodio

dihidratado (80 mg, 0.51 mmol), seguido por la adición lenta de clorito de sodio (25 mg, 0.28 mmol) a 0°C y agitación a 0°C durante 2 horas, bajo una atmósfera de nitrógeno. Se le agregó una solución acuosa de sulfito ácido de sodio (5 mL) a 0°C y se agitó a temperatura ambiente durante 10 minutos. Se le agregó una solución acuosa de sulfito ácido de sodio (15 mL) y se extrajo con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida para producir el compuesto deseado como un sólido amarillo (58 mg, rendimiento de ~100%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 2.33 (3H, s), 3.41 (3H, s), 3.52 (1H, dd, J = 10.6, 4.3 Hz), 3.60 (1H, dd, J = 10.2, 5.9 Hz), 4.62-4.71 (1H, m), 6.54-6.57 (2H, m), 6.85-6.87 (2H, m), 7.08-7.16 (2H, m), 7.15 (1H, d, J = 3.5 Hz), 7.64 (1H, s), 7.64 (1H, d, J = 3.5 Hz), 7.87 (1H, s).

(53b) 2-(5-{3-[4-(Azetidin-1-ilcarbonil)-2-metilfenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol

El ácido 4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-3-metilbenzoico (58 mg, 0.125 mmol) sintetizado en el ejemplo (53a) y clorhidrato de azetidina (29 mg, 0.310 mmol) se disolvieron en diclorometano (10.0 mL) y se les agregó HATU (95 mg, 0.250 mmol) y N,N-diisopropiletilamina (0.15 mL, 0.861 mmol), seguido por agitación a temperatura ambiente durante la noche bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente

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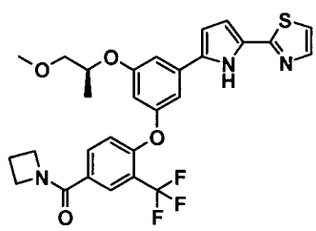
de elución: acetato de etilo/hexano = 75%-90%), para producir el compuesto deseado como un sólido amarillo (58 mg, rendimiento de 92%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 2.30 (3H, s), 2.31-2.39 (2H, m), 3.41 (3H, s), 3.49 (1H, dd, J = 10.4, 4.1 Hz), 3.59 (1H, dd, J = 10.2, 5.9 Hz), 4.22-4.25 (2H, br m), 4.33-4.36 (2H, br m), 4.52-4.60 (1H, m), 6.43 (1H, t, J = 2.3 Hz), 6.50 (1H, dd, J = 3.7, 2.9 Hz), 6.72 (1H, dd, J = 3.9, 2.3 Hz), 6.76 (1H, t, J = 1.8 Hz), 6.90 (1H, s), 6.92-6.93 (1H, m), 7.16 (1H, d, J = 3.1 Hz), 7.42 (1H, dd, J = 8.2, 2.0 Hz), 7.59 (1H, d, J = 1.6 Hz), 7.67 (1H, d, J = 3.1 Hz), 9.73 (1H, br s).

MS (ESI) m/z: 504.19979 $(M+H)^+$.

EJEMPLO 54

2-(5-{3-[4-(Azetidin-1-ilcarbonil)-2-(trifluorometil)fenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol



(54a) 1-[4-Fluoro-3-(trifluorometil)benzoil]azetidina

Se disolvió ácido 4-fluoro-3-(trifluorometil)benzoico (230 mg, 1.10 mmol), disponible comercialmente, en diclorometano (50 mL), y se le agregó clorhidrato de azetidina (120 mg, 1.28 mmol), HATU (550 mg, 1.45 mmol) y N,N-diisopropiletilamina (0.50 mL, 2.87 mmol), seguido por agitación a

temperatura ambiente durante 4 horas bajo una atmósfera de nitrógeno. Se le agregó ácido clorhídrico 0.5N (100 mL) y se extrajo con diclorometano (100 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 60%-80%), para producir el compuesto deseado como un líquido incoloro (211 mg, rendimiento de 78%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.35-2.43 (2H, m), 4.25 (2H, t, J = 7.6 Hz), 4.33 (2H, t, J = 7.4 Hz), 7.83-7.87 (1H, m), 7.93 (1H, dd, J = 6.6, 2.0 Hz).

(54b) 2-(5-{3-[4-(Azetidin-1-ilcarbonil)-2-(trifluorometil)fenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol

El 2-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (119 mg, 0.276 mmol) sintetizado en el ejemplo (38d), y la 1-[4-fluoro-3-(trifluorometil)benzoil]azetidina (145 mg, 0.587 mmol) sintetizada en el ejemplo (54a), se disolvieron en sulfóxido de dimetilo (8.0 mL) y se les agregó hidruro de sodio (60%, 39 mg, 0.97 mmol), seguido por agitación a 100°C durante 2 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente

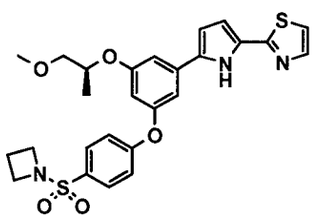
se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 45%-60%), para producir el compuesto deseado como un sólido amarillo (105 mg, rendimiento de 68%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 2.34-2.42 (2H, m), 3.42 (3H, s), 3.50 (1H, dd, J = 10.2, 4.3 Hz), 3.60 (1H, dd, J = 10.2, 5.9 Hz), 4.25 (2H, t, J = 6.8 Hz), 4.36 (2H, t, J = 6.6 Hz), 4.56-4.60 (1H, m), 6.54-6.55 (2H, m), 6.73 (1H, dd, J = 3.7, 2.5 Hz), 6.87 (1H, t, J = 1.6 Hz), 6.99 (1H, d, J = 8.6 Hz), 7.03 (1H, t, J = 1.8 Hz), 7.17 (1H, d, J = 3.1 Hz), 7.68 (1H, d, J = 3.1 Hz), 7.74 (1H, dd, J = 8.6, 2.3 Hz), 8.00 (1H, d, J = 2.0 Hz), 9.73 (1H, br s).

MS (ESI) m/z: 558.16727 $(M+H)^+$.

EJEMPLO 55

2-(5-{3-[4-(Azetidin-1-ilsulfonil)fenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol



(55a) 1-[(4-Fluorofenil)sulfonil]azetidina

Se suspendió en agua (8 mL) cloruro de 4-fluorofenilsulfonilo (225 mg, 1.15 mmol), disponible comercialmente, y se le agregó clorhidrato de

azetidina (90.0 mg, 0.96 mmol) y carbonato de potasio (293 mg, 2.12 mmol), seguido por agitación a temperatura ambiente durante 16 horas. A la solución de reacción se le agregó agua (15 mL), seguido por extracción dos veces con éter dietílico (15 mL) y lavado con salmuera saturada (15 mL), seguido por secado sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida, seguido por secado al vacío, para producir el compuesto deseado como un sólido blanco (170 mg, rendimiento de 82%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.10-2.17 (2H, m), 3.82 (4H, t, J = 7.8 Hz), 7.28-7.30 (2H, m), 7.88-7.92 (2H, m).

(55b) 2-(5-{3-[4-(Azetidin-1-ilsulfonil)fenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol

El 2-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (60.0 mg, 0.139 mmol) sintetizado en el ejemplo (38d), y la 1-[(4-fluorofenil)sulfonil]azetidina (60.0 mg, 0.279 mmol) sintetizada en el ejemplo (55a), se disolvieron en N-metilpirrolidona (5.0 mL) y se les agregó hidruro de sodio (60%, 24 mg, 0.60 mmol), seguido por agitación a 100°C durante 6 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) y se extrajo con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-35%), para producir el

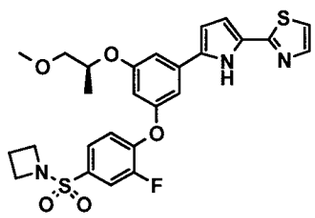
compuesto deseado como un sólido blanco (42 mg, rendimiento de 57%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.37 (3H, d, J = 6.8 Hz), 2.12-2.18 (2H, m), 3.45 (3H, s), 3.54 (1H, dd, J = 10.3, 4.4 Hz), 3.64 (1H, dd, J = 10.0, 6.1 Hz), 3.83 (4H, t, J = 7.6 Hz), 4.59-4.65 (1H, m), 6.57 (1H, t, J = 3.4 Hz), 6.60 (1H, t, J = 2.0 Hz), 6.76 (1H, t, J = 3.7 Hz), 6.92 (1H, s), 7.07 (1H, s), 7.18 (2H, d, J = 8.3 Hz), 7.21 (1H, d, J = 2.9 Hz), 7.71 (1H, d, J = 2.9 Hz), 7.84 (2H, d, J = 8.8 Hz), 9.76 (1H, br s).

MS (ESI) m/z: 526.14773 $(M+H)^+$.

EJEMPLO 56

2-(5-{3-[4-(Azetidin-1-ilsulfonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol



(56a) 1-[(3,4-Difluorofenil)sulfonil]azetidina

Se disolvió en diclorometano (5 mL) cloruro de 3,4-difluorofenilsulfonilo (117 µL, 0.87 mmol), disponible comercialmente, y se le agregó clorhidrato de azetidina (68 mg, 0.73 mmol) y trietilamina (203 µL, 1.45 mmol), seguido por agitación a temperatura ambiente durante 2 horas. A la solución de reacción se le agregó agua (15 mL) y se extrajo dos veces con diclorometano (15 mL). Se lavó con salmuera saturada (15 mL), seguido por

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secado sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-50%), para producir el compuesto deseado como un aceite incoloro (132 mg, rendimiento de 78%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.10-2.18 (2H, m), 3.82 (4H, t, J = 7.6 Hz), 7.35-7.41 (1H, m), 7.66-7.62 (1H, m), 7.72-7.68 (1H, m).

(56b) 2-(5-{3-[4-(Azetidin-1-ilsulfonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol

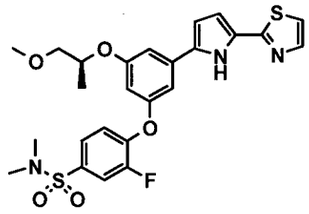
El 2-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (65.0 mg, 0.151 mmol) sintetizado en el ejemplo (38d), y la 1-[(3,4-difluorofenil)sulfonil]azetidina (42.3 mg, 0.181 mmol) sintetizada en el ejemplo (56a), se disolvieron en N-metilpirrolidona (5.0 mL) y se les agregó hidruro de sodio (55%, 20 mg, 0.45 mmol), seguido por agitación a 100°C durante 4 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó una solución acuosa saturada de cloruro de amonio (20 mL) y se extrajo con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó dos veces por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-35%), para producir el compuesto deseado como un sólido blanco (35.6 mg, rendimiento de 43%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 2.11-2.20 (2H, m), 3.42 (3H, s), 3.51 (1H, dd, J = 10.4, 4.1 Hz), 3.60 (1H, dd, J = 10.4, 6.1 Hz), 3.84 (4H, t, J = 7.6 Hz), 4.55-4.63 (1H, m), 6.53-6.56 (2H, m), 6.73 (1H, dd, J = 3.9, 2.3 Hz), 6.89 (1H, t, J = 2.0 Hz), 7.03 (1H, t, J = 1.8 Hz), 7.14 (1H, t, J = 8.0 Hz), 7.18 (1H, d, J = 3.5 Hz), 7.57 (1H, d, J = 8.6 Hz), 7.67-7.71 (2H, m), 9.79 (1H, br s).

MS (ESI) m/z: 544.13720 $(M+H)^+$.

EJEMPLO 57

3-Fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-N,N-dimetilbencenosulfonamida



(57a) 3,4-Difluoro-N,N-dimetilbencenosulfonamida

Se disolvió cloruro de 3,4-difluorofenilsulfonilo (117 μL, 0.87 mmol) en diclorometano (5 mL), y se le agregó clorhidrato de dimetilamina (59 mg, 0.73 mmol) y trietilamina (203 μL, 1.45 mmol), seguido por agitación a temperatura ambiente durante 2 horas. A la solución de reacción se le agregó agua (15 mL), seguido por extracción dos veces con diclorometano (15 mL) y lavado con salmuera saturada (15 mL), seguido por secado sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida, seguido

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por secado al vacío, para producir el compuesto deseado como un aceite incoloro (41.0 mg, rendimiento de 26%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.74 (6H, s), 7.32-7.38 (1H, m), 7.59-7.55 (1H, m), 7.61-7.66 (1H, m).

(57b) 3-Fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-N,N-dimetilbencenosulfonamida

El 2-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (65.0 mg, 0.151 mmol) sintetizado en el ejemplo (38d), y la 3,4-difluoro-N,N-dimetilbencenosulfonamida (40.1 mg, 0.181 mmol) sintetizada en el ejemplo (57a), se disolvieron en N-metilpirrolidona (5.0 mL) y se les agregó hidruro de sodio (55%, 20 mg, 0.45 mmol), seguido por agitación a 100°C durante 4 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó una solución acuosa saturada de cloruro de amonio (20 mL) y se extrajo con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-35%), para producir el compuesto deseado como un sólido blanco (31.0 mg, rendimiento de 39%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 2.76 (6H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 10.4, 4.1 Hz), 3.60 (1H, dd, J = 10.4, 6.1 Hz), 4.55-4.62 (1H, m), 6.53-6.55 (2H, m), 6.73 (1H, dd, J = 3.7, 2.5 Hz), 6.87 (1H,

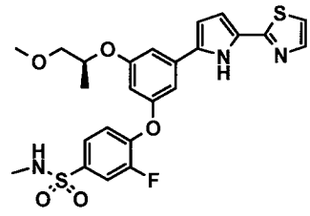
674

t, J = 1.8 Hz), 7.02 (1H, t, J = 1.8 Hz), 7.12 (1H, t, J = 8.0 Hz), 7.18 (1H, d, J = 3.5 Hz), 7.52-7.49 (1H, m), 7.63 (1H, dd, J = 9.8, 2.0 Hz), 7.68 (1H, d, J = 3.1 Hz), 9.79 (1H, s).

MS (ESI) m/z: 532.13886 $(M+H)^+$.

EJEMPLO 58

3-Fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-N-metilbencenosulfonamida



(58a) 3,4-Difluoro-N-metilbencenosulfonamida

Se disolvió cloruro de 3,4-difluorofenilsulfonilo (117 μL, 0.87 mmol), disponible comercialmente, en diclorometano (5 mL), y se le agregó clorhidrato de metilamina (49 mg, 0.73 mmol) y trietilamina (203 μL, 1.45 mmol), seguido por agitación a temperatura ambiente durante 2 horas. A la solución de reacción se le agregó agua (15 mL), se extrajo dos veces con diclorometano (15 mL) y se lavó con salmuera saturada (15 mL), seguido por secado sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida, seguido por secado al vacío, para producir el compuesto deseado como un aceite incoloro (44.7 mg, rendimiento de 30%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.70 (3H, d, J = 5.5 Hz), 4.43 (1H,

br s), 7.36-7.30 (1H, m), 7.64-7.68 (1H, m), 7.69-7.74 (1H, m).

(58b) 3-Fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-N-metilbencenosulfonamida

El 2-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (60.0 mg, 0.139 mmol) sintetizado en el ejemplo (38d), y la 3,4-difluoro-N-metilbencenosulfonamida (47.4 mg, 0.229 mmol) sintetizada en el ejemplo (58a), se disolvieron en N,N-dimetilformamida (5.0 mL) y se les agregó carbonato de potasio (77.0 mg, 0.557 mmol), seguido por agitación a 100°C durante 19 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) y se extrajo con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-25%), para producir el compuesto deseado como un sólido blanco (21.1 mg, rendimiento de 30%).

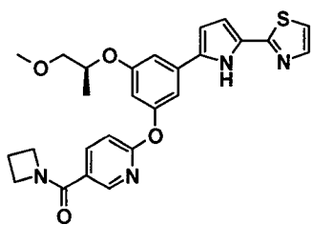
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (4H, d, J = 5.9 Hz), 2.69 (3H, d, J = 5.4 Hz), 3.42 (3H, s), 3.51 (1H, dd, J = 10.3, 4.4 Hz), 3.60 (1H, dd, J = 10.3, 5.9 Hz), 4.55-4.61 (1H, m), 5.22 (1H, s), 6.55 (2H, dt, J = 8.3, 2.7 Hz), 6.74 (1H, t, J = 2.9 Hz), 6.89 (1H, s), 7.01 (1H, t, J = 1.7 Hz), 7.12 (1H, t, J = 8.1 Hz), 7.16-7.18 (1H, m), 7.56-7.61 (2H, m), 7.69 (1H, d, J = 9.8 Hz), 9.96 (1H, br s).

MS (ESI) m/z: 518.12006 $(M+H)^+$.

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EJEMPLO 59

5-(Azetidin-1-ilcarbonil)-2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}piridina



(59a) 5-(Azetidin-1-ilcarbonil)-2-cloropiridina

Se disolvió ácido 6-cloronicotínico (160 mg, 1.01 mmol), disponible comercialmente, en diclorometano (5 mL), y se le agregó clorhidrato de azetidina (130 mg, 1.39 mmol), HATU (420 mg, 1.10 mmol) y N,N-diisopropiletilamina (0.50 mL, 2.87 mmol), seguido por agitación a temperatura ambiente durante la noche bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 40%-50%), para producir el compuesto deseado como un líquido incoloro (210 mg, rendimiento de ~100%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.40 (2H, m), 4.25 (2H, t, J = 7.6 Hz), 4.35 (2H, t, J = 7.6 Hz), 7.40 (1H, dd, J = 0.8, 8.6 Hz), 7.97 (1H, dd, J = 2.4, 8.2 Hz), 8.62 (1H, dd, J = 0.8, 2.4 Hz).

(59b) 5-(Azetidin-1-ilcarbonil)-2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}piridina

El 2-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-

il)-1H-pirrol-1-carboxilato de t-butilo (84 mg, 0.195 mmol) sintetizado en el ejemplo (38d), y la 5-(azetidin-1-ilcarbonil)-2-cloropiridina (110 mg, 0.559 mmol) sintetizada en el ejemplo (59a), se disolvieron en sulfóxido de dimetilo (3.0 mL) y se les agregó hidruro de sodio (60%, 30 mg, 0.75 mmol), seguido por agitación a 100°C durante 2 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó ácido clorhídrico 2N (30 mL), y se extrajo con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 75%-90%), para producir el compuesto deseado como un sólido amarillo (56 mg, rendimiento de 59%).

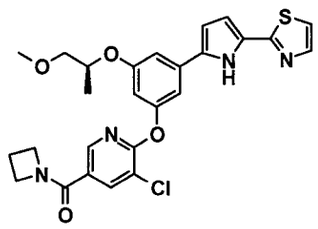
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 2.38 (2H, m), 3.42 (3H, s), 3.50 (1H, dd, J = 4.3, 10.2 Hz), 3.60 (1H, dd, J = 5.9, 10.2 Hz), 4.24 (2H, t, J = 7.4 Hz), 4.36 (2H, t, J = 6.6 Hz), 4,57 (1H, m), 6.54 (1H, dd, J = 2.7, 3.9 Hz), 6.64 (1H, t, J = 2.3 Hz), 6.73 (1H, dd, J = 2.4, 3.9 Hz), 6.97 (2H, m), 7.07 (1H, t, J = 1.8 Hz), 7.16 (1H, d, J = 3.5 Hz), 7.67 (1H, d, J = 3.1 Hz), 8.07 (1H, dd, J = 2.7, 8.6 Hz), 8.45 (1H, d, J = 2.4 Hz), 9.85 (1H, brs).

MS (ESI) m/z: 491.17450 $(M+H)^+$.

678

EJEMPLO 60

5-(Azetidin-1-ilcarbonil)-3-cloro-2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}piridina



(60a) 5-(Azetidin-1-ilcarbonil)-2,3-dicloropiridina

Se disolvió ácido 5,6-dicloronicotínico (200 mg, 1.04 mmol), disponible comercialmente, en diclorometano (5.0 mL), y se le agregó clorhidrato de azetidina (125 mg, 1.34 mmol), HATU (440 mg, 1.16 mmol) y N,N-diisopropiletilamina (0.45 mL, 2.58 mmol), seguido por agitación a temperatura ambiente durante 5 horas bajo una atmósfera de nitrógeno. Se le agregó ácido clorhídrico 0.5N (30 mL) y se extrajo con diclorometano (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 60%-80%), para producir el compuesto deseado como un líquido incoloro (162 mg, rendimiento de 67%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.38-2.46 (2H, m), 4.25 (2H, t, J = 7.6 Hz), 4.37 (2H, t, J = 7.6 Hz), 8.10 (1H, d, J = 2.3 Hz), 8.51 (1H, d, J = 2.3 Hz).

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(60b) 5-(Azetidin-1-ilcarbonil)-3-cloro-2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}piridina

El 2-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (70 mg, 0.163 mmol) sintetizado en el ejemplo (38d), y la 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina (75 mg, 0.325 mmol) sintetizada en el ejemplo (60a), se disolvieron en sulfóxido de dimetilo (5.0 mL) y se les agregó hidruro de sodio (60%, 30 mg, 0.75 mmol), y se agitó a 100°C durante 3.5 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 85%-100%), para producir el compuesto deseado como un sólido amarillo (58 mg, rendimiento de 68%).

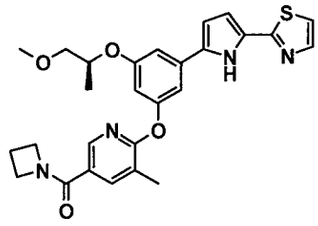
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.35 (3H, d, J = 5.9 Hz), 2.34-2.42 (2H, m), 3.42 (3H, s), 3.51 (1H, dd, J = 10.6, 4.7 Hz), 3.61 (1H, dd, J = 10.4, 5.7 Hz), 4.21-4.27 (2H, m), 4.34-4.37 (2H, m), 4.56-4.59 (1H, m), 6.54 (1H, t, J = 2.9 Hz), 6.66 (1H, t, J = 1.8 Hz), 6.72 (1H, t, J = 2.9 Hz), 6.96 (1H, s), 7.05 (1H, s), 7.16 (1H, dd, J = 3.3, 0.6 Hz), 7.68 (1H, dd, J = 3.3, 0.6 Hz), 8.16 (1H, dd, J = 2.0, 0.8 Hz), 8.26 (1H, dd, J = 1.8, 1.0 Hz), 9.57 (1H, br s).

MS (ESI) m/z: 525.13929 $(M+H)^+$.

680

EJEMPLO 61

5-(Azetidin-1-ilcarbonil)-2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-3-metilpiridina



(61a) 5-(Azetidin-1-ilcarbonil)-2-cloro-3-metilpiridina

Se disolvió ácido 6-cloro-5-metilnicotínico (200 mg, 1.29 mmol) en diclorometano (7.0 mL), y se le agregó clorhidrato de azetidina (160 mg, 1.71 mmol), HATU (1000 mg, 2.63 mmol) y N,N-diisopropiletilamina (0.69 mL, 3.96 mmol), seguido por agitación a temperatura ambiente durante la noche bajo una atmósfera de nitrógeno. Se le agregó ácido clorhídrico 0.5N (30 mL) y se extrajo con diclorometano (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 60%-75%), para producir el compuesto deseado como un líquido incoloro (160 mg, rendimiento de 64%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.32 (3H, s), 2.36-2.42 (2H, m), 4.24 (2H, t, J = 7.6 Hz), 4.35 (2H, t, J = 7.6 Hz), 7.95 (1H, dd, J = 9.3, 1.0 Hz), 8.26 (1H, d, J = 1.0 Hz).

681

(61b) 5-(Azetidin-1-ilcarbonil)-2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-3-metilpiridina

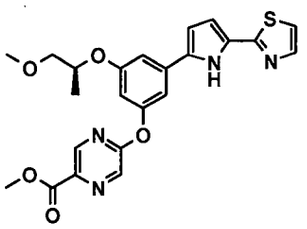
El 2-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (59 mg, 0.137 mmol) sintetizado en el ejemplo (38d), y la 5-(azetidin-1-ilcarbonil)-2-cloro-3-metilpiridina (45 mg, 0.232 mmol) sintetizada en el ejemplo (61a), se disolvieron en sulfóxido de dimetilo (3.0 mL) y se les agregó hidruro de sodio (60%, 25 mg, 0.63 mmol), seguido por agitación a 80°C durante 4.5 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 60%-80%), para producir el compuesto deseado como un sólido amarillo (50 mg, rendimiento de 72%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.35 (3H, d, J = 6.3 Hz), 2.32-2.38 (2H, m), 2.40 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 10.2, 4.3 Hz), 3.60 (1H, dd, J = 10.2, 5.9 Hz), 4.23 (2H, t, J = 7.2 Hz), 4.34 (2H, t, J = 6.6 Hz), 4.56-4.58 (1H, m), 6.53 (1H, dd, J = 3.9, 2.7 Hz), 6.63 (1H, t, J = 2.0 Hz), 6.72 (1H, dd, J = 3.9, 2.3 Hz), 6.92 (1H, t, J = 1.8 Hz), 7.00 (1H, dd, J = 3.9, 1.6 Hz), 7.16 (1H, d, J = 3.1 Hz), 7.67 (1H, d, J = 3.1 Hz), 7.94 (1H, dd, J = 2.3, 0.8 Hz), 8.22 (1H, d, J = 2.3 Hz), 9.46 (1H, br s).

MS (ESI) m/z: 505.19091 $(M+H)^+$.

EJEMPLO 62

5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}pirazin-2-carboxilato de metilo



(62a) 5-Hidroxipirazin-2-carboxilato de metilo

Se disolvió ácido 5-hidroxipirazin-2-carboxílico (1.00 g, 7.14 mmol) en metanol (5 mL), y se le agregó una solución de ácido clorhídrico 4N /dioxano (25 mL), seguido por agitación a 60°C durante 1.5 horas y calentamiento a reflujo a 80°C durante 2.5 horas. La solución de reacción se llevó de vuelta a temperatura ambiente y el disolvente se removió por destilación bajo presión reducida; al residuo resultante se le agregó acetato de etilo (20 mL) para suspenderlo. El precipitado resultante se filtró y se lavó con acetato de etilo, seguido por secado al vacío, para producir el compuesto deseado como un sólido anaranjado-pardo (673 mg, rendimiento de 61%).

^{1}H-RMN (CD_3OD, 400 MHz): δ 3.31 (1H, s), 3.85 (3H, s), 8.00 (1H, d, J = 1.2 Hz), 8.13 (1H, d, J = 1.2 Hz).

(62b) 5-Cloropirazin-2-carboxilato de metilo

El 5-hidroxipirazin-2-carboxilato de metilo (673 mg, 4.37 mmol)

sintetizado en el ejemplo (62a) se disolvió en oxicloruro de fósforo (6.1 mL) y se le agregaron unas gotas de N,N-dimetilformamida, seguido por calentamiento a reflujo durante 2 horas bajo una atmósfera de nitrógeno. La solución de reacción se vació en agua de hielo y se extrajo tres veces con cloroformo (30 mL). La capa orgánica se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada (100 mL de cada una), y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida para producir el compuesto deseado como un sólido gris (611 mg, rendimiento de 81%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 4.05 (3H, s), 8.71 (1H, d, J = 1.6 Hz), 9.10 (1H, d, J = 1.2 Hz).

(62c) 5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}pirazin-2-carboxilato de metilo

El 2-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de metilo (200 mg, 0.464 mmol) sintetizado en el ejemplo (38d), y el 5-cloropirazin-2-carboxilato de metilo (120 mg, 0.695 mmol) sintetizado en el ejemplo (62b), se disolvieron en N,N-dimetilformamida (10 mL) y se les agregó carbonato de potasio (257 mg, 1.86 mmol), seguido por agitación a 80°C durante 7 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (40 mL) y se extrajo con acetato de etilo (40 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el

residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-50%). El sólido amarillo resultante se disolvió en diclorometano (2 mL) y se le agregó ácido trifluoroacético (4 mL), seguido por agitación a temperatura ambiente durante 1.5 horas. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio (40 mL) y se extrajo dos veces con acetato de etilo (40 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-50%), para producir el compuesto deseado como un sólido amarillo (164 mg, rendimiento de 93%).

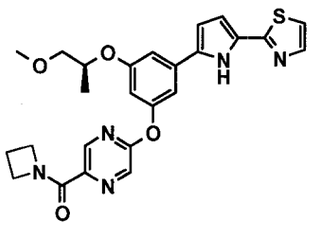
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.35 (3H, d, J = 6.3 Hz), 3.42 (3H, s), 3.52 (1H, dd, J = 10.2, 4.3 Hz), 3.60 (1H, dd, J = 10.2, 5.9 Hz), 4.02 (3H, s), 4.56-4.63 (1H, m), 6.55 (1H, dd, J = 3.9, 2.7 Hz), 6.67 (1H, t, J = 2.2 Hz), 6.75 (1H, dd, J = 3.9, 2.3 Hz), 6.98 (1H, t, J = 1.8 Hz), 7.10 (1H, t, J = 1.8 Hz), 7.18 (1H, d, J = 3.5 Hz), 7.68 (1H, d, J = 3.1 Hz), 8.51 (1H, d, J = 1.2 Hz), 8.87 (1H, d, J = 1.2 Hz), 9.74 (1H, br s).

MS (ESI) m/z: 467 $(M+H)^+$.

685

EJEMPLO 63

2-(Azetidin-1-ilcarbonil)-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}pirazina



(63a) Acido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}pirazin-2-carboxílico

El 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}pirazin-2-carboxilato de metilo (423 mg, 0.907 mmol) sintetizado en el ejemplo (62c) se disolvió en metanol (10 mL), y se le agregó agua (2 mL) e hidróxido de litio monohidratado (76.2 mg, 1.82 mmol), seguido por agitación a 50°C durante 1 hora bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó agua (30 mL) y se extrajo dos veces con acetato de etilo (30 mL), seguido por secado sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: diclorometano/metanol = 0%-10%), para producir el compuesto deseado como un sólido amarillo pálido (269 mg, rendimiento de 66%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.38 (3H, d, J = 6.3 Hz), 3.44 (3H, s), 3.54 (1H, dd, J = 10.2, 4.3 Hz), 3.63 (1H, dd, J = 10.2, 5.9 Hz), 4.60-4.65 (1H, m), 6.62 (1H, dd, J = 3.9, 2.3 Hz), 6.71 (1H, t, J = 2.2 Hz), 6.82 (1H, dd, J

= 3.9, 2.3 Hz), 7.16-7.18 (2H, m), 7.37 (1H, s), 7.67 (1H, d, J = 3.5 Hz), 8.54 (1H, d, J = 1.2 Hz), 8.81 (1H, s), 11.30 (1H, br s).

(63b) 2-(Azetidin-1-ilcarbonil)-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}pirazina

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}pirazin-2-carboxílico (28.0 mg, 0.062 mmol) sintetizado en el ejemplo (63a) se disolvió en tetrahidrofurano (3 mL), y se le agregó clorhidrato de azetidina (17.4 mg, 0.186 mmol), HATU (35.3 mg, 0.093 mmol) y N,N-diisopropiletilamina (65 μL, 0.37 mmol), seguido por agitación a temperatura ambiente durante 28 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó agua (15 mL) y se extrajo con acetato de etilo (15 mL), seguido por secado sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por TLC preparativa (disolvente de desarrollo: metanol/diclorometano = 15%), para producir el compuesto deseado como un sólido blanco (29.1 mg, rendimiento de 96%).

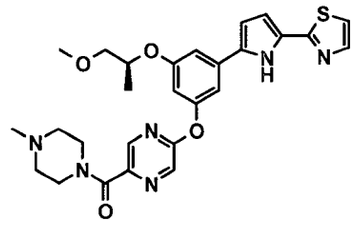
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.35 (3H, d, J = 5.9 Hz), 2.35-2.41 (2H, m), 3.42 (3H, s), 3.51 (1H, dd, J = 10.3, 3.9 Hz), 3.60 (1H, dd, J = 10.3, 5.9 Hz), 4.26 (2H, t, J = 7.8 Hz), 4.54-4.60 (1H, m), 4.69 (2H, t, J = 7.8 Hz), 6.54 (1H, t, J = 3.2 Hz), 6.65 (1H, s), 6.73 (1H, t, J = 2.9 Hz), 6.95 (1H, s), 7.06 (1H, t, J = 1.7 Hz), 7.17 (1H, d, J = 2.9 Hz), 7.67 (1H, d, J = 3.4 Hz), 8.31 (1H, s), 8.88 (1H, s), 9.69 (1H, br s).

MS (ESI) m/z: 492.16821 $(M+H)^+$.

687

EJEMPLO 64

2-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-5-[(4-metilpiperazin-1-il)carbonil]pirazina



El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}pirazin-2-carboxílico (40.4 mg, 0.089 mmol) sintetizado en el ejemplo (63a) se disolvió en tetrahidrofurano (5 mL), y se le agregó 1-metilpiperazina (30 μL, 0.27 mmol), HATU (67.9 mg, 0.18 mmol) y N,N-diisopropiletilamina (93 μL, 0.54 mmol), seguido por agitación a temperatura ambiente durante 12 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó agua (15 mL) y se extrajo con acetato de etilo (15 mL), seguido por secado sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/diclorometano = 0%-5%), para producir el compuesto deseado como un sólido amarillo pálido (47 mg, rendimiento de 98%).

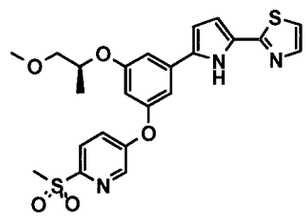
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.35 (3H, d, J = 6.3 Hz), 2.37 (3H, s), 2.50 (2H, br s), 2.56 (2H, br s), 3.42 (3H, s), 3.52 (1H, dd, J = 10.2, 4.3 Hz), 3.61 (1H, dd, J = 10.4, 6.1 Hz), 3.75 (2H, br s), 3.85 (2H, br s), 4.54-4.62 (1H, m), 6.54 (1H, t, J = 3.3 Hz), 6.65 (1H, t, J = 2.0 Hz), 6.73 (1H, dd, J = 3.9, 2.3

Hz), 6.95 (1H, t, J = 1.8 Hz), 7.06 (1H, t, J = 1.8 Hz), 7.17 (1H, d, J = 3.1 Hz), 7.68 (1H, d, J = 3.1 Hz), 8.35 (1H, d, J = 1.2 Hz), 8.56 (1H, d, J = 1.2 Hz), 9.59 (1H, br s).

MS (ESI) m/z: 535.21022 $(M+H)^+$.

EJEMPLO 65

5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-2-(metilsulfonil)piridina



(65a) 5-Bromo-2-(metiltio)piridina

Se disolvió 2,5-dibromo-piridina (6.01 g, 25.4 mmol), disponible comercialmente, en N,N-dimetilformamida (50 mL), y se le agregó tiometóxido de sodio (2.20 g, 31.4 mmol), seguido por agitación a 0°C durante 3.5 horas bajo una atmósfera de nitrógeno. La solución de reacción se llevó de vuelta a temperatura ambiente, se le agregó agua (250 mL) y se extrajo con éter dietílico (250 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 3%-5%), para producir el compuesto deseado como

un sólido blanco (4.90 g, rendimiento de 94%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.54 (3H, s), 7.08 (1H, d, J = 8.2 Hz), 7.58 (1H, dd, J = 8.6, 2.3 Hz), 8.49 (1H, d, J = 2.0 Hz).

(65b) 5-Fluoro-2-(metilsulfonil)piridina

La 5-bromo-2-(metiltio)piridina (4.90 g, 24.0 mmol) sintetizada en el ejemplo (65a) se disolvió en tetrahidrofurano (100 mL), y se le agregó a gotas n-butil-litio (solución en hexano 1.57 mol/L, 17.0 mL, 26.7 mmol) a -78°C, seguido por agitación a -78°C durante 1 hora bajo una atmósfera de nitrógeno. Se disolvió N-fluorobencenosulfonimida (11.0 g, 34.9 mmol) en tetrahidrofurano (25 mL), seguido por su adición, gota a gota, a la solución de reacción a -78°C, y se agitó a -78°C durante 2 horas bajo una atmósfera de nitrógeno. La solución de reacción se llevó de vuelta a temperatura ambiente y se agitó durante 1.5 horas. Se le agregó una solución acuosa saturada de cloruro de amonio (200 mL) y se extrajo con éter dietílico (300 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión ligeramente reducida.

El residuo resultante se disolvió en cloruro de metileno (150 mL), y se le agregó lentamente ácido m-cloroperbenzoico (65%, 16.5 g, 62.1 mmol) a 0°C, seguido por agitación a 0°C durante 1.5 horas, bajo una atmósfera de nitrógeno. Después de remover el material sólido blanco por filtración en Celite, se le agregó una solución acuosa saturada de carbonato ácido de

sodio (100 mL) y se extrajo con cloruro de metileno (400 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 3%-5%), para producir el compuesto deseado como un sólido blanco amarillento (1.95 g, rendimiento de 46%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 3.24 (3H, s), 7.67 (1H, ddd, J = 9.9, 6.9, 1.9 Hz), 8.16 (1H, dd, J = 8.6, 4.3 Hz), 8.59 (1H, d, J = 2.7 Hz).

(65c) 5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-2-(metilsulfonil)piridina

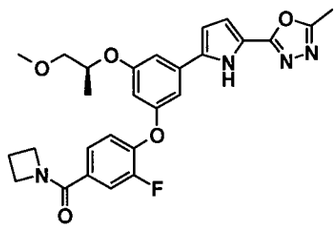
El 2-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (70.0 mg, 0.16 mmol) sintetizado en el ejemplo (38d), y la 5-fluoro-2-(metilsulfonil)piridina (35.0 mg, 0.20 mmol) sintetizada en el ejemplo (65b), se disolvieron en N,N-dimetilformamida (5 mL) y la mezcla se agitó a 90°C durante 3 días bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó agua (15 mL), seguido por extracción con acetato de etilo (30 mL) y lavado con salmuera saturada (30 mL), seguido por secado sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-40%), para producir el compuesto deseado como un sólido amarillo pálido (28 mg, rendimiento de 35%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.24 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 10.4, 4.1 Hz), 3.59 (1H, dd, J = 10.2, 6.3 Hz), 4.58 (1H, dd, J = 10.4, 6.1 Hz), 6.54-6.56 (2H, m), 6.73 (1H, dd, J = 3.7, 2.5 Hz), 6.86 (1H, t, J = 1.8 Hz), 7.04 (1H, t, J = 2.0 Hz), 7.18 (1H, d, J = 3.5 Hz), 7.43 (1H, dd, J = 8.6, 2.7 Hz), 7.68 (1H, d, J = 3.1 Hz), 8.05 (1H, d, J = 9.0 Hz), 8.49 (1H, d, J = 2.7 Hz), 9.62 (1H, br s).

MS (ESI) m/z: 486.11507 $(M+H)^+$.

EJEMPLO 66

2-(5-{3-[4-(Azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-5-metil-1,3,4-oxadiazol



(66a) 2,5-Dibromo-1H-pirrol-1-carboxilato de t-butilo

Se disolvió 1-pirrolcarboxilato de t-butilo (46.68 g, 279 mmol), disponible comercialmente, en tetrahidrofurano (500 mL), y se enfrió a -78°C. A esto se le agregó N-bromosuccinimida (100.48 g, 565 mmol) en pequeñas porciones durante 1 hora. La temperatura de la solución de reacción se elevó naturalmente y la solución se agitó a temperatura ambiente durante 18 horas. La solución de reacción se enfrió a 0°C, seguido por la adición de sulfito de sodio (36.43 g) y agitación durante 30 minutos; subsiguientemente se le

agregó hexano (200 mL) para producir un precipitado que se removió por filtración en Celite. El disolvente del filtrado se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 1%-5%), para producir el compuesto deseado como un aceite incoloro (52.69 g, rendimiento de 58%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.65 (9H, s), 6.25 (2H, s).

MS (EI) m/z: 323 (M^+).

(66b) 5-Bromo-1H-pirrol-1,2-dicarboxilato de 2-bencilo-1-t-butilo

El 2,5-dibromo-1H-pirrol-1-carboxilato de t-butilo (10.98 g, 33.8 mmol) sintetizado en el ejemplo (66a) se disolvió en éter dietílico (135 mL), y se enfrió a -78°C. Se le agregó lentamente, gota a gota, n-butil-litio (solución en hexano 2.77M, 12.8 mL, 35.5 mmol), y se agitó durante 1 hora. A la solución de reacción se le agregó lentamente, gota a gota, cloroformiato de bencilo (6.25 mL, 44.0 mmol), y se agitó durante 30 minutos. Con la temperatura de la solución de reacción elevándose gradualmente a temperatura ambiente, se agitó durante 1 hora. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (200 mL) y éter dietílico (300 mL) y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 5%-45%), para producir el compuesto

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deseado como un aceite pardo rojizo (8.80 g, rendimiento de 68%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.56 (9H, s), 5.26 (2H, s), 6.21 (1H, d, J = 3.9 Hz), 6.85 (1H, d, J = 3.9 Hz), 7.28-7.39 (5H, m).

MS (FAB) m/z: 380 $(M+H)^+$.

(66c) 5-{3-Hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-1,2-dicarboxilato de 2-bencilo-1-t-butilo

El 5-bromo-1H-pirrol-1,2-dicarboxilato de 2-bencilo-1-t-butilo (8.75 g, 23.0 mmol) sintetizado en el ejemplo (66b), y el 3-[(1S)-2-metoxi-1-metiletoxi]-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenol (7.11 g, 23.1 mmol) sintetizado en el ejemplo (38c), se disolvieron en un disolvente mixto de 1,4-dioxano (92 mL) y agua (23 mL), y se les agregó complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano (570 mg, 0.698 mmol) y carbonato de potasio (7.95 g, 57.5 mmol), seguido por agitación a 55°C durante 3 horas bajo una atmósfera de nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente, se le agregó agua (200 mL) y se extrajo con acetato de etilo (200 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 15%-35%), para producir el compuesto deseado como un aceite pardo (8.32 g, rendimiento de 75%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.29 (3H, d, J = 6.3 Hz), 1.41 (9H, s), 3.40 (3H, s), 3.47 (1H, dd, J = 10.3, 4.4 Hz), 3.57 (1H, dd, J = 10.3, 5.9 Hz),

4.48-4.54 (1H, m), 5.20 (1H, s), 5.30 (2H, s), 6.17 (1H, d, J = 3.4 Hz), 6.44 (1H, s), 6.48 (1H, s), 6.57 (1H, s), 6.94 (1H, d, J = 3.4 Hz), 7.42-7.31 (5H, m).

MS (FAB) m/z: 481 (M^+).

(66d) 5-{3-(2-Fluoro-4-formilfenoxi)-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-carboxilato de bencilo

El 5-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-1,2-dicarboxilato de 2-bencilo-1-t-butilo (8.30 g, 17.2 mmol) sintetizado en el ejemplo (66c) se disolvió en N,N-dimetilformamida (86 mL), y se le agregó 3,4-difluorobenzaldehído (2.85 mL, 25.9 mmol) y carbonato de potasio (11.96 g, 86.5 mmol), seguido por agitación a 90°C durante 24 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (100 mL) y se extrajo con éter dietílico (300 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro.

El disolvente se removió por destilación bajo presión reducida para producir un residuo, que se disolvió en diclorometano (20 mL) y se le agregó ácido trifluoroacético (10 mL), seguido por agitación a temperatura ambiente durante 1 hora. El disolvente se removió por destilación bajo presión reducida para producir un residuo, que se disolvió en acetato de etilo (200 mL) y se lavó con una solución acuosa saturada de carbonato ácido de sodio (200 mL). Después de lavar con salmuera saturada, se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida para producir un residuo, que se purificó por cromatografía

en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 15%-35%), para producir el compuesto deseado como un sólido blanco (6.34 g, rendimiento de 73%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 3.40 (3H, s), 3.50 (1H, dd, J = 10.2, 3.9 Hz), 3.58 (1H, dd, J = 10.4, 6.1 Hz), 4.53-4.60 (1H, m), 5.32 (2H, s), 6.50 (1H, t, J = 3.3 Hz), 6.59 (1H, s), 6.83 (1H, s), 6.96-6.98 (2H, m), 7.12 (1H, t, J = 8.0 Hz), 7.32-7.44(5H, m), 7.62 (1H, d, J = 8.2 Hz), 7.72 (1H, dd, J = 10.4, 1.8 Hz), 9.29 (1H, s), 9.92 (1H, d, J = 2.0 Hz).

MS (FAB) m/z: 503 (M^+).

(66e) Acido 4-(3-{5-[(benciloxi)carbonil]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)-3-fluorobenzoico

El 5-{3-(2-fluoro-4-formilfenoxi)-5-[(1S)-2-metoxi-1-metiletoxi]-fenil}-1H-pirrol-2-carboxilato de bencilo (6.33 g, 12.6 mmol) sintetizado en el ejemplo (66d) se suspendió en un disolvente mixto de t-butanol (120 mL) y agua (40 mL), y se le agregó fosfato diácido de sodio dihidratado (8.86 g, 56.8 mmol) y 2-metil-2-buteno (12.05 mL, 113 mmol). Bajo enfriamiento con hielo se le agregó lentamente clorito de sodio (80%, 2.93 g, 25.9 mmol) y se agitó a temperatura ambiente durante 2 horas. Se le agregó salmuera saturada (200 mL), seguido por extracción con diclorometano (200 mL), y se secó sobre sulfato de magnesio anhidro para producir el compuesto deseado como un aceite amarillo pálido (7.17 g, rendimiento de ~100%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.36 (3H, d, J = 6.3 Hz), 3.43 (3H, s), 3.53 (1H, dd, J = 10.2, 3.9 Hz), 3.62 (1H, dd, J = 10.2, 5.9 Hz), 4.58-4.65

(1H, m), 5.34 (2H, s), 6.55 (1H, dd, J = 3.9, 2.7 Hz), 6.69 (1H, t, J = 2.0 Hz), 7.02-7.06 (3H, m), 7.11 (1H, s), 7.34-7.44(5H, m), 7.66 (1H, d, J = 8.6 Hz), 7.77 (1H, dd, J = 10.9, 2.0 Hz), 10.68 (1H, br s).

MS (FAB) m/z: 519 (M^+).

(66f) 5-{3-[4-(Azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-carboxilato de bencilo

El ácido 4-(3-{5-[(benciloxi)carbonil]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)-3-fluorobenzoico (7.14 g, 13.7 mmol) sintetizado en el ejemplo (66e) se disolvió en diclorometano (120 mL). Bajo enfriamiento con hielo, se le agregó clorhidrato de azetidina (1.772 g, 18.9 mmol), WSCI·HCl (3.62 g, 18.9 mmol), trietilamina (2.65 mL, 19.1 mmol) y 4-dimetilaminopiridina (464 mg, 3.80 mmol), y se agitó a temperatura ambiente durante 6 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó ácido clorhídrico 0.5N (300 mL) y se extrajo con diclorometano (300 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 60%-85%), para producir el compuesto deseado como un sólido blanco (4.12 g, rendimiento de 59%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J = 6.3 Hz), 2.34-2.41 (2H, m), 3.40 (3H, s), 3.49 (1H, dd, J = 10.4,4.1 Hz), 3.57 (1H, dd, J = 10.4, 6.1 Hz), 4.21-4.27 (2H, br m), 4.33-4.39 (2H, br m), 4.51-4.57 (1H, m), 5.33

(2H, s), 6.48 (1H, dd, J = 3.9, 2.7 Hz), 6.53 (1H, t, J = 2.2 Hz), 6.78 (1H, t, J = 1.8 Hz), 6.89 (1H, t, J = 1.8 Hz), 6.97 (1H, dd, J = 3.9, 2.3 Hz), 7.06 (1H, t, J = 8.0 Hz), 7.34-7.44 (6H, m), 7.52 (1H, dd, J = 10.9, 2.0 Hz), 9.19 (1H, br s).

MS (FAB) m/z: 558 (M^+).

(66g) Acido 5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-carboxílico

El 5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-carboxilato de bencilo (4.25 g, 7.61 mmol) sintetizado en el ejemplo (66f) se disolvió en etanol (150 mL), y se le agregó un catalizador de paladio al 10% en carbón (804 mg), seguido por agitación durante 2 horas bajo una atmósfera de hidrógeno. El catalizador de paladio en carbón se removió por filtración en Celite y el disolvente se removió por destilación bajo presión reducida, para producir el compuesto deseado como un sólido blanco (3.45 g, rendimiento de 97%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J = 6.3 Hz), 2.32-2.40 (2H, m), 3.44 (3H, s), 3.52 (1H, dd, J = 10.0, 4.1 Hz), 3.64 (1H, dd, J = 10.0, 6.3 Hz), 4.20-4.26 (2H, br m), 4.31-4.38 (2H, br m), 4.66-4.72 (1H, m), 6.48-6.50 (2H, m), 6.86 (1H, s), 7.00 (1H, s), 7.05 (1H, t, J = 7.6 Hz), 7.16 (1H, s), 7.38 (1H, d, J = 7.8 Hz), 7.50 (1H, d, J = 11.3 Hz), 10.17 (1H, br s).

MS (ESI) m/z: 469.17889 $(M+H)^+$.

(66h) N'-Acetil-5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-carbohidrazida

El ácido 5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-

metoxi-1-metiletoxi]fenil}-1H-pirrol-2-carboxílico (126 mg, 0.27 mmol) sintetizado en el ejemplo (66g) y acetohidrazida (40 mg, 0.54 mmol) se disolvieron en diclorometano (5 mL), y se les agregó HATU (153 mg, 0.40 mmol) y N,N-diisopropiletilamina (70 μL, 0.40 mmol) a temperatura ambiente, seguido por agitación durante 1 hora bajo una atmósfera de nitrógeno. La solución de reacción se diluyó con diclorometano (60 mL), se lavó con ácido clorhídrico 1N, solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/diclorometano = 5%), para producir el producto deseado como un sólido blanco (87 mg, rendimiento de 62%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.26 (3H, d, J = 6.3 Hz), 1.91 (3H, s), 2.30-3.38 (2H, m), 3.37 (3H, s), 3.46 (1H, dd, J = 3.8, 10.1 Hz) 3.58 (1H, dd, J = 6.2, 10.1 Hz), 4.18-4.24 (2H, brm), 4.30-4.36 (2H, brm), 4.55-4.59 (1H, m), 6.43 (1H, dd, J = 2.7, 4.0 Hz), 6.46 (1H, t, J = 2.1 Hz), 6.81 (1H, dd, J = 2.4,4.1 Hz), 6.87 (1H, s), 7.01 (1H, t, J = 8.2 Hz), 7.07 (1H, s), 7.35 (1H, d, J = 8.6 Hz), 7.46 (1H, dd, J = 2.0, 10.9 Hz), 9.10 (1H, brs), 9.36 (1H, brs), 10.62 (1H, brs).

(66i) 2-(5-{3-[4-(Azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-5-metil-1,3,4-oxadiazol

La N'-acetil-5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-carbohidrazida (86 mg, 0.16 mmol)

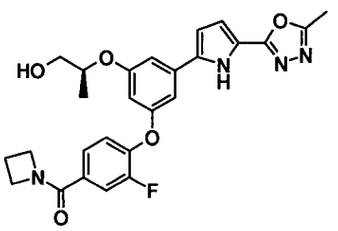
sintetizada en el ejemplo (66h), se disolvió en diclorometano (5 mL) y se le agregó trietilamina (0.1 mL, 0.72 mmol) y cloruro de ácido p-toluenosulfónico (69 mg, 0.36 mmol), seguido por agitación a temperatura ambiente durante la noche. La solución de reacción se diluyó con diclorometano (60 mL), se lavó con ácido clorhídrico 1N, solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-100%), para producir el producto deseado como un sólido blanco (57 mg, rendimiento de 69%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 2.34-3.42 (2H, m), 2.58 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 3.9, 10.4 Hz) 3.59 (1H, dd, J = 6.1, 10.3 Hz), 4.22-4.27 (2H, brm), 4.35-4.40 (2H, brm), 4.54-4.59 (1H, m), 6.54 (1H, t, J = 2.2 Hz), 6.55 (1H, dd, J = 2.2, 2.7 Hz), 6.80 (1H, t, J = 1.7 Hz), 6.85 (1H, dd, J = 1.9, 2.4 Hz), 6.93 (1H, dd, J = 1.2, 1.6 Hz), 7.08 (1H, t, J = 8.2 Hz), 7.41 (1H, d, J = 8.5 Hz), 7.52 (1H, dd, J = 2.0, 11.1 Hz), 9.49 (1H, brs).

MS (ESI) m/z: 507.20129 $(M+H)^+$.

EJEMPLO 67

(2S)-2-{3-[4-(Azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]fenoxi}propan-1-ol



El 2-(5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-5-metil-1,3,4-oxadiazol (379.2 mg, 0.748 mmol) sintetizado en el ejemplo (66i) se disolvió en diclorometano (15 mL), y se le agregó una solución de tribromuro de boro/diclorometano (1M, 750 μL, 0.75 mmol) a -78°C, bajo una atmósfera de nitrógeno, seguido por agitación a 0°C durante 3 horas. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/diclorometano = 2%-8%), para producir el compuesto deseado como un sólido amarillo pálido (76.9 mg, rendimiento de 21%).

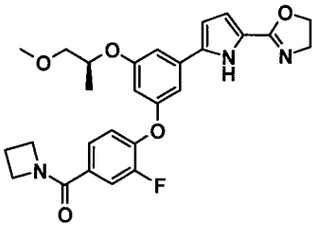
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.29 (3H, d, J = 6.3 Hz), 2.34-2.42 (2H, m), 2.58 (3H, s), 2.80 (1H, t, J = 6.1 Hz), 3.76-3.79 (2H, m), 4.22-4.26 (2H, br m), 4.35-4.39 (2H, br m), 4.52-4.59 (1H, m), 6.45 (1H, t, J = 2.2 Hz),

6.53 (1H, dd, J = 3.9, 2.7 Hz), 6.79 (1H, t, J = 1.8 Hz), 6.84 (1H, dd, J = 3.9, 2.3 Hz), 6.91 (1H, t, J = 1.8 Hz), 7.05 (1H, t, J = 8.2 Hz), 7.38-7.41 (1H, m), 7.51 (1H, dd, J = 10.9, 2.0 Hz), 9.92 (1H, br s).

MS (ESI) m/z: 493.18999 $(M+H)^+$.

EJEMPLO 68

2-(5-{3-[4-(Azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol



(68a) 5-{3-[4-(Azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-N-(2-cloroetil)-1H-pirrol-2-carboxamida

El ácido 5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-carboxílico (66 mg, 0.15 mmol) sintetizado en el ejemplo (66g), clorhidrato de 2-cloroetilamina (34 mg, 0.30 mmol) y 4-dimetilaminopiridina (18 mg, 0.15 mmol), se disolvieron en diclorometano (10 mL), y se les agregó WSCI·HCl (31 mg, 0.16 mmol) a temperatura ambiente, seguido por agitación durante 1 hora bajo una atmósfera de nitrógeno. La solución de reacción se diluyó con diclorometano (60 mL), se lavó con ácido clorhídrico 1N, solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, y subsiguientemente se secó

sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-60%), para producir el producto deseado como un sólido blanco (56 mg, rendimiento de 79%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 2.35-3.49 (2H, m), 3.41 (3H, s), 3.50 (1H, dd, J = 4.1,10.7 Hz) 3.58 (1H, dd, J = 6.1,10.3 Hz), 3.71 (2H, t, J = 5.4 Hz), 3.77 (2H, t, J = 5.6 Hz), 4.22-4.27 (2H, brm), 4.35-4.40 (2H, brm), 4.53-4.57 (1H, m), 6.24-6.28 (1H, m), 6.47 (1H, t, J = 3.0 Hz), 6.52 (1H, t, J = 2.1 Hz), 6.62 (1H, dd, J = 2.5, 4.1 Hz), 6.78 (1H, t, J = 1.6 Hz), 6.90 (1H, t, J = 1.6 Hz), 7.06 (1H, t, J = 8.0 Hz), 7.40 (1H, d, J = 8.5 Hz), 7.52 (1H, dd, J = 2.0, 11.0 Hz), 9.43 (1H, brs).

(68b) 2-(5-{3-[4-(Azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol

La 5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-N-(2-cloroetil)-1H-pirrol-2-carboxamida (85 mg, 0.16 mmol) sintetizada en el ejemplo (68a) se disolvió en tetrahidrofurano (3 mL), y se le agregó hidruro de sodio (37 mg, 0.82 mmol) a 0°C, seguido por agitación a temperatura ambiente durante 20 horas. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con acetato de etilo (50 mL). Después de lavar con salmuera saturada, se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por

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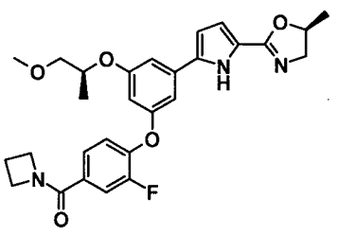
cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo 100%-metanol/cloroformo = 2%), para producir el producto deseado como un sólido amarillo pálido (33 mg, rendimiento de 41%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 2.34-3.41 (2H, m), 3.41 (3H, s), 3.49 (1H, dd, J = 3.9, 10.5 Hz) 3.58 (1H, dd, J = 5.9, 10.2 Hz), 4.00 (2H, t, J = 9.3 Hz), 4.22-4.26 (2H, brm), 4.35-4.39 (2H, brm), 4.40 (2H, t, J = 9.3 Hz), 4.53-4.57 (1H, m), 6.48 (1H, d, J = 3.8 Hz), 6.51 (1H, t, J = 2.0 Hz), 6.75 (1H, d, J = 3.8 Hz), 6.78 (1H, t, J = 1.6 Hz), 6.91 (1H, s), 7.06 (1H, t, J = 8.1 Hz), 7.40 (1H, d, J = 8.5 Hz), 7.52 (1H, dd, J = 2.0, 11.0 Hz).

MS (ESI) m/z: 494.20834 $(M+H)^+$.

EJEMPLO 69

(5S)-2-(5-{3-[4-(Azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol



(69a) 5-{3-[4-(Azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-N-[(2R)-2-hidroxipropil]-1H-pirrol-2-carboxamida

El ácido 5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-carboxílico (580 mg, 1.24 mmol) sintetizado en el ejemplo (66g) se disolvió en diclorometano (15 mL), y se le

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agregó (R)-(-)-1-amino-2-propanol (196 μL, 2.48 mmol), WSCI·HCl (366 mg, 1.91 mmol) y 4-dimetilaminopiridina (228 mg, 1.87 mmol), seguido por agitación a temperatura ambiente durante 18 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó ácido clorhídrico 0.25 N (100 mL) y se extrajo con acetato de etilo (100 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/diclorometano = 3%-9%), para producir el compuesto deseado como un sólido blanco (486 mg, rendimiento de 75%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.22 (3H, d, J = 6.3 Hz), 1.30 (3H, d, J = 6.3 Hz), 2.33-2.41 (2H, m), 2.77 (1H, d, J = 3.9 Hz), 3.22-3.29 (1H, m), 3.41 (3H, s), 3.50 (1H, dd, J = 10.2, 3.9 Hz), 3.55-3.62 (2H, m), 3.94-4.01 (1H, br m), 4.20-4.26 (2H, br m), 4.33-4.39 (2H, br m), 4.51-4.59 (1H, m), 6.43-6.46 (2H, m), 6.51 (1H, t, J = 2.2 Hz), 6.62 (1H, dd, J = 3.9, 2.3 Hz), 6.80 (1H, t, J = 1.8 Hz), 6.91 (1H, t, J = 1.8 Hz), 7.04 (1H, t, J = 8.2 Hz), 7.37 (1H, d, J = 8.6 Hz), 7.50 (1H, dd, J = 11.3,2.0 Hz), 9.80 (1H, br s).

MS (FAB) m/z: 526 $(M+H)^+$.

(69b) (5S)-2-(5-{3-[4-(Azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol

La 5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-N-[(2R)-2-hidroxipropil]-1H-pirrol-2-carboxamida (464 mg, 0.883 mmol) sintetizada en el ejemplo (69a) se disolvió en tetrahidrofurano (17

mL), y se le agregó ácido metanosulfónico anhidro (558 mg, 3.20 mmol) y trietilamina (860 μL, 6.20 mmol), seguido por agitación a temperatura ambiente durante 3 días bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/diclorometano = 3%-9%), para producir el compuesto deseado como un sólido blanco (228 mg, rendimiento de 51%).

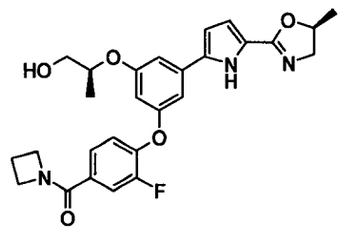
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J = 6.3 Hz), 1.43 (3H, d, J = 6.3 Hz), 2.34-2.41 (2H, m), 3.41 (3H, s), 3.50 (1H, dd, J = 10.2, 3.9 Hz), 3.52-3.59 (2H, m), 4.08 (1H, dd, J = 13.9, 9.2 Hz), 4.22-4.26 (2H, br m), 4.35-4.38 (2H, br m), 4.53-4.60 (1H, m), 4.80-4.89 (1H, m), 6.48 (1H, d, J = 3.9 Hz), 6.51 (1H, t, J = 2.2 Hz), 6.77 (1H, d, J = 3.9 Hz), 6.79 (1H, t, J = 1.8 Hz), 6.93 (1H, s), 7.05 (1H, t, J = 8.2 Hz), 7.37-7.40 (1H, m), 7.51 (1H, dd, J = 10.9, 2.0 Hz).

MS (ESI) m/z: 508.22382 $(M+H)^+$.

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EJEMPLO 70

(2S)-2-(3-[4-(Azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)propan-1-ol



El (5S)-2-(5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol (337.8 mg, 0.666 mmol) sintetizado en el ejemplo (69b) se disolvió en diclorometano (10 mL), y se le agregó una solución de tribromuro de boro/diclorometano (1M, 1 mL, 1 mmol) a -78°C y bajo una atmósfera de nitrógeno, seguido por agitación a temperatura ambiente durante 1 hora. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/diclorometano = 2%-8%), para producir el compuesto deseado como un sólido amarillo pálido (93.7 mg, rendimiento de 29%).

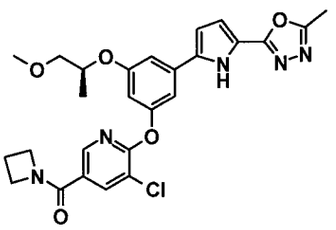
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.26 (3H, d, J = 6.3 Hz), 1.43 (3H, d, J = 6.3 Hz), 2.33-2.41 (2H, m), 3.55 (1H, dd, J = 13.7, 7.4 Hz), 3.73-3.81 (2H, m), 4.08 (1H, dd, J = 13.7, 9.4 Hz), 4.22-4.26 (2H, br m), 4.33-4.37 (2H,

br m), 4.56-4.64 (1H, m), 4.81-4.90 (1H, m), 6.30 (1H, t, J = 2.2 Hz), 6.44 (1H, d, J = 3.9 Hz), 6.74-6.76 (2H, m), 6.86 (1H, s), 7.00 (1H, t, J = 8.2 Hz), 7.34-7.37 (1H, m), 7.49 (1H, dd, J = 10.9, 2.0 Hz).

MS (ESI) m/z: 494.20864 $(M+H)^+$.

EJEMPLO 71

5-(Azetidin-1-ilcarbonil)-3-cloro-2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]fenoxi}piridina



(71a) Acido 5-(3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(1S)-2-metoxi-1-metiletoxi]fenil)-1H-pirrol-2-carboxílico

El 5-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-1,2-dicarboxilato de 2-bencilo-1-t-butilo (5.21 g, 10.82 mmol) sintetizado en el ejemplo (66c), y la 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina (2.55 g, 11.04 mmol) sintetizada en el ejemplo (60a), se disolvieron en acetonitrilo (100 mL) y se les agregó carbonato de potasio (4.30 g, 31.11 mmol), seguido por agitación durante 1 día con calentamiento a reflujo bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (200 mL) y se extrajo con acetato de etilo (200 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre

sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 75%-90%).

El compuesto resultante se disolvió en ácido trifluoroacético (15 mL) y se agitó a temperatura ambiente durante 1.5 horas bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 75%-90%).

El compuesto resultante se disolvió en tetrahidrofurano (20 mL) y se le agregó paladio carbón (800mg), seguido por agitación a temperatura ambiente durante 4 horas bajo una atmósfera de hidrógeno. Después de filtración en Celite, el disolvente se removió por destilación. Al residuo resultante se le agregó una solución acuosa saturada de carbonato ácido de sodio (30 mL) y se extrajo con éter dietílico. A la capa acuosa resultante se le agregó ácido clorhídrico 2N (50 mL) y se extrajo con acetato de etilo. La capa orgánica resultante se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida para producir el compuesto deseado como un sólido blanco (3.52 g, rendimiento de 67%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.35 (3H, d, J = 6.3 Hz), 2.35-2.42 (2H, m), 3.45 (3H, s), 3.54 (1H, dd, J = 10.0, 4.1 Hz), 3.65 (1H, dd, J = 10.4, 6.1 Hz), 4.24 (2H, t, J = 7.6 Hz), 4.35 (2H, t, J = 6.3 Hz), 4.65-4.71 (1H, m),

6.53 (1H, dd, J = 3.5, 2.7 Hz), 6.70 (1H, t, J = 2.2 Hz), 7.01-7.02 (2H, br m), 7.21 (1H, s), 8.16 (1H, d, J = 2.3 Hz), 8.27 (1H, d, J = 2.0 Hz), 9.97 (1H, br s).

(71b) 5-(Azetidin-1-ilcarbonil)-3-cloro-2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]fenoxi}piridina

El ácido 5-(3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(1S)-2-metoxi-1-metiletoxi]fenil)-1H-pirrol-2-carboxílico (600 mg, 1.23 mmol) sintetizado en el ejemplo (71a) se disolvió en diclorometano (15 mL), y se le agregó acetohidrazida (200 mg, 2.70 mmol), WSCI·HCl (510 mg, 2.66 mmol) y 4-dimetilaminopiridina (300 mg, 2.46 mmol), seguido por agitación a temperatura ambiente durante 1 día bajo una atmósfera de nitrógeno. Se le agregó una solución acuosa saturada de cloruro de amonio (100 mL) y se extrajo con diclorometano (100 mL). La capa orgánica se lavó con salmuera saturada; subsiguientemente se secó sobre sulfato de magnesio anhidro y el disolvente se removió por destilación bajo presión reducida.

Este residuo se disolvió en diclorometano (15 mL) y se le agregó cloruro de p-toluenosulfonilo (500 mg, 2.62 mmol) y trietilamina (1.0 mL, 7.17 mmol), seguido por agitación a temperatura ambiente durante 5 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo con diclorometano (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución:

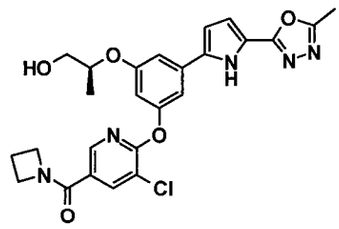
acetato de etilo), para producir el compuesto deseado como un sólido blanco (520 mg, rendimiento de 81%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.35 (3H, d, J = 6.3 Hz), 2.35-2.43 (1H, m), 2.59 (3H, s), 3.42 (3H, s), 3.52 (1H, dd, J = 10.2, 4.3 Hz), 3.61 (1H, dd, J = 10.2, 5.9 Hz), 4.24 (2H, t, J = 7.4 Hz), 4.37 (2H, t, J = 7.6 Hz), 4.56-4.62 (1H, m), 6.58 (1H, dd, J = 3.9, 2.7 Hz), 6.70 (1H, t, J = 2.2 Hz), 6.85 (1H, dd, J = 3.9, 2.3 Hz), 6.96 (1H, t, J = 1.6 Hz), 7.05 (1H, t, J = 2.0 Hz), 8.17 (1H, d, J = 2.0 Hz), 8.27 (1H, d, J = 2.0 Hz), 9.57 (1H, br s).

MS (ESI) m/z: 524.17210 $(M+H)^+$.

EJEMPLO 72

(2S)-2-(3-{[5-(Azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]fenoxi)propan-1-ol



La 5-(azetidin-1-ilcarbonil)-3-cloro-2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]fenoxi}piridina (370 mg, 0.706 mmol) sintetizada en el ejemplo (71b) se disolvió en diclorometano (10 mL), y se le agregó a gotas a -78°C tribromuro de boro (solución en diclorometano 1.0 mol/L, 1.10 mL, 1.10 mmol), seguido por agitación a temperatura ambiente durante 1 hora bajo una atmósfera de nitrógeno. A esta

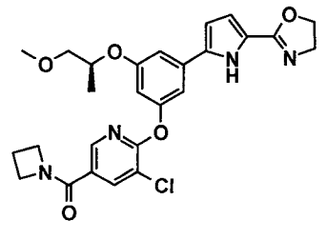
solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (20 mL) y se extrajo con diclorometano (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/diclorometano = 1%-3%), para producir el compuesto deseado como un sólido blanco (205 mg, rendimiento de 57%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.30 (3H, d, J = 6.3 Hz), 1.78 (1H, d, J = 7.8 Hz), 2.34-2.42 (2H, m), 2.57 (3H, s), 2.71-2.87 (1H, m), 3.73-3.80 (2H, m), 4.23 (2H, t, J = 7.6 Hz), 4.35 (2H, t, J = 7.4 Hz), 4.52-4.58 (1H, m), 6.56 (1H, t, J = 2.9 Hz), 6.64 (1H, d, J = 1.6 Hz), 6.84 (1H, dd, J = 3.9, 2.3 Hz), 6.96 (1H, t, J = 1.8 Hz), 7.01 (1H, t, J = 1.8 Hz), 8.16 (1H, d, J = 2.0 Hz), 8.26 (1H, d, J = 2.3 Hz), 9.92 (1H, s).

MS (ESI) m/z: 510.15468 $(M+H)^+$.

EJEMPLO 73

5-(Azetidin-1-ilcarbonil)-3-cloro-2-{3-[5-(4,5-dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi}piridina



(73a) 5-(3-{[5-(Azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(1S)-2-metoxi-1-metiletoxi]fenil)-N-(2-cloroetil)-1H-pirrol-2-carboxamida

El ácido 5-(3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(1S)-2-metoxi-1-metiletoxi]fenil)-1H-pirrol-2-carboxílico (800 mg, 1.65 mmol) sintetizado en el ejemplo (71a) se disolvió en diclorometano (10.0 mL), y se le agregó clorhidrato de 2-cloroetilamina (300 mg, 2.59 mmol), WSCI·HCl (630 mg, 3.29 mmol) y 4-dimetilaminopiridina (400 mg, 3.27 mmol), seguido por agitación a temperatura ambiente bajo una atmósfera de nitrógeno durante 2.5 días. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo con diclorometano (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo), para producir el compuesto deseado como un sólido blanco (210 mg, rendimiento de 23%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 2.35-2.42

(2H, m), 3.42 (3H, s), 3.51 (1H, dd, J = 10.6, 4.7 Hz), 3.60 (1H, dd, J = 10.2, 5.9 Hz), 3.68-3.73 (2H, m), 3.75-3.80 (2H, m), 4.24 (2H, t, J = 7.8 Hz), 4.36 (2H, t, J = 7.0 Hz), 4.55-4.60 (1H, m), 6.27 (1H, t, J = 5.7 Hz), 6.50 (1H, dd, J = 3.9, 2.7 Hz), 6.63 (1H, dd, J = 3.7, 2.5 Hz), 6.68 (1H, t, J = 2.2 Hz), 6.95 (1H, t, J = 1.8 Hz), 7.03 (1H, t, J = 1.8 Hz), 8.16 (1H, d, J = 2.3 Hz), 8.26 (1H, d, J = 2.0 Hz), 9.55 (1H, br s).

(73b) 5-(Azetidin-1-ilcarbonil)-3-cloro-2-{3-[5-(4,5-dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi}piridina

La 5-(3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(1S)-2-metoxi-1-metiletoxi]fenil)-N-(2-cloroetil)-1H-pirrol-2-carboxamida (210 mg, 0.384 mmol) sintetizada en el ejemplo (73a) se disolvió en tetrahidrofurano (10.0 mL), y se le agregó hidruro de sodio (60%, 80 mg, 2.00 mmol), seguido por agitación a temperatura ambiente durante 7.5 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo con diclorometano (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo), para producir el compuesto deseado como un sólido blanco (120 mg, rendimiento de 62%).

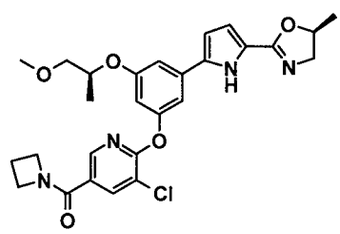
^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 2.35-2.42 (2H, m), 3.41 (3H, s), 3.50 (1H, dd, J = 10.3, 4.4 Hz), 3.60 (1H, dd, J = 10.3,

5.9 Hz), 4.00 (2H, t, J = 9.3 Hz), 4.24 (2H, t, J = 6.8 Hz), 4.36 (2H, t, J = 6.3 Hz), 4.40 (2H, t, J = 9.3 Hz), 4.55-4.61 (1H, m), 6.50 (1H, d, J = 3.9 Hz), 6.66 (1H, t, J = 2.0 Hz), 6.75 (1H, d, J = 3.9 Hz), 6.94 (1H, s), 7.04 (1H, t, J = 5.1 Hz), 8.15 (1H, d, J = 2.0 Hz), 8.26 (1H, d, J = 2.0 Hz).

MS (ESI) m/z: 511.17658 $(M+H)^+$.

EJEMPLO 74

5-(Azetidin-1-ilcarbonil)-3-cloro-2-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)piridina



El ácido 5-(3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(1S)-2-metoxi-1-metiletoxi]fenil)-1H-pirrol-2-carboxílico (800 mg, 1.65 mmol) sintetizado en el ejemplo (71a) se disolvió en diclorometano (15 mL), y se le agregó (R)-(-)-1-amino-2-propanol (0.35 mL, 4.45 mmol), WSCI·HCl (630 mg, 3.29 mmol) y 4-dimetilaminopiridina (800 mg, 6.55 mmol), seguido por agitación a temperatura ambiente durante 8 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo con diclorometano (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por

destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice para producir un sólido amarillo (disolvente de elución: metanol/diclorometano = 3%-8%).

Este se disolvió en tetrahidrofurano (15 mL) y se le agregó ácido metanosulfónico anhidro (500 mg, 2.87 mmol) y trietilamina (0.80 mL, 5.74 mmol), seguido por agitación a temperatura ambiente durante la noche bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo con diclorometano (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo), para producir el compuesto deseado como un sólido amarillo (520 mg, rendimiento de 60%).

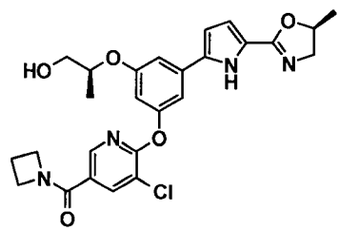
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 1.43 (3H, d, J = 6.3 Hz), 2.35-2.42 (2H, m), 3.41 (3H, s), 3.45-3.64 (3H, m), 4.08-4.12 (1H, m), 4.23 (2H, t, J = 7.0 Hz), 4.36 (2H, t, J = 8.4 Hz), 4.54-4.62 (1H, m), 4.84-4.87 (1H, m), 6.51 (1H, d, J = 3.5 Hz), 6.66 (1H, t, J = 2.2 Hz), 6.75-6.78 (1H, m), 6.94 (1H, s), 7.02-7.09 (1H, m), 8.16 (1H, d, J = 2.0 Hz), 8.26 (1H, d, J = 2.0 Hz).

MS (ESI) m/z: 525.19126 $(M+H)^+$.

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EJEMPLO 75

(2S)-2-(3-{[5-(Azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)propan-1-ol



La 5-(azetidin-1-ilcarbonil)-3-cloro-2-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-piridina (320 mg, 0.610 mmol) sintetizada en el ejemplo 74 se disolvió en diclorometano (10 mL), y se le agregó a gotas a -78°C tribromuro de boro (solución en diclorometano 1.0 mol/L, 0.92 mL, 0.92 mmol), seguido por agitación a temperatura ambiente durante 1 hora bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (20 mL) y se extrajo con diclorometano (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/diclorometano = 1%-3%), para producir el compuesto deseado como un sólido amarillo (165 mg, rendimiento de 53%).

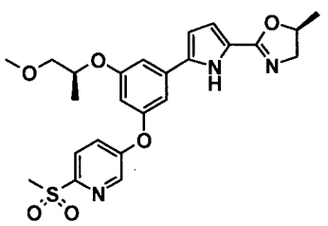
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.28 (3H, d, J = 6.3 Hz), 1.40 (3H, d, J = 5.9 Hz), 2.34-2.42 (2H, m), 3.52 (1H, dd, J = 13.7, 7.4 Hz), 3.76 (2H, d, J

= 5.5 Hz), 4.06 (1H, dd, J = 13.9, 9.2 Hz), 4.23 (2H, t, J = 7.8 Hz), 4.34 (2H, t, J = 7.4 Hz), 4.51-4.60 (1H, m), 4.76-4.86 (1H, m), 6.44 (1H, d, J = 3.1 Hz), 6.53 (1H, s), 6.72 (1H, d, J = 3.5 Hz), 6.87-6.92 (2H, m), 8.15 (1H, d, J = 2.0 Hz), 8.23 (1H, d, J = 1.2 Hz), 10.05 (1H, br s).

MS (ESI) m/z: 511.17339 $(M+H)^+$.

EJEMPLO 76

5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-2-(metilsulfonil)piridina



(76a) 5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxilato de bencilo

El 5-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-1,2-dicarboxilato de 2-bencilo-1-t-butilo (5.05 g, 10.49 mmol) sintetizado en el ejemplo (66c), y la 5-fluoro-2-(metilsulfonil)piridina (2.05 g, 11.70 mmol) sintetizada en el ejemplo (65b), se disolvieron en N,N-dimetilformamida (30 mL), y se les agregó carbonato de potasio (4.50 g, 32.56 mmol), seguido por agitación a 80°C durante 3 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (150 mL) y se extrajo con éter dietílico (150 mL). La capa orgánica se lavó

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con salmuera saturada; subsiguientemente se secó sobre sulfato de magnesio anhidro y el disolvente se removió por destilación bajo presión reducida.

El compuesto resultante se disolvió en ácido trifluoroacético (10 mL) y se agitó a temperatura ambiente durante 1 hora bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 35%-50%), para producir el compuesto deseado como un aceite blanco (5.08 g, rendimiento de 90%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.51 (1H, dd, J = 10.3, 3.9 Hz), 3.58 (1H, dd, J = 10.3, 6.3 Hz), 4.54-4.61 (1H, m), 5.33 (2H, s), 6.51 (1H, t, J = 3.2 Hz), 6.59 (1H, s), 6.86 (1H, s), 6.99 (1H, t, J = 2.9 Hz), 7.02 (1H, s), 7.32-7.45 (7H, m), 8.04 (1H, d, J = 8.8 Hz), 8.48 (1H, s), 9.36 (1H, br s).

(76b) Acido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxílico

El 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxilato de bencilo (5.08 g, 9.47 mmol) sintetizado en el ejemplo (76a) se disolvió en acetato de etilo (30 mL), y se le agregó un catalizador de paladio al 10% en carbón (1.10 g), seguido por agitación a temperatura ambiente durante 3 horas bajo una atmósfera de hidrógeno. Después de filtración en Celite, el disolvente se removió por destilación bajo presión reducida para producir el compuesto deseado como un sólido blanco (4.30 g, rendimiento de ~100%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 5.9 Hz), 3.23 (3H, s), 3.47 (3H, s), 3.57 (1H, dd, J = 9.8, 3.9 Hz), 3.67 (1H, dd, J = 10.0, 6.6 Hz), 4.72-4.80 (1H, m), 6.52 (1H, s), 6.59 (1H, s), 6.92 (1H, s), 7.03 (1H, s), 7.32 (1H, s), 7.45 (1H, dd, J = 8.5, 1.7 Hz), 8.05 (1H, d, J = 8.8 Hz), 8.49 (1H, d, J = 2.4 Hz), 10.31 (1H, br s).

(76c) 5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-2-(metilsulfonil)piridina

El ácido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxílico (1000 mg, 2.24 mmol) sintetizado en el ejemplo (76b) se disolvió en metanol (20 mL), y se le agregó (R)-(-)-1-amino-2-propanol (0.40 mL, 5.08 mmol) y cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio n-hidratado (1000 mg, 3.61 mmol), seguido por agitación a temperatura ambiente durante la noche bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 1%-3%), para producir un sólido amarillo.

Este se disolvió en tetrahidrofurano (20 mL) y se le agregó ácido metanosulfónico anhidro (600 mg, 3.44 mmol) y trietilamina (0.70 mL, 5.02 mmol), seguido por agitación a temperatura ambiente durante la noche bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con cloruro de metileno (50 mL). La capa orgánica se lavó con salmuera saturada

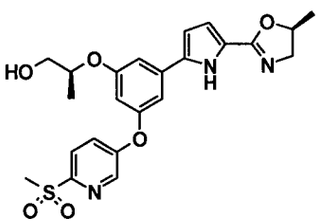
y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 1%-3%), para producir el compuesto deseado como un sólido blanco (450 mg, rendimiento de 41%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 1.43 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.42 (3H, s), 3.49-3.61 (4H, m), 4.09 (1H, dd, J = 13.9, 8.8 Hz), 4.53-4.63 (1H, m), 4.79-4.88 (1H, m), 6.51 (1H, d, J = 3.9 Hz), 6.57 (1H, d, J = 1.6 Hz), 6.76 (1H, d, J = 3.9 Hz), 6.83 (1H, s), 7.02 (1H, s), 7.44 (1H, dd, J = 8.6, 2.3 Hz), 8.05 (1H, d, J = 8.6 Hz), 8.49 (1H, s).

MS (ESI) m/z: 486.17067 $(M+H)^+$.

EJEMPLO 77

(2S)-2-(3-{5-[(5S)-5-Metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol



La 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-2-(metilsulfonil)piridina (310 mg, 0.638 mmol) sintetizada en el ejemplo (76c) se disolvió en cloruro de metileno (7.0 mL), y se le agregó a gotas a -78°C tribromuro de boro (solución en

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diclorometano 1.0 mol/L, 1.00 mL, 1.0 mmol), seguido por agitación a temperatura ambiente durante 1 hora bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (20 mL) y se extrajo con cloruro de metileno (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 1%-3%), para producir el compuesto deseado como un sólido blanco (245 mg, rendimiento de 81%).

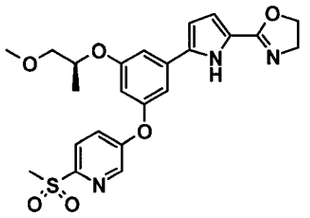
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.29 (3H, d, J = 6.3 Hz), 1.43 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.55 (1H, dd, J = 13.9, 7.2 Hz), 3.79 (2H, d, J = 5.1 Hz), 4.09 (1H, dd, J = 14.1,9.4 Hz), 4.56-4.63 (1H, m), 4.81-4.88 (1H, m), 6.38 (1H, br s), 6.48 (1H, t, J = 3.3 Hz), 6.75 (1H, d, J = 3.5 Hz), 6.80 (1H, br s), 6.96 (1H, br s), 7.39 (1H, br s), 8.03 (1H, d, J = 8.2 Hz), 8.45 (1H, s).

MS (ESI) m/z: 472.15208 $(M+H)^+$.

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EJEMPLO 78

5-{3-[5-(4,5-Dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi}-2-(metilsulfonil)piridina



(78a) 3-Bromo-5-metoxifenol

Se disolvió 1-bromo-3,5-dimetoxibenceno (18.74 g, 86.3 mmol), disponible comercialmente, en 1-metil-2-pirrolidona (100 mL), y se le agregó tiometóxido de sodio (6.74 g, 96.2 mmol), seguido por agitación a 100°C durante 3 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó ácido clorhídrico 1N (200 mL) y se extrajo con éter dietílico (500 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-25%), para producir el compuesto deseado como un sólido blanco (15.03 g, rendimiento de 86%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 3.77 (3H, s), 4.82 (1H, s), 6.33 (1H, t, J = 2.4 Hz), 6.61 (1H, t, J = 2.0 Hz), 6.66 (1H, t, J = 2.0 Hz).

(78b) 1-Bromo-3-metoxi-5-[(1S)-2-metoxi-1-metiletoxi]benceno

El 3-bromo-5-metoxifenol (7.60 g, 37.4 mmol) sintetizado en el

ejemplo (78a) se disolvió en tolueno (100 mL), y se le agregó R-(-)-1-metoxi-2-propanol (4.40 mL, 44.9 mmol) y trifenilfosfina (13.8 g, 52.6 mmol), seguido por la adición de azodicarboxilato de dietilo (solución en tolueno 2.2 mol/l, 24 mL, 52.8 mmol), gota a gota a 0°C, y agitación a temperatura ambiente durante 1.5 horas bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida, se le agregó éter dietílico (100 mL) y el depósito se filtró para removerlo. El licor madre se destiló bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-20%), para producir el compuesto deseado como un líquido incoloro (9.22 g, rendimiento de 89%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.30 (3H, d, J = 6.3 Hz), 3.40 (3H, s), 3.47 (1H, dd, J = 10.6, 4.3 Hz), 3.55 (1H, dd, J = 10.4, 6.1 Hz), 3.76 (3H, s), 4.46-4.52 (1H, m), 6.42 (1H, t, J = 2.2 Hz), 6.65 (1H, dd, J = 2.3, 1.6 Hz), 6.69 (1H, t, J = 2.0 Hz).

MS (EI) m/z: 274 $(M)^+$.

(78c) 3-Bromo-5-[(1S)-2-metoxi-1-metiletoxi]fenol

El 1-bromo-3-metoxi-5-[(1S)-2-metoxi-1-metiletoxi]benceno (9.21 g, 33.5 mmol) sintetizado en el ejemplo (78b) se disolvió en 1-metil-2-pirrolidona (100 mL), y se le agregó tiometóxido de sodio (2.75 g, 37.3 mmol), seguido por agitación a 130°C durante 3 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó ácido clorhídrico 2N (500 mL) y se extrajo con éter dietílico (300 mL).

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La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-25%), para producir el compuesto deseado como un líquido incoloro (8.30 g, rendimiento de 95%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.29 (3H, d, J = 6.3 Hz), 3.41 (3H, s), 3.46 (1H, dd, J = 10.2, 4.3 Hz), 3.55 (1H, dd, J = 10.6, 5.9 Hz), 4.45-4.51 (1H, m), 4.96 (1H, br s), 6.36 (1H, t, J = 2.0 Hz), 6.59 (1H, t, J = 2.0 Hz), 6.68 (1H, t, J = 2.0 Hz).

MS (EI) m/z: 260 $(M)^+$.

(78d) 3-[(1S)-2-Metoxi-1-metiletoxi]-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenol

El 3-bromo-5-[(1S)-2-metoxi-1-metiletoxi]fenol (8.30 g, 31.8 mmol) sintetizado en el ejemplo (78c) se disolvió en N,N-dimetilformamida (100 mL), y se le agregó bis(pinacolato)diboro (10.50 g, 41.3 mmol), complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano (810 mg, 0.992 mmol) y acetato de potasio (15.50 g, 158 mmol), seguido por agitación a 90°C durante 3 horas bajo una atmósfera de nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente, se le agregó agua (500 mL) y se extrajo con éter dietílico (300 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión

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reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-30%), para producir el compuesto deseado como un aceite pardo (8.75 g, rendimiento de 89%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.26 (3H, d, J = 4.1 Hz), 1.33 (12H, s), 3.41 (1H, s), 3.47 (1H, dd, J = 10.2, 4.7 Hz), 3.57 (1H, dd, J = 10.6, 5.9 Hz), 4.52-4.58 (1H, m), 4.80 (1H, brs), 6.55 (1H, t, J = 2.4 Hz), 6.83 (1H, d, J = 2.4 Hz), 6.95 (1H, d, J = 2.4 Hz).

MS (FAB) m/z: 309 $(M+H)^+$.

(78e) 2,5-Dibromo-1H-pirrol-1-carboxilato de t-butilo

Se disolvió 1-pirrolcarboxilato de t-butilo (46.68 g, 279 mmol), disponible comercialmente, en tetrahidrofurano (500 mL), y se enfrió a -78°C. A esto se le agregó N-bromosuccinimida (100.48 g, 565 mmol) en pequeñas porciones durante 1 hora. La temperatura de la solución de reacción se elevó naturalmente, y la solución se agitó a temperatura ambiente durante 18 horas. La solución de reacción se enfrió a 0°C, se le agregó sulfito de sodio (36.43g), seguido por agitación durante 30 minutos, y subsiguientemente se le agregó hexano (200 mL) para producir un precipitado, que se removió por filtración en Celite. El disolvente del filtrado se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 1%-5%), para producir el compuesto deseado como un aceite incoloro (52.69 g, rendimiento de 58%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.65 (9H, s), 6.25 (2H, s).

MS (EI) m/z: 323 (M^+).

(78f) 5-Bromo-1H-pirrol-1,2-dicarboxilato de 2-bencilo-1-t-butilo

El 2,5-dibromo-1H-pirrol-1-carboxilato de t-butilo (10.98 g, 33.8 mmol) sintetizado en el ejemplo (78e) se disolvió en éter dietílico (135 mL) y se enfrió a -78°C. Lentamente se le agregó n-butil-litio (solución en hexano 2.77 mol/L, 12.8 mL, 35.5 mmol), gota a gota, y se agitó durante 1 hora. A la solución de reacción se le agregó lentamente, gota a gota, cloroformiato de bencilo (6.25 mL, 44.0 mmol), y se agitó durante 30 minutos. Con la temperatura de la solución de reacción elevándose gradualmente a la temperatura ambiente, se agitó durante 1 hora. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (200 mL) y éter dietílico (300 mL), y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 5%-45%), para producir el compuesto deseado como un aceite pardo rojizo (8.80 g, rendimiento de 68%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.56 (9H, s), 5.26 (2H, s), 6.21 (1H, d, J = 3.9 Hz), 6.85 (1H, d, J = 3.9 Hz), 7.28-7.39 (5H, m).

MS (FAB) m/z: 380 $(M+H)^+$.

(78g) 5-{3-Hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-1,2-dicarboxilato de 2-bencilo-1-t-butilo

El 5-bromo-1H-pirrol-1,2-dicarboxilato de 2-bencilo-1-t-butilo (8.75 g, 23.0 mmol) sintetizado en el ejemplo (78f), y el 3-[(1S)-2-metoxi-1-metiletoxi]-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenol (7.11 g, 23.1 mmol) sintetizado en el ejemplo (78d), se disolvieron en un disolvente mixto de 1,4-dioxano (92 mL) y agua (23 mL), y se les agregó complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano (570 mg, 0.698 mmol) y carbonato de potasio (7.95 g, 57.5 mmol), seguido por agitación a 55°C durante 3 horas bajo una atmósfera de nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente, se le agregó agua (200 mL) y se extrajo con acetato de etilo (200 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 15%-35%), para producir el compuesto deseado como un aceite pardo (8.32 g, rendimiento de 75%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.29 (3H, d, J = 6.3 Hz), 1.41 (9H, s), 3.40 (3H, s), 3.47 (1H, dd, J = 10.3, 4.4 Hz), 3.57 (1H, dd, J = 10.3, 5.9 Hz), 4.48-4.54 (1H, m), 5.20 (1H, s), 5.30 (2H, s), 6.17 (1H, d, J = 3.4 Hz), 6.44 (1H, s), 6.48 (1H, s), 6.57 (1H, s), 6.94 (1H, d, J = 3.4 Hz), 7.42-7.31 (5H, m).

MS (FAB) m/z: 481 (M^+).

(78h) 5-Bromo-2-(metiltio)piridina

Se disolvió 2,5-dibromo-piridina (6.01 g, 25.4 mmol), disponible comercialmente, en N,N-dimetilformamida (50 mL), y se le agregó tiometóxido de sodio (2.20 g, 31.4 mmol), seguido por agitación a 0°C durante 3.5 horas bajo una atmósfera de nitrógeno. La solución de reacción se llevó de vuelta a la temperatura ambiente, se le agregó agua (250 mL) y se extrajo con éter dietílico (250 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 3%-5%), para producir el compuesto deseado como un sólido blanco (4.90 g, rendimiento de 94%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.54 (3H, s), 7.08 (1H, d, J = 8.2 Hz), 7.58 (1H, dd, J = 8.6, 2.3 Hz), 8.49 (1H, d, J = 2.0 Hz).

(78i) 5-Fluoro-2-(metilsulfonil)piridina

La 5-bromo-2-(metiltio)piridina (4.90 g, 24.0 mmol) sintetizada en el ejemplo (78h) se disolvió en tetrahidrofurano (100 mL), y se le agregó a gotas a -78°C n-butil-litio (solución en hexano 1.57 mol/L, 17.0 mL, 26.7 mmol), seguido por agitación a -78°C durante 1 hora, bajo una atmósfera de nitrógeno. Se disolvió N-fluorobencenosulfonimida (11.0 g, 34.9 mmol) en tetrahidrofurano (25 mL), seguido por su adición a gotas a la solución de reacción a -78°C, y se agitó a -78°C durante 2 horas bajo una atmósfera de nitrógeno. La solución de reacción se llevó de vuelta a la temperatura

ambiente y se agitó durante 1.5 horas. Se le agregó una solución acuosa saturada de cloruro de amonio (200 mL) y se extrajo con éter dietílico (300 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión ligeramente reducida.

El residuo resultante se disolvió en cloruro de metileno (150 mL), y se le agregó lentamente ácido m-cloroperbenzoico (65%, 16.5 g, 62.1 mmol) a 0°C, seguido por agitación a 0°C durante 1.5 horas bajo una atmósfera de nitrógeno. Después de que el material sólido blanco se removió por filtración en Celite, se le agregó una solución acuosa saturada de carbonato ácido de sodio (100 mL) y se extrajo con cloruro de metileno (400 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 3%-5%), para producir el compuesto deseado como un sólido blanco amarillento (1.95 g, rendimiento de 46%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 3.24 (3H, s), 7.67 (1H, ddd, J = 9.9, 6.9, 1.9 Hz), 8.16 (1H, dd, J = 8.6, 4.3 Hz), 8.59 (1H, d, J = 2.7 Hz).

(78j) 5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxilato de bencilo

El 5-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-1,2-dicarboxilato de 2-bencilo-1-t-butilo (5.05 g, 10.49 mmol) sintetizado en el

ejemplo (78g), y la 5-fluoro-2-(metilsulfonil)piridina (2.05 g, 11.70 mmol) sintetizada en el ejemplo (78i), se disolvieron en N,N-dimetilformamida (30 mL), y se les agregó carbonato de potasio (4.50 g, 32.56 mmol), seguido por agitación a 80°C durante 3 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (150 mL) y se extrajo con éter dietílico (150 mL). La capa orgánica se lavó con salmuera saturada, subsiguientemente se secó sobre sulfato de magnesio anhidro, y el disolvente se removió por destilación bajo presión reducida.

El compuesto resultante se disolvió en ácido trifluoroacético (10 mL) y se agitó a temperatura ambiente durante 1 hora bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 35%-50%), para producir el compuesto deseado como un aceite blanco (5.08 g, rendimiento de 90%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.51 (1H, dd, J = 10.3, 3.9 Hz), 3.58 (1H, dd, J = 10.3, 6.3 Hz), 4.54-4.61 (1H, m), 5.33 (2H, s), 6.51 (1H, t, J = 3.2 Hz), 6.59 (1H, s), 6.86 (1H, s), 6.99 (1H, t, J = 2.9 Hz), 7.02 (1H, s), 7.32-7.45 (7H, m), 8.04 (1H, d, J = 8.8 Hz), 8.48 (1H, s), 9.36 (1H, br s).

(78k) Acido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxílico

El 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxilato de bencilo (5.08 g, 9.47 mmol) sintetizado

en el ejemplo (78j) se disolvió en acetato de etilo (30 mL), y se le agregó un catalizador de paladio al 10% en carbón (1.10 g), seguido por agitación a temperatura ambiente durante 3 horas bajo una atmósfera de hidrógeno. Después de filtración en Celite, el disolvente se removió por destilación bajo presión reducida para producir el compuesto deseado como un sólido blanco (4.30 g, rendimiento de ~100%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 5.9 Hz), 3.23 (3H, s), 3.47 (3H, s), 3.57 (1H, dd, J = 9.8, 3.9 Hz), 3.67 (1H, dd, J = 10.0, 6.6 Hz), 4.72-4.80 (1H, m), 6.52 (1H, s), 6.59 (1H, s), 6.92 (1H, s), 7.03 (1H, s), 7.32 (1H, s), 7.45 (1H, dd, J = 8.5, 1.7 Hz), 8.05 (1H, d, J = 8.8 Hz), 8.49 (1H, d, J = 2.4 Hz), 10.31 (1H, br s).

(78l) 5-{3-[5-(4,5-Dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi}-2-(metilsulfonil)piridina

El ácido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxílico (1.00 g, 2.24 mmol) sintetizado en el ejemplo (78k) se disolvió en metanol (20 mL), y se le agregó etanolamina (0.30 mL, 4.97 mmol) y cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio n-hidratado (1.00 g, 3.61 mmol), seguido por agitación a temperatura ambiente durante 1 día bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 1%-3%), para producir un compuesto como un sólido blanco.

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Este se disolvió en tetrahidrofurano (20 mL) y se le agregó ácido metanosulfónico anhidro (700 mg, 4.02 mmol) y trietilamina (0.85 mL, 6.10 mmol), seguido por agitación a 50°C durante 5 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo con cloruro de metileno (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 1%-3%), para producir el compuesto deseado como un sólido blanco (410 mg, rendimiento de 39%).

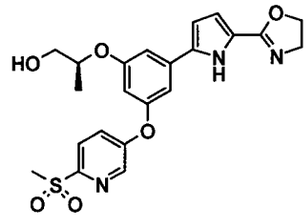
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 10.2, 3.9 Hz), 3.59 (1H, dd, J = 10.6, 6.3 Hz), 4.00 (2H, t, J = 9.2 Hz), 4.43 (2H, t, J = 9.4 Hz), 4.55-4.61 (1H, m), 6.51 (1H, d, J = 3.5 Hz), 6.57 (1H, t, J = 2.2 Hz), 6.77 (1H, d, J = 3.9 Hz), 6.84 (1H, t, J = 1.8 Hz), 7.03 (1H, t, J = 1.6 Hz), 7.44 (1H, dd, J = 8.6, 2.7 Hz), 8.05 (1H, d, J = 8.6 Hz), 8.49 (1H, d, J = 2.7 Hz).

MS (ESI) m/z: 472.15408 $(M+H)^+$.

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EJEMPLO 79

(2S)-2-(3-[5-(4,5-Dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol



La 5-{3-[5-(4,5-dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi}-2-(metilsulfonil)piridina (230 mg, 0.49 mmol) sintetizada en el ejemplo (78l) se disolvió en cloruro de metileno (10 mL), y se le agregó a gotas a -78°C tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 0.75 mL, 0.75 mmol), seguido por agitación a temperatura ambiente durante 1.5 horas bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (20 mL) y se extrajo con cloruro de metileno (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 2%-4%), para producir el compuesto deseado como un sólido blanco (170 mg, rendimiento de 76%).

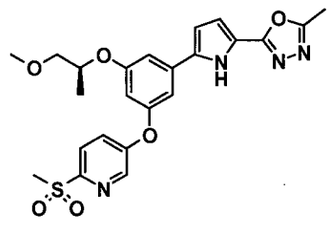
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.30 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.79 (2H, d, J = 5.9 Hz), 4.01 (2H, t, J = 9.4 Hz), 4.43 (2H, t, J = 9.4 Hz),

4.55-4.61 (1H, m), 6.44 (1H, t, J = 2.2 Hz), 6.49 (1H, d, J = 3.9 Hz), 6.76 (1H, d, J = 3.5 Hz), 6.81 (1H, t, J = 2.0 Hz), 6.96 (1H, s), 7.40 (1H, dd, J = 8.6, 2.3 Hz), 8.04 (1H, d, J = 8.6 Hz), 8.46 (1H, d, J = 2.3 Hz).

MS (ESI) m/z: 458.13852 $(M+H)^+$.

EJEMPLO 80

5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]fenoxi}-2-(metilsulfonil)piridina



El ácido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxílico (600 mg, 1.34 mmol) sintetizado en el ejemplo (78k) se disolvió en cloruro de metileno (20 mL), y se le agregó acetohidrazida (220 mg, 2.97 mmol), WSCI·HCl (580 mg, 3.03 mmol) y 4-dimetilaminopiridina (150 mg, 1.23 mmol), seguido por agitación a temperatura ambiente durante la noche bajo una atmósfera de nitrógeno. Se le agregó una solución acuosa saturada de cloruro de amonio (100 mL) y se extrajo con cloruro de metileno (100 mL). La capa orgánica se lavó con salmuera saturada, subsiguientemente se secó sobre sulfato de magnesio anhidro y el disolvente se removió por destilación bajo presión reducida.

Este residuo se disolvió en cloruro de metileno (20 mL) y se le

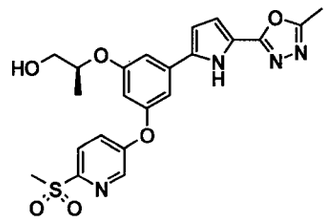
agregó cloruro de p-toluenosulfonilo (510 mg, 2.68 mmol) y trietilamina (0.75 mL, 5.38 mmol), seguido por agitación a temperatura ambiente durante 4 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con cloruro de metileno (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 60-80%), para producir el compuesto deseado como un sólido blanco (450 mg, rendimiento de 69%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.35 (3H, d, J = 6.3 Hz), 2.59 (3H, s), 3.24 (3H, s), 3.42 (3H, s), 3.52 (1H, dd, J = 10.6, 3.5 Hz), 3.61 (1H, dd, J = 11.3, 5.5 Hz), 4.51-4.72 (1H, m), 6.59-6.61 (2H, br m), 6.87-6.90 (2H, br m), 7.06 (1H, br s), 7.46 (1H, d, J = 8.6 Hz), 8.06 (1H, d, J = 8.6 Hz), 8.50 (1H, d, J = 1.6 Hz), 9.66 (1H, br s).

MS (ESI) m/z: 485.14739 $(M+H)^+$.

EJEMPLO 81

(2S)-2-(3-[5-(5-Metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol



La 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]fenoxi}-2-(metilsulfonil)piridina (320 mg, 0.660 mmol) sintetizada en el ejemplo 80 se disolvió en cloruro de metileno (10 mL), y se le agregó a gotas a -78°C tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 1.00 mL, 1.00 mmol), y se agitó a temperatura ambiente durante 1 hora bajo una atmósfera de nitrógeno. A esta solución de reacción, se le agregó una solución acuosa saturada de cloruro de amonio (20 mL) y se extrajo con cloruro de metileno (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 1%-3%), para producir el compuesto deseado como un sólido amarillo (190 mg, rendimiento de 61%).

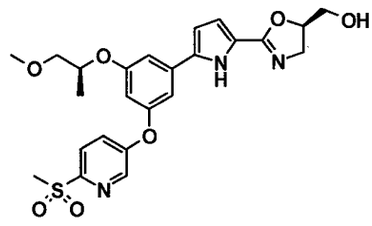
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.29 (3H, d, J = 6.3 Hz), 2.34 (1H, br s), 2.55 (3H, s), 3.21 (3H, s), 3.76 (2H, br s), 4.49-4.58 (1H, m), 6.52 (1H, s), 6.55 (1H, dd, J = 3.9, 2.7 Hz), 6.81-6.84 (2H, m), 7.00 (1H, t, J = 2.0 Hz),

7.42 (1H, dd, J = 8.6, 2.7 Hz), 8.03 (1H, d, J = 8.6 Hz), 8.45 (1H, d, J = 2.7 Hz), 9.76 (1H, br s).

MS (ESI) m/z: 471.13599 $(M+H)^+$.

EJEMPLO 82

{(5R)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol



(82a) 5-(3-{[(2S)-1-Metoxipropan-2-il]oxi}-5-{5-[(5R)-5-{[(tripropan-2-ilsilil)oxi]metil}-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-2-(metilsulfonil)piridina

El ácido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxílico (1.70 g, 3.81 mmol) sintetizado en el ejemplo (78k) se disolvió en metanol (30 mL), y se le agregó (S)-(-)-3-amino-1,2-propanodiol (0.80 g, 8.78 mmol) y cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio n-hidratado (1.70 g, 6.14 mmol), seguido por agitación a temperatura ambiente durante 3 días bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 7%-10%), para producir

un sólido amarillo.

Este se disolvió en cloruro de metileno (40 mL) y se le agregó triisopropilclorosilano (1.32 mL, 6.17 mmol), 4-dimetilaminopiridina (0.75 g, 6.14 mmol) y trietilamina (2.87 mL, 20.59 mmol), seguido por agitación a temperatura ambiente durante 1 día, bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con cloruro de metileno (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice para producir un sólido amarillo (disolvente de elución: metanol/cloruro de metileno = 1%).

Este se disolvió en tetrahidrofurano (30 mL) y se le agregó ácido metanosulfónico anhidro (1.05 g, 6.03 mmol) y trietilamina (1.70 mL, 12.20 mmol), seguido por agitación a 50°C durante 4.5 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con cloruro de metileno (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-70%), para producir el compuesto deseado como un sólido amarillo pálido (1.18 g, rendimiento de 47%).

739

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 0.99-1.16 (21H, m), 1.32 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.40 (3H, s), 3.50 (1H, dd, J = 10.3, 3.9 Hz), 3.58 (1H, dd, J = 10.3, 5.9 Hz), 3.81-3.90 (2H, m), 3.92-4.01 (2H, m), 4.51-4.62 (1H, br s), 4.70-4.78 (1H, br s), 6.49 (1H, d, J = 3.9 Hz), 6.56 (1H, s), 6.72 (1H, t, J = 2.0 Hz), 6.83 (1H, s), 7.01 (1H, s), 7.43 (1H, dd, J = 7.6, 1.7 Hz), 8.04 (1H, d, J = 8.3 Hz), 8.48 (1H, d, J = 2.4 Hz).

(82b) {(5R)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}-metanol

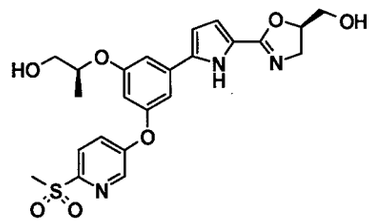
La 5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{5-[(5R)-5-{[(tripropan-2-ilsilil)oxi]metil}-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-2-(metilsulfonil)-piridina (1.18 g, 1.79 mmol) sintetizada en el ejemplo (82a) se disolvió en tetrahidrofurano (10 mL), y se le agregó fluoruro de tetrabutilamonio (solución en tetrahidrofurano 1.0 mol/L, 2.00 mL, 2.00 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante 30 minutos bajo una atmósfera de nitrógeno. A esta solución de reacción, se le agregó una solución acuosa saturada de cloruro de amonio (20 mL) y se extrajo con cloruro de metileno (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 2%-3%), para producir el compuesto deseado como un sólido blanco (680 mg, rendimiento de 76%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.27 (3H, d, J = 6.3 Hz), 3.21 (3H, s), 3.40 (3H, s), 3.48 (1H, dd, J = 10.2, 3.9 Hz), 3.56 (1H, dd, J = 10.2, 6.3 Hz), 3.68 (1H, dd, J = 12.1, 5.1 Hz), 3.75 (1H, dd, J = 14.5, 7.4 Hz), 3.85 (1H, d, J = 9.4 Hz), 4.00 (1H, dd, J = 14.1, 9.8 Hz), 4.53 (1H, br s), 4.78 (1H, br s), 6.46 (1H, d, J = 3.9 Hz), 6.55 (1H, t, J = 2.2 Hz), 6.72 (1H, d, J = 3.9 Hz), 6.81 (1H, d, J = 2.0 Hz), 6.97 (1H, s), 7.42 (1H, dd, J = 8.6, 2.7 Hz), 8.03 (1H, d, J = 8.6 Hz), 8.46 (1H, d, J = 2.7 Hz).

MS (ESI) m/z: 502.16243 $(M+H)^+$.

EJEMPLO 83

(2S)-2-(3-{5-[(5R)-5-(Hidroximetil)-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol



El {(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol (520 mg, 1.04 mmol) sintetizado en el ejemplo (82b) se disolvió en cloruro de metileno (10 mL), y se le agregó a gotas a -78°C tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 2.00 mL, 2.00 mmol), seguido por agitación a temperatura ambiente durante 4 horas bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa de hidróxido de

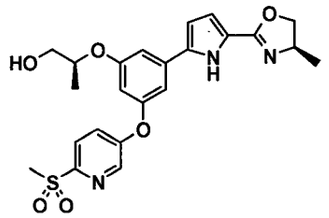
sodio 1N (20 mL) y se extrajo con cloruro de metileno (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 3%-5%), para producir el compuesto deseado como un sólido blanco (148 mg, rendimiento de 29%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.30 (3H, d, J = 5.9 Hz), 3.23 (3H, s), 3.70-3.82 (3H, m), 3.90-3.99 (2H, m), 4.07 (1H, t, J = 11.5 Hz), 4.62 (1H, br s), 4.95 (1H, br s), 6.47 (2H, d, J = 3.9 Hz), 6.86 (2H, d, J = 3.9 Hz), 7.15 (1H, s), 7.40 (1H, dd, J = 8.8, 2.4 Hz), 8.03 (1H, d, J = 8.8 Hz), 8.45 (1H, d, J = 2.4 Hz), 11.26 (1H, br s).

MS (ESI) m/z: 488.14896 $(M+H)^+$.

EJEMPLO 84

(2S)-2-(3-{5-[(4R)-4-Metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol



(84a) N-[(1R)-2-Hidroxi-1-metiletil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxamida

El ácido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxílico (2.00 g, 4.48 mmol) sintetizado en el ejemplo (78k), D-alaninol (0.52 mL, 6.72 mmol), HOBT·H_2O (0.73 g, 5.38 mmol) y N-metilmorfolina (0.99 mL, 8.96 mmol), se disolvieron en cloruro de metileno (40 mL), y se les agregó WSCI·HCl (0.94 g, 4.93 mmol) a temperatura ambiente, seguido por agitación durante 30 horas bajo una atmósfera de nitrógeno. La solución de reacción se diluyó con cloruro de metileno (100 mL), se lavó con ácido clorhídrico 1N, solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-90%), para producir el compuesto deseado como un sólido blanco (1.94 g, 86%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.27 (3H, d, J = 6.8 Hz), 1.33 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.51 (1H, dd, J = 3.9, 10.3 Hz), 3.57-3.64 (2H, m), 3.76 (1H, dd, J = 3.5, 11.0 Hz), 4.21-4.27 (1H, brm), 4.55-4.60 (1H, m), 6.06 (1H, d, J = 7.3 Hz), 6.48 (1H, dd, J = 2.7, 4.0 Hz), 6.57 (1H, t, J = 2.1 Hz), 6.60 (1H, dd, J = 2.0, 2.3 Hz), 6.84 (1H, t, J = 1.7 Hz), 7.01 (1H, t, J = 1.7 Hz), 7.44 (1H, dd, J = 2.7, 8.7 Hz), 8.04 (1H, d, J = 8.7 Hz), 8.47 (1H, d, J = 2.7 Hz), 9.71 (1H, brs).

(84b) 5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-2-(metilsulfonil)piridina

La N-[(1R)-2-hidroxi-1-metiletil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxamida (1.94 g, 3.85 mmol) sintetizada en el ejemplo (84a) se disolvió en tetrahidrofurano (35 mL), y se le agregó ácido metanosulfónico anhidro (1.38 g, 7.70 mmol) y trietilamina (2.15 mL, 15.41 mmol), seguido por agitación a 50°C durante 1.5 horas, bajo una atmósfera de nitrógeno. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (30 mL) y la solución se separó con acetato de etilo (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-75%), para producir el compuesto deseado como un sólido blanco (1.59 g, rendimiento de 85%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (6H, d, J = 6.3 Hz), 3.23 (3H,

s), 3.41 (3H, s), 3.50 (1H, dd, J = 3.9, 10.2 Hz), 3.59 (1H, dd, J = 6.1,10.4 Hz), 3.93 (1H, t, J = 7.8 Hz), 4.30-4.36 (1H, m), 4.50 (1H, dd, J = 8.2, 9.2 Hz), 4.56-4.60 (1H, m), 6.51 (1H, d, J = 3.9 Hz), 6.57 (1H, t, J = 2.2 Hz), 6.75 (1H, d, J = 3.8 Hz), 6.84 (1H, t, J = 1.8 Hz), 7.04 (1H, t, J = 1.8 Hz), 7.44 (1H, dd, J = 2.8, 8.7 Hz), 8.05 (1H, d, J = 8.8 Hz), 8.45 (1H, d, J = 2.7 Hz).

(84c) (2S)-2-(3-{5-[(4R)-4-Metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol

La 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-2-(metilsulfonil)piridina (1.20 g, 2.47 mmol) sintetizada en el ejemplo (84b) se disolvió en cloruro de metileno (25 mL), seguido por enfriamiento a -78°C, y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 2.72 mL, 2.72 mmol) bajo una atmósfera de nitrógeno. Después de que la temperatura se elevó naturalmente y se agitó a temperatura ambiente durante 30 minutos, se le agregó una solución acuosa saturada de carbonato ácido de sodio para neutralizar la solución de reacción, seguido por extracción con cloruro de metileno (80 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 70%-100%), para producir el compuesto deseado como un sólido blanco (895 mg, 77%).

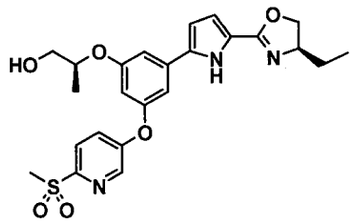
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.29 (3H, d, J = 6.2 Hz), 1.34 (1H,

d, J = 6.6 Hz), 3.23 (3H, s), 3.79-3.81 (2H, m), 3.95 (1H, t, J = 7.9 Hz), 4.32-4.38 (1H, m), 4.52 (1H, dd, J = 8.1, 9.3 Hz), 4.61-4.65 (1H, m), 6.35 (1H, t, J = 2.2 Hz), 6.47 (1H, d, J = 3.9 Hz), 6.75 (1H, d, J = 3.8 Hz), 6.80 (1H, dd, J = 1.4, 2.4 Hz), 6.97 (1H, t, J = 1.8 Hz), 7.37 (1H, dd, J = 2.7, 8.8 Hz), 8.02 (1H, d, J = 8.8 Hz), 8.43 (1H, d, J = 2.7 Hz).

MS (ESI) m/z: 472.15382 $(M+H)^+$.

EJEMPLO 85

(2S)-2-(3-{5-[(4R)-4-Etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol



(85a) N-[(1R)-1-(Hidroximetil)propil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxamida

El ácido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxílico (1.20 g, 2.69 mmol) sintetizado en el ejemplo (78k), (R)-(-)-2-amino-1-butanol (0.38 mL, 4.03 mmol), HOBT·H_2O (0.44 g, 3.23 mmol) y N-metilmorfolina (0.59 mL, 5.38 mmol), se disolvieron en cloruro de metileno (30 mL) y se les agregó WSCI·HCl (0.62 g, 3.23 mmol) a temperatura ambiente, seguido por agitación durante 6 horas bajo una atmósfera de nitrógeno. La solución de reacción se diluyó con cloruro de

metileno (50 mL), se lavó con ácido clorhídrico 1N, solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-90%), para producir el compuesto deseado como un sólido blanco (1.18 g, 85%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.01 (3H, t, J = 7.4 Hz), 1.33 (3H, d, J = 6.3 Hz), 1.67-1.74 (2H, m), 3.23 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 3.9, 10.4 Hz), 3.59 (1H, dd, J = 6.2, 10.4 Hz), 3.69 (1H, dd, J = 5.7, 10.9 Hz), 3.79 (1H, dd, 3.4, 11.0 Hz), 4.01-4.06 (1H, brm), 4.56-4.60 (1H, m), 6.02 (1H, d, J = 8.3 Hz), 6.49 (1H, dd, J = 2.9, 3.9 Hz), 6.58 (1H, t, J = 2.3 Hz), 6.61 (1H, dd, J = 2.5, 4.1 Hz), 6.84 (1H, t, J = 1.8 Hz), 7.02 (1H, t, J = 1.8 Hz), 7.45 (1H, dd, J = 2.8, 8.7 Hz), 8.05 (1H, d, J = 8.7 Hz), 8.45 (1H, dd, J = 0.8, 2.8 Hz), 9.60 (1H, brs).

(85b) 5-(3-{5-[(4R)-4-Etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)-2-(metilsulfonil)piridina

La N-[(1R)-1-(hidroximetil)propil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxamida (1.18 g, 2.28 mmol) sintetizada en el ejemplo (85a) se disolvió en tetrahidrofurano (20 mL), y se le agregó ácido metanosulfónico anhidro (0.82 g, 4.56 mmol) y trietilamina (1.27 mL, 9.12 mmol), seguido por agitación a 50°C durante 1.5 horas, bajo una atmósfera de nitrógeno. Se le agregó una

solución acuosa saturada de carbonato ácido de sodio (30 mL) y la solución se separó con acetato de etilo (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 40%-70%), para producir el compuesto deseado como un sólido blanco (1.06 g, rendimiento de 93%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 0.99 (3H, t, J = 7.4 Hz), 1.34 (3H, d, J = 6.4 Hz), 1.56-1.65 (1H, m), 1.66-1.74 (1H, m), 3.23 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 4.0, 10.2 Hz), 3.60 (1H, dd, J = 6.1,10.3 Hz), 4.02 (1H, t, J = 7.8 Hz), 4.16-4.20 (1H, m), 4.46 (1H, t, J = 8.7 Hz), 4.56-4.60 (1H, m), 6.51 (1H, d, J = 3.9 Hz), 6.56 (1H, t, J = 2.2 Hz), 6.74 (1H, d, J = 3.8 Hz), 6.85 (1H, t, J = 1.7 Hz), 7.05 (1H, t, J = 1.7 Hz), 7.44 (1H, dd, J = 2.7, 8.7 Hz), 8.05 (1H, dd, J = 0.8, 8.5 Hz), 8.45 (1H, dd, J = 0.8, 2.7 Hz).

(85c) (2S)-2-(3-{5-[(4R)-4-Etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol

La 5-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)-2-(metilsulfonil)piridina (1.06 g, 2.12 mmol) sintetizada en el ejemplo (85b) se disolvió en cloruro de metileno (20 mL), seguido por enfriamiento a -78°C, y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 2.33 mL, 2.33 mmol) bajo una atmósfera de nitrógeno. Después de que la temperatura se elevó naturalmente y se agitó a temperatura ambiente durante 30 minutos, se le agregó una solución acuosa

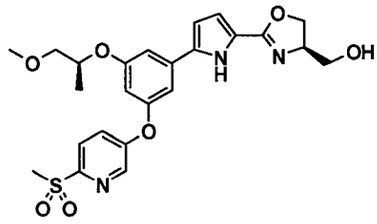
saturada de carbonato ácido de sodio para neutralizar la solución de reacción, seguido por extracción con cloruro de metileno (80 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 70%-100%), para producir el compuesto deseado como un sólido blanco (738 mg, 71%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.02 (3H, t, J = 7.4 Hz), 1.28 (3H, d, J = 6.2 Hz), 1.58-1.66 (1H, m), 1.67-1.74 (1H, m), 3.22 (3H, s), 3.80-3.82 (2H, m), 4.03 (1H, t, J = 8.0 Hz), 4.16-4.23 (1H, m), 4.49 (1H, t, J = 8.7 Hz), 4.62-4.68 (1H, m), 6.29 (1H, d, J = 2.2 Hz), 6.45 (1H, t, J = 3.7 Hz), 6.74 (1H, d, J = 3.9 Hz), 6.79 (1H, t, J = 1.8 Hz), 6.95 (1H, t, J = 1.7 Hz), 7.35 (1H, dd, J = 2.7, 8.7 Hz), 8.01 (1H, d, 8.7 Hz), 8.42 (1H, d, J = 2.7 Hz).

MS (ESI) m/z: 486.16955 $(M+H)^+$.

EJEMPLO 86

{(4R)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}metanol



(86a) N-{[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]carbonil}-L-serinato de metilo

El ácido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxílico (1.60 g, 3.58 mmol) sintetizado en el ejemplo (78k), clorhidrato del éster metílico de L-serina (0.61 g, 3.94 mmol), HOBT·H_2O (0.53 g, 3.94 mmol) y N-metilmorfolina (0.79 mL, 7.17 mmol), se disolvieron en un disolvente mixto de cloruro de metileno (30 mL) y N,N-dimetilformamida (7 mL), y se le agregó WSCI·HCl (0.82 g, 4.30 mmol) a temperatura ambiente, seguido por agitación durante 15 horas bajo una atmósfera de nitrógeno. La solución de reacción se diluyó con cloruro de metileno (100 mL), se lavó con ácido clorhídrico 1N, solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-80%), para producir el compuesto deseado como un

sólido blanco (1.91 g, 97%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.33 (3H, d, J = 6.4 Hz), 3.22 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 3.8, 10.3 Hz), 3.58 (1H, dd, J = 6.3, 10.3 Hz), 3.78 (3H, s), 3.98 (1H, dd, J = 3.4, 11.3 Hz), 4.04 (1H, dd, J = 3.9, 11.3 Hz), 4.56-4.59 (1H, brm), 4.80-4.83 (1H, m), 6.48 (1H, dd, J = 2.7, 3.8 Hz), 6.56 (1H, t, J = 2.0 Hz), 6.74 (1H, dd, J = 2.0, 2.4 Hz), 6.88 (1H, t, J = 1.7 Hz), 6.97 (1H, d, J = 7.5 Hz), 7.04 (1H, t, J = 1.9 Hz), 7.43 (1H, dd, J = 2.8, 8.8 Hz), 8.03 (1H, d, J = 8.8 Hz), 8.46 (1H, d, J = 2.8 Hz), 10.5 (1H, brs).

(86b) (4S)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-carboxilato de metilo

El N-{[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]carbonil}-L-serinato de metilo (1.91 g, 3.57 mmol) sintetizado en el ejemplo (86a) se disolvió en cloruro de metileno (40 mL), y se le agregó a gotas a -78°C trifluoruro de bis(2-metoxietil)aminoazufre (0.85 mL, 4.64 mmol). Después de agitar durante 30 minutos bajo una atmósfera de nitrógeno, se le agregó carbonato de potasio (0.74 g, 5.35 mmol) y se agitó a 0°C durante 10 minutos,. seguido por agitación a temperatura ambiente durante 3 horas. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (30 mL), seguido por extracción con cloruro de metileno (100 mL), y la capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de

gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-70%), para producir el compuesto deseado como un polvo blanco (1.76 g, 93%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.34 (3H, d, J = 6.2 Hz), 3.23 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 4.1,10.3 Hz), 3.59 (1H, dd, J = 6.3, 10.3 Hz), 3.82 (1H, s), 4.56-4.60 (2H, m), 4.67 (1H, t, J = 8.2 Hz), 4.90 (1H, dd, J = 5.2, 7.8 Hz), 6.50 (1H, d, J = 3.8 Hz), 6.59 (1H, t, J = 2.2 Hz), 6.81 (1H, d, J = 3.9 Hz), 6.84 (1H, t, J = 1.7 Hz), 7.03 (1H, s), 7.45 (1H, dd, J = 2.7, 8.6 Hz), 8.06 (1H, d, J = 8.7 Hz), 8.48 (1H, d, J = 2.7 Hz).

(86c) {(4R)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-metanol

El (4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-carboxilato de metilo (1.76 g, 3.32 mmol) sintetizado en el ejemplo (86b) se disolvió en tetrahidrofurano (30 mL), y se le agregó hidruro de litio y aluminio (0.25 g, 6.65 mmol) a 0°C. Después de agitar 30 minutos bajo una atmósfera de nitrógeno, se le agregó agua (0.25 mL), una solución acuosa de hidróxido de sodio 5N (0.25 mL) y agua (0.75 mL), en este orden, y se agitó durante 10 minutos. Se le agregó acetato de etilo (100 mL), seguido por agitación durante 5 minutos, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado

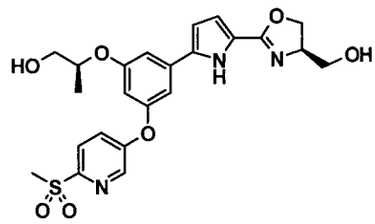
como un polvo blanco (1.15 g, 69%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.51 (1H, dd, J = 4.1, 10.4 Hz), 3.58-3.62 (2H, m), 3.97 (1H, d, J = 12.2 Hz), 4.10-4.15 (2H, m), 4.31-4.39 (2H, m), 4.56-4.60 (1H, m), 6.37 (1H, d, J = 3.8 Hz), 6.47 (1H, d, J = 3, 9 Hz), 6.57 (1H, t, J = 2.2 Hz), 6.87 (1H, dd, J = 1.2, 1.4 Hz), 7.05 (1H, t, J = 1.8 Hz), 7.46 (1H, dd, J = 2.8, 8.8 Hz), 8.05 (1H, dd, J = 0.7, 8.8 Hz), 8.50 (1H, dd, J = 0.7, 2.8 Hz).

MS (ESI) m/z: 502.16431 $(M+H)^+$.

EJEMPLO 87

(2S)-2-(3-{5-[(4R)-4-(Hidroximetil)-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol



El {(4R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}metanol (200 mg, 0.40 mmol) sintetizado en el ejemplo (86c) se disolvió en cloruro de metileno (5 mL), seguido por enfriamiento a -78°C, y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 0.80 mL, 0.80 mmol), bajo una atmósfera de nitrógeno. Después de que la temperatura se elevó naturalmente y se agitó a temperatura ambiente durante 30 minutos, se le

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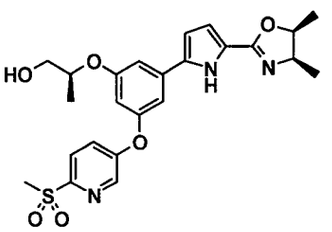
agregó una solución acuosa saturada de carbonato ácido de sodio para neutralizar la solución de reacción, seguido por extracción con cloruro de metileno (80 mL). La capa orgánica se lavó con una solución acuosa de hidróxido de sodio 1N y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-4%), para producir el compuesto deseado como un sólido blanco (143 mg, 74%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.65 (1H, dd, J = 3.5, 12.1 Hz), 3.74-3.80 (2H, m), 3.95 (1H, dd, J = 2.7, 12.2 Hz), 4.20 (1H, t, J = 6.8 Hz), 4.34-4.41 (1H, m), 4.41 (1H, t, J = 9.8 Hz), 4.57-4.61 (1H, m), 6.37 (1H, d, J = 3.9 Hz), 6.48 (1H, t, J = 2.2 Hz), 6.53 (1H, d, J = 3.9 Hz), 6.85 (1H, t, J = 1.8 Hz), 7.01 (1H, t, J = 1.8 Hz), 7.42 (1H, dd, J = 2.7, 8.8 Hz), 8.04 (1H, d, J = 8.8 Hz), 8.47 (1H, d, J = 2.7 Hz)

MS (ESI) m/z: 488.14910 $(M+H)^+$.

EJEMPLO 88

(2S)-2-(3-{5-[(4R,5S)-4,5-Dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol



(88a) (2R,3R)-3-Aminobutan-2-ol

El (2R,3R)-3-(dibencilamino)butan-2-ol ($[\alpha]^{23}_D$ -82°, c: 1.60, solución en cloroformo) (2.70 g, 10.0 mmol), sintetizado de acuerdo con un método conocido (*J. Org. Chem.*, 2006, 71, 6420), se disolvió en metanol (20 mL), y se le agregó hidróxido de paladio en carbón (0.85 g), seguido por agitación a 0.41368 MPa y a temperatura ambiente durante 4 horas bajo una atmósfera de hidrógeno. Después de filtración en Celite, el disolvente se removió por destilación bajo presión reducida para producir el compuesto deseado como un líquido incoloro (0.73 g, rendimiento de 82%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.10 (3H, d, J = 6.6 Hz), 1.17 (3H, d, J = 6.3 Hz), 2.60-2.67 (1H, m), 3.31-3.37 (1H, m).

(88b) N-[(1R,2R)-2-Hidroxi-1-metilpropil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxamida

El ácido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxílico (2.00 g, 4.48 mmol) sintetizado en el ejemplo (78k), y el (2R,3R)-3-aminobutan-2-ol (0.94 g, 8.96 mmol)

sintetizado en el ejemplo (88a), se disolvieron en metanol (30 mL), y se les agregó cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio n-hidratado (2.84 g, 8.96 mmol) a temperatura ambiente, seguido por agitación durante 3 días bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida, se le agregó agua (30 mL) y la solución se separó con acetato de etilo (70 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-90%), para producir el compuesto deseado como un sólido blanco (1.33 g, 57%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.23 (3H, t, J = 6.3 Hz), 1.27 (3H, d, J = 6.6 Hz), 1.33 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.52 (1H, dd, J = 3.9, 10.3 Hz), 3.59 (1H, dd, J = 6.2, 10.3 Hz), 3.82-3.86 (1H, m), 4.05-4.09 (1H, m), 4.58-4.62 (1H, m), 6.17 (1H, d, J = 8.7 Hz), 6.49 (1H, dd, J = 2.9, 3.9 Hz), 6.57 (1H, t, J = 2.2 Hz), 6.63 (1H, dd, J = 2.3, 3.9 Hz), 6.86 (1H, t, J = 1.8 Hz), 7.05 (1H, t, J = 1.8 Hz), 7.44 (1H, dd, J = 2.8, 8.7 Hz), 8.04 (1H, d, J = 8.7 Hz), 8.48 (1H, d, J = 2.8 Hz), 9.83 (1H, brs).

(88c) 5-(3-{5-[(4R,5S)-4,5-Dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)-2-(metilsulfonil)piridina

La N-[(1R,2R)-2-hidroxi-1-metilpropil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxamida (1.33 g, 2.57 mmol) sintetizada en el ejemplo (88b) se disolvió en

tetrahidrofurano (25 mL), y se le agregó ácido metanosulfónico anhidro (0.92 g, 5.14 mmol) y trietilamina (1.43 mL, 10.28 mmol), seguido por agitación a 50°C durante 5 horas bajo una atmósfera de nitrógeno. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (40 mL) y la solución se separó con acetato de etilo (80 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 40%-70%), para producir el compuesto deseado como un sólido blanco (0.95 g, rendimiento de 74%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.20 (3H, t, J = 6.9 Hz), 1.33 (3H, d, J = 6.3 Hz), 1.33 (3H, d, J = 6.6 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 4.0, 10.4 Hz), 3.58 (1H, dd, J = 6.1,10.4 Hz), 4.24-4.29 (1H, m), 4.55-4.58 (1H, m), 4.79-4.84 (1H, m), 6.50 (1H, d, J = 3.8 Hz), 6.56 (1H, t, J = 2.2 Hz), 6.74 (1H, d, J = 3.8 Hz), 6.83 (1H, t, J = 1.8 Hz), 7.01 (1H, t, J = 1.8 Hz), 7.43 (1H, dd, J = 2.8, 8.6 Hz), 8.05 (1H, d, J = 8.6 Hz), 8.48 (1H, d, J = 2.8 Hz).

(88d) (2S)-2-(3-{5-[(4R,5S)-4,5-Dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol

La 5-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)-2-(metilsulfonil)piridina (0.95 g, 1.96 mmol) sintetizada en el ejemplo (88c) se disolvió en cloruro de metileno (20 mL), se enfrió a -78°C y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 2.15 mL, 2.15 mmol), bajo una atmósfera de

nitrógeno. Después de que la temperatura se elevó naturalmente y la solución se agitó a temperatura ambiente durante 30 minutos, se le agregó una solución acuosa saturada de carbonato ácido de sodio para neutralizar la solución de reacción, seguido por extracción con cloruro de metileno (80 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 70%-100%), para producir el compuesto deseado como un sólido blanco (617 mg, 67%).

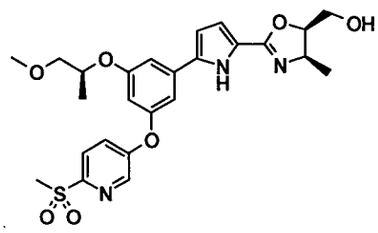
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.23 (3H, t, J = 7.0 Hz), 1.27 (3H, d, J = 6.2 Hz), 1.34 (3H, d, J = 6.6 Hz), 3.23 (3H, s), 3.81-3.83 (2H, m), 4.27-4.35 (1H, m), 4.65-4.70 (1H, m), 4.81-4.89 (1H, m), 6.24 (1H, t, J = 2.2 Hz), 6.44 (1H, d, J = 3.8 Hz), 6.73 (1H, d, J = 3.8 Hz), 6.76 (1H, dd, J = 1.2, 2.2 Hz), 6.92 (1H, t, J = 1.7 Hz), 7.32 (1H, dd, J = 2.8, 8.8 Hz), 8.00 (1H, d, J = 8.8 Hz), 8.41 (1H, d, J = 2.8 Hz).

MS (ESI) m/z: 486.17002 $(M+H)^+$.

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EJEMPLO 89

{(4R,5R)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4-metil-4,5-dihidro-1,3-oxazol-5-il}metanol



(89a) (2R,3R)-3-[(Difenilmetil)amino]-1-[(tripropan-2-ilsilil)oxi]-butan-2-ol

A cloruro de metileno (200 mL) deshidratado se le agregaron tamices moleculares de 4A (10 g). A este sistema se le agregó tetraisopropóxido de titanio (8.8 mL, 30 mmol) y ácido dietil L-(+)-tartárico (6.2 mL, 36 mmol) a -20°C, y se agitó a la misma temperatura durante 15 minutos. Se le agregó a gotas a -20°C (2E)-2-buten-1-ol (25 mL, 295 mmol) disuelto en cloruro de metileno deshidratado (50 mL), agitando a la misma temperatura durante 15 minutos. Subsiguientemente se agregó al sistema, a -20°C, hidroperóxido de t-butilo (se le agregó cloruro de metileno para separar la solución, seguido por la adición de tamices moleculares de 4A (5g) y agitación durante 20 minutos) (solución en decano 5-6 mol/L, 100 mL, 0.5-0.6 mmol)), y se agitó a -20°C durante 8.5 horas bajo una atmósfera de nitrógeno; la solución se dejó en reposo durante la noche a -30°C.

A este sistema se le agregó n-tributilfosfina (75 mL, 300 mmol),

tetraisopropóxido de titanio (135 mL, 460 mmol) y 1,1-difenilmetanamina (75 mL, 440 mmol) a temperatura ambiente, y se agitó a la misma temperatura durante 1 semana. A la solución de reacción se le agregó agua (30 mL) y el depósito se filtró. Al licor madre se le agregó agua (400 mL) y se extrajo con cloruro de metileno (1L). El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 15%-40%), para producir un líquido pardo oscuro.

Este líquido se disolvió en cloruro de metileno (300 mL) y se le agregó trietilamina (85 mL, 610 mmol) y cloruro de triisopropilsililo (50 mL, 234 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante 1.5 días. Se le agregó una solución acuosa saturada de cloruro de amonio (500 mL), y se extrajo con cloruro de metileno (500 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-5%), para producir el compuesto deseado como un sólido blanco (80.5 g, rendimiento de 64%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 0.96-1.07 (21H, m), 1.10 (3H, d, J = 6.3 Hz), 2.72-2.81 (1H, m), 3.28 (1H, br s), 3.56-3.63 (1H, m), 3.72 (1H, dd, J = 10.2, 5.9 Hz), 3.80 (1H, dd, J = 10.2, 3.9 Hz), 4.98 (1H, s), 7.15-7.20 (2H, m), 7.23-7.29 (4H, m), 7.34-7.40 (4H, m).

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(89b) {(2R,3R)-3-Hidroxi-4-[(tripropan-2-ilsilil)oxi]butan-2-il}carbamato de bencilo

El (2R,3R)-3-[(difenilmetil)amino]-1-[(triisopropan-2-ilsilil)oxi]-butan-2-ol (10.3 g, 24.1 mmol) sintetizado en el ejemplo (89a) se disolvió en etanol (40 mL), y se le agregó paladio en carbón (3.20g), seguido por agitación a temperatura ambiente durante 6 horas bajo una atmósfera de hidrógeno. Después de filtración en Celite, el disolvente se removió por destilación bajo presión reducida para producir un compuesto como un líquido incoloro.

Este se disolvió en agua (40 mL) calentada a 50°C, y se le agregó carbonato ácido de sodio (4.50 g, 53.6 mmol) y cloroformiato de bencilo (3.50 mL, 24.5 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante 5 horas. Se le agregó cloruro de metileno (100 mL) y se extrajo. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-15%), para producir el compuesto deseado como un líquido incoloro (7.00 g, rendimiento de 73%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.04-1.09 (21H, m), 1.18 (3H, d, J = 6.8 Hz), 2.67 (1H, br s), 3.65-3.73 (2H, m), 3.77 (1H, dd, J = 10.0, 3.7 Hz), 3.86 (1H, br s), 5.10 (2H, s), 5.27 (1H, br s), 7.30-7.38 (5H, m).

(89c) 4-Nitrobenzoato de (5R,6S)-5,10-dimetil-3-oxo-1-fenil-9,9-di(propan-2-il)-2,8-dioxa-4-aza-9-silaundecan-6-ilo

El {(2R,3R)-3-hidroxi-4-[(tripropan-2-ilsilil)oxi]butan-2-il}-carbamato de bencilo (7.00 g, 17.7 mmol) sintetizado en el ejemplo (89b) se disolvió en tolueno (80 mL), y se le agregó ácido 4-nitro-benzoico (6.10 g, 36.5 mmol) y trifenilfosfina (11.85g, 45.2 mmol), seguido por enfriamiento a 0°C. Bajo una atmósfera de nitrógeno, se le agregó a gotas durante 10 minutos azodicarboxilato de dietilo (solución en tolueno al 40%, 20.3 mL, 44.7 mmol), y se agitó a temperatura ambiente durante 4 horas. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-15%), para producir el compuesto deseado como un líquido amarillo (7.90 g, rendimiento de 82%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 0.96-1.09 (21H, m), 1.29 (3H, d, J = 7.0 Hz), 3.90-4.01 (1H, m), 4.25-4.32 (1H, m), 4.95-5.10 (3H, m), 5.13-5.20 (1H, m), 7.24-7.39 (5H, m), 8.14-8.21 (2H, m), 8.23-8.30 (2H, m).

(89d) {(2R,3S)-3-Hidroxi-4-[(tripropan-2-ilsilil)oxi]butan-2-il}-carbamato de bencilo

El 4-nitrobenzoato de (5R,6S)-5,10-dimetil-3-oxo-1-fenil-9,9-di(propan-2-il)-2,8-dioxa-4-aza-9-silaundecan-6-ilo (7.90 g, 14.5 mmol) sintetizado en el ejemplo (89c) se disolvió en cloruro de metileno (150 mL), y se le agregó hidruro de diisobutilaluminio (solución en hexano 1.0 mol/L, 30.0 mL, 30.0 mmol), seguido por agitación a -40°C durante 8 horas, bajo una

atmósfera de nitrógeno. La solución de reacción se llevó a 0°C y se le agregó metanol (5.0 mL), seguido por la adición de una solución acuosa de hidróxido de sodio 5N (150 mL), y se extrajo con cloruro de metileno (200 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-15%), para producir el compuesto deseado como un líquido incoloro (3.70 g, rendimiento de 65%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.01-1.13 (21H, m), 1.26 (3H, d, J = 6.6 Hz), 2.72 (1H, br s), 3.55-3.67 (2H, m), 3.73 (2H, br s), 5.10 (2H, s), 5.13 (1H, br s), 7.31-7.36 (5H, m).

(89e) (2S,3R)-3-Amino-1-[(tripropan-2-ilsilil)oxi]butan-2-ol

El {(2R,3S)-3-hidroxi-4-[(tripropan-2-ilsilil)oxi]butan-2-il}-carbamato de bencilo (3.70 g, 9.35 mmol) sintetizado en el ejemplo (89d) se disolvió en etanol (30 mL), y se le agregó paladio en carbón (1.00g), seguido por agitación a temperatura ambiente durante 8 horas bajo una atmósfera de hidrógeno. Después de filtración en Celite, el disolvente se removió por destilación bajo presión reducida para producir el compuesto deseado como un líquido amarillo pálido (2.65 g, rendimiento de ~100%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.04-1.14 (24H, m), 2.95-3.02 (1H, m), 3.30-3.35 (1H, m), 3.66 (1H, dd, J = 9.8, 6.3 Hz), 3.76 (1H, dd, J = 9.8, 4.3 Hz).

(89f) N-{(1R,2S)-2-Hidroxi-1-metil-3-[(triisopropilsilil)oxi]propil}-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxamida

El ácido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxílico (1.20 g, 2.69 mmol) sintetizado en el ejemplo (78k), el (2S,3R)-3-amino-1-[(tripropan-2-ilsilil)oxi]butan-2-ol (1.08 g, 4.11 mmol) sintetizado en el ejemplo (89e), HOBT·H_2O (0.44 g, 3.23 mmol) y N-metilmorfolina (0.59 mL, 5.38 mmol), se disolvieron en N,N-dimetilformamida (20 mL), y se les agregó WSCI·HCl (0.62 g, 3.23 mmol) a temperatura ambiente, seguido por agitación durante 18 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó salmuera saturada (30 mL) y se extrajo con acetato de etilo (60 mL). Después de lavar con ácido clorhídrico 1N, solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-50%), para producir el compuesto deseado como un polvo blanco (1.69 g, 91%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.03-1.13 (21H, m), 1.34 (3H, d, J = 6.3 Hz), 1.35 (3H, d, J = 6.8 Hz), 3.23 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 4.0, 10.3 Hz), 3.54-3.61 (2H, m), 3.73-3.78 (2H, m), 4.14-4.18 (1H, m), 4.56-4.60 (1H, m), 6.31 (1H, brm), 6.49 (1H, dd, J = 2.9, 3.9 Hz), 6.57-6.60 (2H, m), 6.84 (1H, dd, J = 1.5, 2.3 Hz), 7.02 (1H, t, J = 1.8 Hz), 7.45 (1H, dd, J = 2.8,

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8.8 Hz), 8.09 (1H, d, J = 8.7 Hz), 8.49 (1H, d, J = 2.7 Hz), 9.52 (1H, brs).

(89g) 5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(4R,5R)-4-metil-5-{[(triisopropilsilil)oxi]metil}-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-2-(metilsulfonil)piridina

La N-[(1R,2S)-2-hidroxi-1-metil-3-[(triisopropilsilil)oxi]propil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxamida (1.69 g, 2.45 mmol) sintetizada en el ejemplo (89f) se disolvió en tetrahidrofurano (25 mL), y se le agregó ácido metanosulfónico anhidro (0.88 g, 4.90 mmol) y trietilamina (1.37 mL, 9.80 mmol), seguido por agitación a 50°C durante 5 horas bajo una atmósfera de nitrógeno. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (40 mL) y la solución se separó con acetato de etilo (60 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-50%), para producir el compuesto deseado como un sólido blanco (1.23 g, rendimiento de 75%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.04-1.14 (21H, m), 1.34 (6H, d, J = 6.3 Hz), 3.23 (3H, s), 3.42 (3H, s), 3.50 (1H, dd, J = 4.0, 10.3 Hz), 3.59 (1H, dd, J = 6.1,10.3 Hz), 3.94 (2H, d, J = 5.3 Hz), 4.37-4.41 (1H, m), 4.56-4.60 (1H, m), 4.65-4.69 (1H, m), 6.49 (1H, d, J = 3.9 Hz), 6.56 (1H, t, J = 2.1 Hz), 6.74 (1H, d, J = 3.8 Hz), 6.85 (1H, s), 7.04 (1H, s), 7.44 (1H, dd, J = 2.8, 8.6 Hz), 8.05 (1H, d, J = 8.6 Hz), 8.48 (1H, d, J = 2.8 Hz).

(89h) {(4R,5R)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4-metil-4,5-dihidro-1,3-oxazol-5-il}metanol

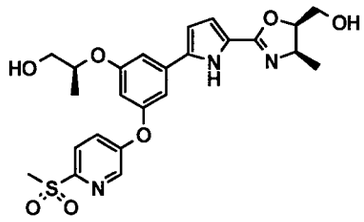
La 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(4R,5R)-4-metil-5-{[(triisopropilsilil)oxi]metil}-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-2-(metilsulfonil)piridina (1.23 g, 1.83 mmol) sintetizada en el ejemplo (89g) se disolvió en tetrahidrofurano (20 mL), y se le agregó fluoruro de tetrabutilamonio (solución en tetrahidrofurano 1.0 mol/L, 2.11 mL, 2.11 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante 1 hora bajo una atmósfera de nitrógeno. Se le agregó agua (20 mL) y se extrajo con acetato de etilo (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 90%-100%), para producir el compuesto deseado como un sólido blanco (715 mg, rendimiento de 76%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.26 (3H, d, J = 7.1 Hz), 1.31 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.42 (3H, s), 3.50 (1H, dd, J = 3.9, 10.3 Hz), 3.59 (1H, dd, J = 6.3, 10.3 Hz), 3.85 (2H, d, J = 5.4 Hz), 4.36-4.42 (1H, m), 4.53-4.48 (1H, m), 4.70-4.76 (1H, m), 6.50 (1H, d, J = 3.8 Hz), 6.57 (1H, t, J = 2.1 Hz), 6.77 (1H, d, J = 3.8 Hz), 6.84 (1H, t, 1.8 Hz), 7.00 (1H, t, 1.8 Hz), 7.43 (1H, dd, J = 2.8, 8.8 Hz), 8.04 (1H, d, J = 8.8 Hz), 8.48 (1H, d, J = 2.8 Hz).

MS (ESI) m/z: 516.17829 $(M+H)^+$.

EJEMPLO 90

(2S)-2-(3-{5-[(4R,5R)-5-(Hidroximetil)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol



El {(4R,5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4-metil-4,5-dihidro-1,3-oxazol-2-il}metanol (200 mg, 0.39 mmol) sintetizado en el ejemplo (89h) se disolvió en cloruro de metileno (5 mL), y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 0.78 mL, 0.78 mmol) a -78°C y bajo una atmósfera de nitrógeno; subsiguientemente la temperatura se regresó a la temperatura ambiente y se agitó durante 45 minutos. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con cloruro de metileno. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-4%), para producir el compuesto deseado como un sólido blanco (87 mg, rendimiento de 45%).

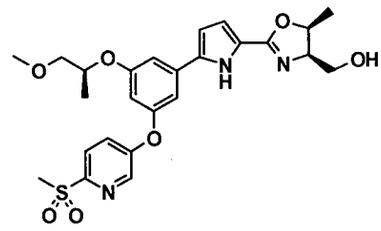
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.29 (6H, t, J = 5.9 Hz), 3.23 (3H, s), 3.79 (2H, d, J = 4.9 Hz), 3.85 (2H, d, J = 6.3 Hz), 4.41 (1H, dt, J = 16.3, 7.1

Hz), 4.59 (1H, dd, J = 11.5, 5.6 Hz), 4.73-4.77 (1H, m), 6.38 (1H, s), 6.46 (1H, d, J = 3.4 Hz), 6.77 (1H, d, J = 3.9 Hz), 6.81 (1H, s), 6.98 (1H, s), 7.35 (1H, d, J = 8.8 Hz), 8.01 (1H, d, J = 8.8 Hz), 8.44 (1H, s).

MS (ESI) m/z: 502.16510 $(M+H)^+$.

EJEMPLO 91

{(4R,5S)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol



(91a) N-[(1R,2R)-2-Hidroxi-1-(hidroximetil)propil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxamida

El ácido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxílico (1.20 g, 2.69 mmol) sintetizado en el ejemplo (78k), y L-treoninol (0.57 g, 5.38 mmol), disponible comercialmente, se disolvieron en metanol (25 mL) y se les agregó cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio n-hidratado (1.70 g, 5.38 mmol) a temperatura ambiente, seguido por agitación durante 3.5 horas bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se diluyó con acetato de etilo (100 mL).

Después de lavar con ácido clorhídrico 1N, solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio anhidro; el disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-6%), para producir el compuesto deseado como un sólido blanco (883 mg, 62%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.23 (3H, d, J = 6.4 Hz), 1.30 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 3.9, 10.2 Hz), 3.58 (1H, dd, J = 6.4, 10.4 Hz), 3.87 (2H, d, J = 4.0 Hz), 3.97-4.03 (1H, brm), 4.22-4.26 (1H, m), 4.55-4.58 (1H, m), 6.49 (1H, dd, J = 2.8, 3.9 Hz), 6.57 (1H, t, J = 2.2 Hz), 6.68-6.71 (2H, m), 6.86 (1H, t, J = 1.7 Hz), 7.02 (1H, t, J = 1.8 Hz), 7.44 (1H, dd, J = 2.7, 8.7 Hz), 8.04 (1H, d, J = 8.8 Hz), 8.47 (1H, d, J = 2.7 Hz), 10.05 (1H, brs).

(91b) N-[(1R,2R)-2-Hidroxi-1-{[(triisopropilsilil)oxi]metil}propil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxamida

La N-[(1R,2R)-2-hidroxi-1-(hidroximetil)propil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxamida (883 mg, 1.65 mmol) sintetizada en el ejemplo (91a), trietilamina (1.15 mL, 8.27 mmol) y 4-dimetilaminopiridina (404 mg, 3.31 mmol), se disolvieron en cloruro de metileno (20 mL) y se les agregó cloruro de triisopropilsililo (0.60 mL, 2.81 mmol) a temperatura ambiente, seguido por agitación durante 20 horas bajo una atmósfera de nitrógeno. El disolvente se

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removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-60%), para producir el compuesto deseado como un sólido blanco (1.03 g, 90%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.05-1.08 (18H, m), 1.09-1.16 (3H, m), 1.23 (3H, d, J = 6.4 Hz), 1.34 (3H, d, J = 6.3 Hz), 3.24 (3H, s), 3.42 (3H, s), 3.52 (1H, dd, J = 4.0, 10.2 Hz), 3.60 (1H, dd, J = 6.2, 10.4 Hz), 3.99-4.04 (1H, m), 4.03-4.06 (2H, m), 4.30-4.35 (1H, m), 4.56-4.61 (1H, m), 6.51 (1H, t, J = 3.4 Hz), 6.59 (1H, t, J = 2.2 Hz), 6.62-6.66 (2H, m), 6.85 (1H, t, J = 1.8 Hz), 7.03 (1H, t, J = 1.7 Hz), 7.46 (1H, dd, J = 2.7, 8.8 Hz), 8.06 (1H, d, J = 8.8 Hz), 8.49 (1H, d, J = 2.7 Hz), 9.49 (1H, brs).

(91c) 5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(4R,5S)-5-metil-4-{[(triisopropilsilil)oxi]metil}-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-2-(metilsulfonil)piridina

La N-[(1R,2R)-2-hidroxi-1-{[(triisopropilsilil)oxi]metil}propil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxamida (1.03 g, 1.49 mmol) sintetizada en el ejemplo (91b) se disolvió en tetrahidrofurano (20 mL), y se le agregó ácido metanosulfónico anhidro (0.54 g, 2.99 mmol) y trietilamina (0.83 mL, 5.97 mmol), seguido por agitación a 50°C durante 4.5 horas bajo una atmósfera de nitrógeno. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (30 mL) y la solución se separó con acetato de etilo (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio

anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-50%), para producir el compuesto deseado como un sólido blanco (901 mg, rendimiento de 90%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.03-1.13 (21H, m), 1.33 (3H, d, J = 6.3 Hz), 1.52 (3H, d, J = 6.6 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 3.9, 10.4 Hz), 3.58 (1H, dd, J = 6.2, 10.5 Hz), 3.81 (1H, t, J = 9.5 Hz), 3.95 (1H, dd, J = 3.9, 10.4 Hz), 4.21-4.25 (2H, m), 4.56-4.59 (1H, m), 4.89-4.93 (1H, m), 6.50 (1H, d, J = 3.9 Hz), 6.56 (1H, t, J = 2.2 Hz), 6.76 (1H, d, J = 3.9 Hz), 6.84 (1H, s), 7.02 (1H, s), 7.44 (1H, dd, J = 2.7, 8.8 Hz), 8.05 (1H, d, J = 8.8 Hz), 8.48 (1H, d, J = 2.7 Hz).

(91d) {(4R,5S)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol

La 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(4R,5S)-5-metil-4-{[(triisopropilsilil)oxi]metil}-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-2-(metilsulfonil)piridina (901 mg, 1.34 mmol) sintetizada en el ejemplo (91c) se disolvió en tetrahidrofurano (15 mL), y se le agregó fluoruro de tetrabutilamonio (solución en tetrahidrofurano 1 mol/L, 1.54 mL, 1.54 mmol) a 0°C, seguido por agitación a temperatura ambiente durante 1 hora bajo una atmósfera de nitrógeno. Se le agregó agua (20 mL) y se extrajo con acetato de etilo (40 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente

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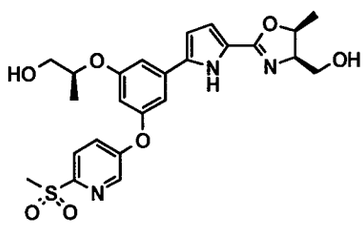
se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 80%-100%), para producir el compuesto deseado como un sólido blanco (578 mg, rendimiento de 84%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 1.39 (3H, d, J = 6.8 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 4.1, 10.4 Hz), 3.59 (1H, dd, J = 6.1, 10.4 Hz), 3.77 (1H, dd, J = 6.2, 11.2 Hz), 3.84 (1H, dd, J = 3.7, 11.8 Hz), 4.22-4.27 (1H, m), 4.54-4.61 (1H, m), 4.83-4.90 (1H, m), 6.45 (1H, d, J = 3.8 Hz), 6.55 (1H, t, J = 2.2 Hz), 6.68 (1H, d, J = 3.9 Hz), 6.90 (1H, t, 1.8 Hz), 7.07 (1H, t, 1.8 Hz), 7.43 (1H, dd, J = 2.8, 8.7 Hz), 8.04 (1H, d, J = 8.7 Hz), 8.49 (1H, d, J = 2.8 Hz).

MS (ESI) m/z: 516.17933 $(M+H)^+$.

EJEMPLO 92

(2S)-2-(3-{5-[(4R,5S)-4-(Hidroximetil)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol



El {{(4R,5S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol (178 mg, 0.35 mmol) sintetizado en el ejemplo (91d) se disolvió

en cloruro de metileno (5 mL), y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 0.70 mL, 0.70 mmol) a -78°C, y subsiguientemente la temperatura se regresó a la temperatura ambiente y se agitó durante 45 minutos. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con cloruro de metileno. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-4%), para producir el compuesto deseado como un sólido blanco (142 mg, rendimiento de 82%).

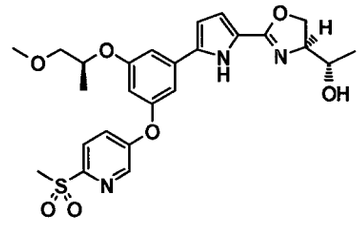
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.30 (3H, d, J = 6.3 Hz), 1.43 (3H, d, J = 6.6 Hz), 3.23 (3H, s), 3.76-3.87 (4H, m), 4.22-4.27 (1H, m), 4.53-4.60 (1H, m), 4.92-4.84 (1H, m), 6.45 (1H, d, J = 3.9 Hz), 6.48 (1H, s), 6.69 (1H, d, J = 3.9 Hz), 6.87 (1H, t, J = 1.8 Hz), 7.02 (1H, s), 7.41 (1H, dd, J = 8.6, 2.7 Hz), 8.03 (1H, d, J = 8.6 Hz), 8.47 (1H, d, J = 2.7 Hz).

MS (ESI) m/z: 502.16583 $(M+H)^+$.

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EJEMPLO 93

(1S)-1-{(4S)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol



(93a) N-[(1S,2S)-2-Hidroxi-1-(hidroximetil)propil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxamida

El ácido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxílico (1.20 g, 2.69 mmol) sintetizado en el ejemplo (78k), D-treoninol (0.34 g, 3.23 mmol), disponible comercialmente, HOBT·H_2O (0.40 g, 3.23 mmol) y N-metilmorfolina (0.59 mL, 5.38 mmol), se disolvieron en N,N-dimetilformamida (20 mL) y se les agregó WSCI·HCl (0.62 g, 3.23 mmol) a temperatura ambiente, seguido por agitación durante 20 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó salmuera saturada (30 mL) y se extrajo con acetato de etilo (60 mL). Después de lavar con ácido clorhídrico 1N, solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-7%), para producir el

compuesto deseado como un sólido blanco (1.24 g, 86%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.25 (3H, d, J = 6.3 Hz), 1.33 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 3.9, 10.3 Hz), 3.59 (1H, dd, J = 6.3, 10.4 Hz), 3.90-3.91 (2H, m), 3.98-4.03 (1H, brm), 4.23-4.29 (1H, m), 4.56-4.60 (1H, m), 6.50 (1H, t, J = 3.2 Hz), 6.58 (1H, t, J = 2.2 Hz), 6.66 (1H, brm), 6.69-6.70 (1H, m), 6.85 (1H, t, J = 1.7 Hz), 7.03 (1H, t, J = 1.7 Hz), 7.44 (1H, dd, J = 2.7, 8.7 Hz), 8.04 (1H, d, J = 8.7 Hz), 8.48 (1H, d, J = 2.7 Hz), 9.77 (1H, brs).

(93b) (1S)-1-{(4S)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol

La N-[(1S,2S)-2-hidroxi-1-(hidroximetil)propil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxamida (1.24 g, 2.32 mmol) sintetizada en el ejemplo (93a) se disolvió en tetrahidrofurano (20 mL), y se le agregó ácido metanosulfónico anhidro (0.63 g, 3.49 mmol) y trietilamina (0.97 mL, 6.97 mmol) a 0°C, seguido por agitación durante 1 hora bajo una atmósfera de nitrógeno. La temperatura se elevó naturalmente, y la solución se agitó a temperatura ambiente durante 2 horas, seguido por agitación a 50°C durante 2 horas. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (30 mL) y la solución se separó con acetato de etilo (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo

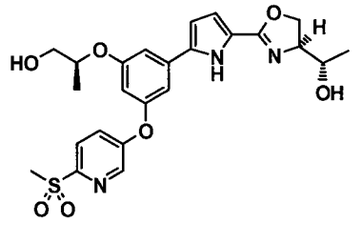
resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 60%-100%), para producir el compuesto deseado como un sólido blanco (800 mg, rendimiento de 67%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.24 (3H, d, J = 6.3 Hz), 1.33 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.40 (3H, s), 3.50 (1H, dd, J = 4.0, 10.3 Hz), 3.58 (1H, dd, J = 6.3, 10.3 Hz), 3.71 (1H, t, J = 6.2 Hz), 4.08-4.14 (2H, m), 4.41-4.44 (1H, m), 4.54-4.59 (1H, m), 6.50 (1H, d, J = 3.9 Hz), 6.56 (1H, t, J = 2.1 Hz), 6.74 (1H, d, J = 3.9 Hz), 6.86 (1H, t, 2.0 Hz), 7.05 (1H, t, 1.9 Hz), 7.42 (1H, dd, J = 2.7, 8.8 Hz), 8.03 (1H, d, J = 8.8 Hz), 8.47 (1H, d, J = 2.8 Hz).

MS (ESI) m/z: 516.17981 $(M+H)^+$.

EJEMPLO 94

(2S)-2-[3-(5-{(4S)-4-[(1S)-1-Hidroxietil]-4,5-dihidro-1,3-oxazol-2-il}-1H-pirrol-2-il)-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi]propan-1-ol



El (1S)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol (187 mg, 0.36 mmol) sintetizado en el ejemplo (93b) se disolvió en cloruro de metileno (5 mL) y subsiguientemente se enfrió a -78°C; se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 0.73 mL,

0.73 mmol) bajo una atmósfera de nitrógeno. La temperatura se elevó naturalmente, seguido por agitación a temperatura ambiente durante 30 minutos; subsiguientemente se le agregó una solución acuosa saturada de carbonato ácido de sodio para neutralizar la solución de reacción, seguido por extracción con cloruro de metileno (70 mL). La capa orgánica se lavó con una solución acuosa de hidróxido de sodio 1N y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-4%), para producir el compuesto deseado como un sólido blanco (134 mg, 74%).

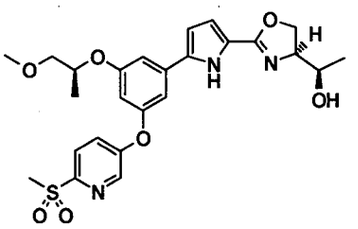
^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.28 (6H, d, J = 6.6 Hz), 3.22 (3H, s), 3.72-3.81 (3H, m), 4.13-4.19 (2H, m), 4.42-4.45 (1H, m), 4.59-4.65 (1H, m), 6.41 (1H, t, J = 2.2 Hz), 6.45 (1H, d, J = 3.9 Hz), 6.72 (1H, d, J = 3.9 Hz), 6.83 (1H, s), 6.99 (1H, s), 7.37 (1H, dd, J = 2.7, 8.8 Hz), 8.02 (1H, d, J = 8.8 Hz), 8.44 (1H, d, J = 2.7 Hz).

MS (ESI) m/z: 502.16521 $(M+H)^+$.

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EJEMPLO 95

(1R)-1-{(4S)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol



(95a) N-[(1S,2R)-2-Hidroxi-1-(hidroximetil)propil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxamida

El ácido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxílico (1.47 g, 3.29 mmol) sintetizado en el ejemplo (78k), D-alo-treoninol (0.52 g, 4.94 mmol), disponible comercialmente, HOBT·H_2O (0.49 g, 3.62 mmol) y N-metilmorfolina (0.72 mL, 6.58 mmol), se disolvieron en N,N-dimetilformamida (10 mL), y se les agregó WSCI·HCl (0.76 g, 3.95 mmol) a temperatura ambiente, seguido por agitación durante 5.5 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó salmuera saturada (40 mL) y se extrajo con acetato de etilo (70 mL). Después de lavar con salmuera saturada, se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-6%), para producir el compuesto deseado como un sólido blanco (1.42 g, 81%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.31 (3H, d, J = 6.2 Hz), 1.32 (3H, d, J = 6.6 Hz), 2.84-2.86 (1H, m), 2.89 (1H, d, J = 6.2 Hz), 3.23 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 3.9, 10.3 Hz), 3.59 (1H, dd, J = 6.3, 10.3 Hz), 3.80-3.84 (1H, brm), 3.92-3.96 (1H, m), 4.07-4.11 (2H, brm), 4.54-4.59 (1H, m), 6.49 (1H, dd, J = 2.9, 3.9 Hz), 6.57 (1H, t, J = 2.2 Hz), 6.67 (1H, dd, J = 2.3, 3.9 Hz), 6.80 (1H, d, J = 8.0 Hz), 6.86 (1H, t, J = 1.8 Hz), 7.01 (1H, t, J = 1.8 Hz), 7.43 (1H, dd, J = 2.8, 8.7 Hz), 8.03 (1H, d, J = 8.7 Hz), 8.47 (1H, d, J = 2.8 Hz), 9.94 (1H, brs).

(95b) (1R)-1-{(4S)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol

La N-[(1S,2R)-2-hidroxi-1-(hidroximetil)propil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxamida (1.42 g, 2.66 mmol) sintetizada en el ejemplo (95a) se disolvió en tetrahidrofurano (25 mL), y se le agregó ácido metanosulfónico anhidro (0.72 g, 3.99 mmol) y trietilamina (1.11 mL, 7.98 mmol) a 0°C, seguido por agitación durante 1 hora bajo una atmósfera de nitrógeno. La temperatura se elevó naturalmente, y la solución se agitó a temperatura ambiente durante 1 hora, seguido por agitación a 50°C durante 2 horas. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (30 mL) y la solución se separó con acetato de etilo (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo

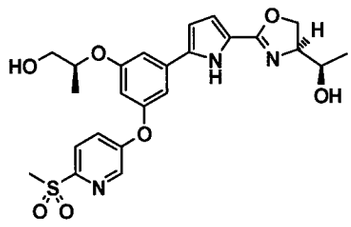
resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-100%), para producir el compuesto deseado como un sólido blanco (758 mg, rendimiento de 55%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.15 (3H, d, J = 6.3 Hz), 1.35 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.51 (1H, dd, J = 4.0, 10.4 Hz), 3.59 (1H, dd, J = 6.2, 10.4 Hz), 4.20-4.27 (4H, m), 4.56-4.62 (1H, m), 6.36 (1H, d, J = 3.8 Hz), 6.41 (1H, d, J = 3.8 Hz), 6.57 (1H, t, J = 2.1 Hz), 6.90 (1H, t, 1.8 Hz), 7.07 (1H, t, 1.8 Hz), 7.45 (1H, dd, J = 2.8, 8.7 Hz), 8.05 (1H, d, J = 8.7 Hz), 8.50 (1H, d, J = 2.8 Hz).

MS (ESI) m/z: 516.17893 $(M+H)^+$.

EJEMPLO 96

(2S)-2-[3-(5-{(4S)-4-[(1R)-1-Hidroxietil]-4,5-dihidro-1,3-oxazol-2-il}-1H-pirrol-2-il)-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi]propan-1-ol



El (1R)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol (178 mg, 0.35 mmol) sintetizado en el ejemplo (95b) se disolvió en cloruro de metileno (5 mL), y subsiguientemente se enfrió a -78°C y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 0.69 mL,

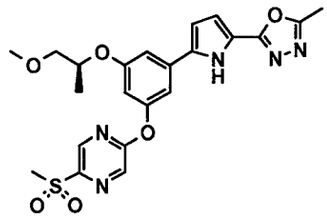
0.69 mmol) bajo una atmósfera de nitrógeno. La temperatura se elevó naturalmente, seguido por agitación a temperatura ambiente durante 30 minutos; subsiguientemente se le agregó una solución acuosa saturada de carbonato ácido de sodio para neutralizar la solución de reacción, seguido por extracción con cloruro de metileno (70 mL). La capa orgánica se lavó con una solución acuosa de hidróxido de sodio 1N y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-4%), para producir el compuesto deseado como un sólido blanco (132 mg, 76%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.19 (3H, d, 6.3 Hz), 1.31 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.73-3.81 (2H, m), 4.17-4.25 (2H, m), 4.32 (1H, s), 4.34 (1H, d, J = 1.5 Hz), 4.57-4.61 (1H, m), 6.39 (1H, d, J = 3.9 Hz), 6.49 (1H, d, J = 2.1 Hz), 6.54 (1H, d, J = 3.9 Hz), 6.87 (1H, t, J = 1.8 Hz), 7.02 (1H, t, J = 1.8 Hz), 7.42 (1H, dd, J = 2.8, 8.6 Hz), 8.04 (1H, d, J = 8.6 Hz), 8.47 (1H, d, J = 2.8 Hz).

MS (ESI) m/z: 502.16427 $(M+H)^+$.

EJEMPLO 97

2-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]fenoxi}-5-(metilsulfonil)pirazina



(97a) 5-(Metilsulfanil)pirazin-2-amina

Se disolvió 2-aminopirazina (50.8 g, 0.53 mol) en cloruro de metileno (1.0 L) y se le agregó N-bromosuccinimida (97.9 g, 0.55 mol) a 0°C durante 30 minutos, seguido por agitación a 0°C durante 2.5 horas, bajo una atmósfera de nitrógeno. La solución de reacción se llevó de vuelta a la temperatura ambiente y el depósito se filtró. El depósito que se filtró se lavó con acetato de etilo. El licor madre se recogió y el disolvente se removió por destilación bajo presión reducida. Esta operación se repitió dos veces para producir un licor madre, del cual se removió el disolvente por destilación bajo presión reducida para producir un compuesto como un sólido amarillo.

Este se disolvió en N,N-dimetilformamida (300 mL) y se le agregó tiometóxido de sodio (75.0 g, 1.07 mol), seguido por agitación a 100°C durante 3 horas bajo una atmósfera de nitrógeno. La solución de reacción se llevó a temperatura ambiente y se le agregó agua (1.5L), seguido por extracción con acetato de etilo (1.0 L). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El

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disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-30%), para producir el compuesto deseado como un sólido anaranjado (42.5 g, rendimiento de 56%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.52 (3H, s), 4.41 (2H, br s), 7.92 (1H, d, J = 1.6 Hz), 7.98 (1H, d, J = 1.6 Hz).

(97b) 2-Cloro-5-(metilsulfanil)pirazina

Se disolvió nitrito de sodio (50.9 g, 0.74 mol) en agua (150 mL), seguido por su adición a gotas a una solución acuosa de ácido clorhídrico 5N (1.0 L) a 0°C durante 1 hora. Subsiguientemente se le agregó la 5-(metilsulfanil)pirazin-2-amina (40.4 g, 0.28 mol) sintetizada en el ejemplo (97a) a 0°C durante 40 minutos, y se agitó a 0°C durante 1 hora. La solución de reacción se llevó de vuelta a la temperatura ambiente y se le agregó agua (500 mL), seguido por extracción con acetato de etilo (1.0 L). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-20%), para producir el compuesto deseado como un sólido blanco (11.9 g, rendimiento de 26%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.57 (3H, s), 8.24 (1H, d, J = 1.2 Hz), 8.39 (1H, d, J = 1.2 Hz).

(97c) 2-Cloro-5-(metilsulfonil)pirazina

La 2-cloro-5-(metilsulfanil)pirazina (10.82 g, 67.4 mmol) sintetizada en el ejemplo (97b) se disolvió en cloruro de metileno (200 mL), y se le agregó lentamente ácido m-cloroperbenzoico (aproximadamente 65%, 37.4 g, aproximadamente 140 mmol) a 0°C, seguido por agitación a 0°C durante 1.5 horas bajo una atmósfera de nitrógeno. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (300 mL) y se extrajo con cloruro de metileno (400 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-50%), para producir el compuesto deseado como un sólido blanco (10.1 g, rendimiento de 78%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 3.27 (3H, s), 8.70 (1H, d, J = 1.2 Hz), 9.09 (1H, d, J = 1.2 Hz).

(97d) 5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-carboxilato de bencilo

El 5-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-1,2-dicarboxilato de 2-bencilo-1-t-butilo (3.40 g, 7.06 mmol) sintetizado en el ejemplo (78g), y la 2-cloro-5-(metilsulfonil)pirazina (1.92 g, 7.06 mmol) sintetizada en el ejemplo (97c), se disolvieron en acetonitrilo (35 mL), y se les agregó carbonato de potasio (2.93 g, 21.2 mmol), seguido por calentamiento a reflujo durante 11 horas bajo una atmósfera de nitrógeno. La solución de

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reacción se enfrió a temperatura ambiente y se le agregó agua (100 mL), seguido por extracción dos veces con acetato de etilo (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-50%).

El sólido pardo resultante (3.85g) se disolvió en cloruro de metileno (5 mL) y se le agregó ácido trifluoroacético (5 mL), seguido por agitación a temperatura ambiente durante 1 hora. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio (50 mL) y se extrajo dos veces con acetato de etilo (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-60%), para producir el compuesto deseado como un sólido blanco (3.58 g, rendimiento de 88%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.35 (3H, d, J = 6.3 Hz), 3.24 (3H, s), 3.42 (3H, s), 3.52 (1H, dd, J = 10.3, 3.9 Hz), 3.60 (1H, dd, J = 10.3, 5.9 Hz), 4.57-4.61 (1H, m), 5.34 (2H, s), 6.53 (1H, dd, J = 3.9, 2.9 Hz), 6.70 (1H, t, J = 2.2 Hz), 6.93 (1H, t, J = 1.5 Hz), 6.99 (1H, dd, J = 3.9, 2.4 Hz), 7.06 (1H, t, J = 1.7 Hz), 7.34-7.45 (5H, m), 8.50 (1H, d, J = 1.5 Hz), 8.81 (1H, d, J = 1.5 Hz),

9.18 (1H, s).

(97e) Acido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-carboxílico

El 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-carboxilato de bencilo (3.58 g, 6.66 mmol) sintetizado en el ejemplo (97d) se disolvió en metanol (100 mL), y se le agregó un catalizador de paladio al 10% en carbón (2.00 g), seguido por agitación a temperatura ambiente durante 3 horas bajo una atmósfera de hidrógeno. El catalizador de paladio en carbón se removió por filtración en Celite, seguido por lavado con tetrahidrofurano. El disolvente se removió por destilación bajo presión reducida para producir el compuesto deseado como un sólido blanco (2.56 g, 86%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 3.22 (3H, s), 3.45 (3H, s), 3.55 (1H, dd, J = 10.2, 3.9 Hz), 3.66 (1H, dd, J = 9.4, 5.9 Hz), 4.72 (1H, s), 6.49 (1H, s), 6.66 (1H, s), 6.99 (2H, s), 7.29 (1H, s), 8.47 (1H, s), 8.79 (1H, s), 10.23 (1H, br s).

(97f) 2-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]fenoxi}-5-(metilsulfonil)pirazina

El ácido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-carboxílico (700 mg, 1.56 mmol) sintetizado en el ejemplo (97e) y 4-dimetilaminopiridina (172 mg, 1.41 mmol), se disolvieron en cloruro de metileno (15 mL), y se les agregó WSCI·HCl (689 mg, 3.60 mmol) y acetohidrazida (255 mg, 3.44 mmol) a temperatura ambiente, seguido

por agitación durante 14 horas bajo una atmósfera de nitrógeno. La solución de reacción se diluyó con cloruro de metileno (50 mL) y se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, seguido por secado sobre sulfato de magnesio anhidro; subsiguientemente el disolvente se removió por destilación bajo presión reducida.

El sólido amarillo resultante (788 mg) se disolvió en cloruro de metileno (10 mL) y se le agregó cloruro de p-toluenosulfonilo (597 mg, 3.13 mmol) y trietilamina (0.87 mL, 6.26 mmol), seguido por agitación a temperatura ambiente durante 6 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio (30 mL) y se extrajo dos veces con cloruro de metileno (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido amarillo pálido (456 mg, rendimiento de 60%).

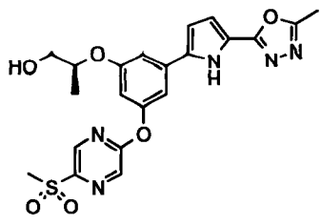
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.36 (3H, d, J = 6.3 Hz), 2.59 (3H, s), 3.24 (3H, s), 3.42 (3H, s), 3.53 (1H, dd, J = 10.4, 4.1 Hz), 3.61 (1H, dd, J = 10.2, 5.9 Hz), 4.56-4.63 (1H, m), 6.59 (1H, t, J = 3.1 Hz), 6.69 (1H, t, J = 2.0 Hz), 6.86 (1H, dd, J = 3.7, 2.5 Hz), 6.95 (1H, t, J = 1.6 Hz), 7.08 (1H, t, J = 1.8 Hz), 8.51 (1H, d, J = 1.2 Hz), 8.81 (1H, d, J = 1.2 Hz), 9.43 (1H, s).

MS (ESI) m/z: 486.14274 $(M+H)^+$.

787

EJEMPLO 98

(2S)-2-(3-[5-(5-Metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenoxi)propan-1-ol



La 2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]fenoxi}-5-(metilsulfonil)pirazina (382 mg, 0.79 mmol) sintetizada en el ejemplo (97f) se disolvió en cloruro de metileno (10 mL), y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 1.58 mL, 1.58 mmol) a -78°C y bajo una atmósfera de nitrógeno. Subsiguientemente la temperatura se regresó a la temperatura ambiente, seguido por agitación durante 1.5 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido blanco (219 mg, rendimiento de 59%).

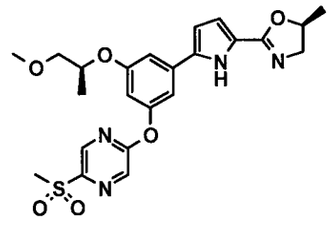
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 2.59 (3H, s), 2.70 (1H, br s), 3.25 (3H, s), 3.79-3.82 (2H, m), 4.54-4.61 (1H, m), 6.57

(1H, t, J = 3.1 Hz), 6.63 (1H, t, J = 2.0 Hz), 6.86 (1H, dd, J = 3.7, 2.5 Hz), 6.96 (1H, t, J = 1.8 Hz), 7.07 (1H, t, J = 1.8 Hz), 8.50 (1H, d, J = 1.6 Hz), 8.80 (1H, d, J = 1.2 Hz), 9.84 (1H, br s).

MS (ESI) m/z: 472.12965 $(M+H)^+$.

EJEMPLO 99

2-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-5-(metilsulfonil)pirazina



El ácido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-carboxílico (700 mg, 1.56 mmol) sintetizado en el ejemplo (97e), y 4-dimetilaminopiridina (96 mg, 0.78 mmol), se disolvieron en cloruro de metileno (20 mL) y se les agregó WSCI·HCl (480 mg, 2.50 mmol) y (R)-1-amino-2-propanol (283 μL, 3.60 mmol) a temperatura ambiente, seguido por agitación durante 14 horas bajo una atmósfera de nitrógeno. La solución de reacción se diluyó con cloruro de metileno (60 mL), se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente

de elución: metanol/cloruro de metileno = 0%-8%).

El sólido blanco resultante (546 mg) se disolvió en tetrahidrofurano (15 mL) y se le agregó ácido metanosulfónico anhidro (377 mg, 2.16 mmol) y trietilamina (0.45 mL, 3.25 mmol), seguido por agitación a 50°C durante 4 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio (30 mL) y se extrajo dos veces con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido amarillo pálido (509 mg, rendimiento de 67%).

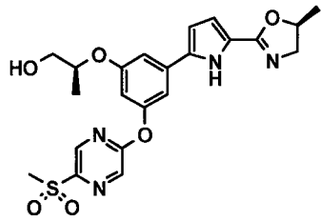
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 1.42 (3H, d, J = 6.3 Hz), 3.24 (3H, s), 3.42 (3H, s), 3.49-3.62 (3H, m), 4.07 (1H, dd, J = 13.5, 8.8 Hz), 4.53-4.61 (1H, m), 4.79-4.87 (1H, m), 6.51 (1H, d, J = 3.9 Hz), 6.65 (1H, t, J = 2.0 Hz), 6.75 (1H, d, J = 3.9 Hz), 6.91 (1H, t, J = 1.6 Hz), 7.06 (1H, t, J = 1.8 Hz), 8.49 (1H, s), 8.81 (1H, s).

MS (ESI) m/z: 487.16506 $(M+H)^+$.

7990

EJEMPLO 100

(2S)-2-(3-{5-[(5S)-5-Metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol



La 2-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-5-(metilsulfonil)pirazina (426 mg, 0.88 mmol) sintetizada en el ejemplo 99 se disolvió en cloruro de metileno (10 mL), y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 1.76 mL, 1.76 mmol) a -78°C y bajo una atmósfera de nitrógeno. Subsiguientemente, la temperatura se regresó a la temperatura ambiente, seguido por agitación durante 1.5 horas. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con cloruro de metileno. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido blanco (243 mg, rendimiento de 59%).

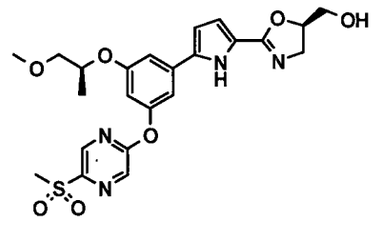
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J = 6.3 Hz), 1.44 (3H, d, J = 6.3 Hz), 3.25 (3H, s), 3.56 (1H, dd, J = 13.9, 7.2 Hz), 3.80 (2H, d, J = 5.5

Hz), 4.10 (1H, dd, J = 14.1, 9.4 Hz), 4.61 (1H, q, J = 5.6 Hz), 4.86 (1H, dt, J = 11.6, 4.5 Hz), 6.47 (1H, d, J = 3.5 Hz), 6.50 (1H, s), 6.75 (1H, d, J = 3.5 Hz), 6.89 (1H, s), 6.99 (1H, s), 8.47 (1H, d, J = 1.2 Hz), 8.80 (1H, d, J = 1.2 Hz).

MS (ESI) m/z: 473.14774 $(M+H)^+$.

EJEMPLO 101

{(5R)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol



(101a) N-[(2S)-2,3-Dihidroxipropil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-carboxamida

El ácido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-carboxílico (1.07 g, 2.39 mmol) sintetizado en el ejemplo (97e) se disolvió en cloruro de metileno (20 mL), y se le agregó WSCI·HCl (732 mg, 3.82 mmol), (S)-(-)-3-amino-1,2-propanodiol (500 mg, 5.49 mmol) y 4-dimetilaminopiridina (146 mg, 1.19 ~~m~~mol) a temperatura ambiente, seguido por agitación durante 25 horas bajo una atmósfera de nitrógeno. La solución de reacción se diluyó con acetato de etilo (50 mL), se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio

anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el producto deseado como un sólido blanco (666 mg, 54%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.35 (4H, d, J = 6.1 Hz), 3.24 (4H, s), 3.42 (3H, s), 3.53 (1H, dd, J = 10.3, 3.9 Hz), 3.59-3.63 (5H, m), 3.84-3.87 (1H, m), 4.58 (1H, dt, J = 11.7, 5.2 Hz), 6.41 (1H, s), 6.50 (1H, t, J = 3.2 Hz), 6.64 (1H, dd, J = 3.7, 2.7 Hz), 6.68 (1H, d, J = 2.0 Hz), 6.95 (1H, s), 7.08 (1H, s), 8.50 (1H, s), 8.81 (1H, s), 9.79 (1H, s).

(101b) N-{(2S)-2-Hidroxi-3-[(triisopropilsilil)oxi]propil}-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-carboxamida

La N-[(2S)-2,3-dihidroxipropil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-carboxamida (666 mg, 1.28 mmol) sintetizada en el ejemplo (101a) se disolvió en cloruro de metileno (20 mL), y se le agregó trietilamina (0.89 mL, 6.40 mmol), cloruro de triisopropilsililo (410 μL, 1.92 mmol) y 4-dimetilaminopiridina (234 mg, 1.92 ~~m~~mol), seguido por agitación durante 14 horas bajo una atmósfera de nitrógeno. La solución de reacción se diluyó con cloruro de metileno (50 mL), se lavó con agua y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano =

10%-60%), para producir el producto deseado como un sólido blanco (558 mg, 64%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.06-1.15 (21H, m), 1.35 (3H, d, J = 6.3 Hz), 3.13 (1H, d, J = 3.9 Hz), 3.24 (3H, s), 3.42 (3H, s), 3.52 (1H, dd, J = 10.3, 3.9 Hz), 3.60 (1H, dd, J = 10.3, 6.8 Hz), 3.68 (1H, dd, J = 10.0, 6.1 Hz), 3.73 (1H, td, J = 7.0, 3.1 Hz), 3.77 (1H, dd, J = 10.0, 4.6 Hz), 3.87 (1H, s), 4.58 (1H, dd, J = 10.3, 6.3 Hz), 6.33 (1H, t, J = 5.6 Hz), 6.50 (1H, t, J = 3.2 Hz), 6.60 (1H, t, J = 3.2 Hz), 6.67 (1H, s), 6.92 (1H, s), 7.06 (1H, s), 8.50 (1H, d, J = 1.0 Hz), 8.81 (1H, d, J = 1.0 Hz), 9.44 (1H, s).

(101c) 2-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5R)-5-{[(triisopropilsilil)oxi]metil}-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-5-(metilsulfonil)pirazina

La N-{(2S)-2-hidroxi-3-[(triisopropilsilil)oxi]propil}-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-carboxamida (558 mg, 0.82 mmol) sintetizada en el ejemplo (101b) se disolvió en tetrahidrofurano (20 mL), y se le agregó ácido metanosulfónico anhidro (287 mg, 1.65 mmol) y trietilamina (0.34 mL, 2.47 mmol), seguido por agitación a 50°C durante 6 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó agua (40 mL) y se extrajo dos veces con cloruro de metileno (40 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente

de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido blanco (496 mg, rendimiento de 94%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.00-1.13 (21H, m), 1.34 (3H, d, J = 6.3 Hz), 3.24 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 10.6, 3.9 Hz), 3.60 (1H, dd, J = 10.4, 6.1 Hz), 3.83-4.04 (4H, m), 4.57 (1H, td, J = 6.3, 4.3 Hz), 4.72-4.79 (1H, m), 6.50 (1H, d, J = 3.9 Hz), 6.65 (1H, t, J = 2.0 Hz), 6.73 (1H, d, J = 3.9 Hz), 6.90 (1H, t, J = 1.8 Hz), 7.05 (1H, t, J = 1.8 Hz), 8.49 (1H, d, J = 1.2 Hz), 8.81 (1H, d, J = 1.2 Hz).

(101d) {(5R)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}-metanol

La 2-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5R)-5-{[(triisopropilsilil)-oxi]metil}-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-5-(metilsulfonil)-pirazina (496 mg, 0.82 mmol) sintetizada en el ejemplo (101c) se disolvió en tetrahidrofurano (20 mL), y se le agregó fluoruro de tetrabutilamonio (solución en tetrahidrofurano 1.0 mol/L, 0.82 mL, 0.82 mmol), seguido por agitación durante 2 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó agua (40 mL) y se extrajo dos veces con acetato de etilo (40 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido blanco (133 mg,

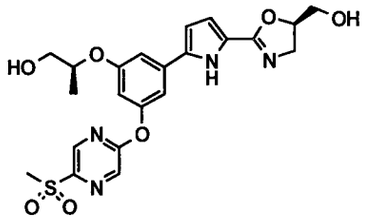
rendimiento de 35%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 3.24 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 10.4, 4.1 Hz), 3.60 (1H, dd, J = 10.2, 5.9 Hz), 3.71 (1H, dd, J = 12.5, 5.5 Hz), 3.79 (1H, dd, J = 14.3, 7.6 Hz), 3.88 (1H, dd, J = 12.5, 3.1 Hz), 4.04 (1H, dd, J = 14.3, 10.0 Hz), 4.57 (1H, dd, J = 10.0, 5.7 Hz), 4.85-4.78 (1H, m), 6.50 (1H, d, J = 3.9 Hz), 6.66 (1H, t, J = 2.2 Hz), 6.77 (1H, d, J = 3.9 Hz), 6.93 (1H, s), 7.06 (1H, s), 8.49 (1H, d, J = 1.2 Hz), 8.81 (1H, d, J = 1.6 Hz).

MS (ESI) m/z: 503.15918 $(M+H)^+$.

EJEMPLO 102

(2S)-2-(3-{5-[(5R)-5-(Hidroximetil)-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol



El {{(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol (105 mg, 0.21 mmol) sintetizado en el ejemplo (101d) se disolvió en cloruro de metileno (10 mL), y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 315 μL, 0.315 mmol) a -78°C y bajo una atmósfera de nitrógeno; subsiguientemente la temperatura se regresó a la temperatura ambiente,

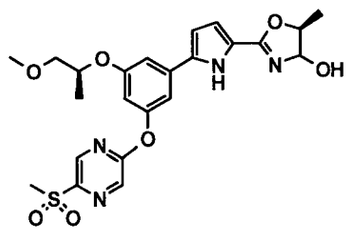
seguido por agitación durante 1 hora. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con cloruro de metileno. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-7.5%), para producir el compuesto deseado como un sólido blanco (67 mg, rendimiento de 66%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.29 (3H, d, J = 6.3 Hz), 3.24 (3H, s), 3.70-3.91 (5H, m), 4.03 (1H, dd, J = 14.1, 9.8 Hz), 4.55 (1H, dd, J = 10.6, 5.9 Hz), 4.85-4.78 (1H, m), 6.47 (1H, d, J = 3.9 Hz), 6.58 (1H, t, J = 2.0 Hz), 6.75 (1H, d, J = 3.5 Hz), 6.92 (1H, t, J = 1.8 Hz), 7.01 (1H, t, J = 1.6 Hz), 8.48 (1H, d, J = 1.2 Hz), 8.80 (1H, d, J = 1.2 Hz).

MS (ESI) m/z: 489.14448 $(M+H)^+$.

EJEMPLO 103

(5S)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)pirazin-2-il]-oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-ol



(103a) L-Treoninato de bencilo

Se disolvió L-treonina 21.2g (178 mmol) en tolueno (100 mL) y se le agregó alcohol bencílico (100 mL, 966 mmol) y ácido p-toluenosulfónico monohidrato (35.0 g, 194 mmol), seguido por calentamiento a reflujo durante 17 horas bajo una atmósfera de nitrógeno. Después de enfriar a temperatura ambiente se le agregó agua (200 mL), seguido por lavado tres veces con acetato de etilo (100 mL). A la capa acuosa se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo tres veces con acetato de etilo (100 mL). Después de que la capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-15%), para producir el producto deseado como un sólido blanco (10.6 g, rendimiento de 28%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.22 (3H, d, J = 6.3 Hz), 3.30 (1H, d, J = 6.3 Hz), 3.49 (1H, brs), 5.19 (2H, s), 7.34-7.39 (5H, m).

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(103b) N-{[5-(3-[(1S)-2-Metoxi-1-metoxietoxi]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]carbonil}-L-treoninato de bencilo

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-[5-(metilsulfonil)-pirazin-2-il]oxi)fenil}-1H-pirrol-2-carboxílico (9.49 g, 21.2 mmol) sintetizado en el ejemplo (97e) se disolvió en N,N-dimetilformamida (200 mL), y se le agregó L-treoninato de bencilo (4.44 g, 21.2 mmol) sintetizado en el ejemplo (103a), WSCI·HCl (4.88 g, 25.5 mmol), HOBT·H_2O (3.15 g, 23.3 mmol) y N-metilmorfolina (4.66 mL, 42.4 mmol), seguido por agitación a temperatura ambiente durante 1.5 horas bajo una atmósfera de nitrógeno. Se le agregó agua (200 mL) y se extrajo dos veces con acetato de etilo (200 ml). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 70%-100%), para producir el producto deseado como un aceite amarillo pálido (13.5 g, rendimiento de ~100%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.27 (3H, d, J = 6.3 Hz), 1.35 (3H, d, J = 6.3 Hz), 3.24 (3H, s), 3.42 (3H, s), 3.52 (1H, dd, J = 4.3, 10.2 Hz), 3.61 (1H, dd, J = 5.9, 10.2 Hz), 4.44 (1H, m), 4.59 (1H, m), 4.81 (1H, dd, J = 2.7, 8.6 Hz), 5.21 (1H, d, J = 12.5 Hz), 5.25 (1H, d, J = 12.5 Hz), 6.52 (1H, t, J = 3.9 Hz), 6.67 (1H, t, J = 2.0 Hz), 6.71 (1H, brd, J = 8.6 Hz), 6.75 (1H, dd, J = 2.4, 3.9 Hz), 6.94 (1H, t, J = 1.9 Hz), 7.08 (1H, t, J = 1.9 Hz), 7.33-7.38 (5H, m), 8.49 (2H, m), 8.81 (2H, m), 9.63 (1H, brs).

(103c) (4S,5S)-2-[5-(3-[(1S)-2-Metoxi-1-metoxietoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-carboxilato de bencilo

El N-{[5-(3-[(1S)-2-metoxi-1-metoxietoxi]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]carbonil}-L-treoninato de bencilo (13.5 g, 21.2 mmol) sintetizado en el ejemplo (103b) se disolvió en cloruro de metileno (150 mL) y se enfrió a -78°C. Se le agregó a gotas trifluoruro de bis(2-metoxietil)aminoazufre (5.47 mL, 29.7 mmol) y se agitó a -78°C durante 40 minutos. Se le agregó carbonato de potasio (5.86 g, 42.4 mmol) y se agitó durante 1.5 horas, aumentando la temperatura gradualmente a la temperatura ambiente. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (100 mL) a 0°C y se extrajo dos veces con cloruro de metileno (100 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 40%-70%), para producir el producto deseado como un sólido blanco (9.68 g, rendimiento de 74%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.29 (3H, d, J = 6.3 Hz), 1.35 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.51 (1H, dd, J = 3.9, 10.2 Hz), 3.60 (1H, dd, J = 5.9, 10.2 Hz), 4.58 (1H, m), 4.94 (1H, d, J = 9.8 Hz), 5.02 (1H, m), 5.19 (1H, d, J = 12.1 Hz), 5.24 (1H, d, J = 12.1 Hz), 6.51 (1H, t, J = 3.9 Hz), 6.66 (1H, t, J = 2.4 Hz), 6.78 (1H, t, J = 3.9 Hz), 6.94 (1H, t, J = 2.0 Hz), 7.08

(1H, t, J = 2.4 Hz), 7.35-7.39 (5H, m), 8.48 (2H, d, J = 1.2 Hz), 8.81 (2H, d, J = 1.2 Hz).

(103d) (5S)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-ol

El (4S,5S)-2-[5-(3-[(1S)-2-metoxi-1-metoxietoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-carboxilato de bencilo (1.53 g, 2.47 mmol) sintetizado en el ejemplo (103c) se disolvió en tetrahidrofurano (50 mL), y se le agregó un catalizador de paladio al 10% en carbón (600 mg), seguido por agitación a temperatura ambiente durante 2.5 horas bajo una atmósfera de hidrógeno. El catalizador de paladio en carbón se removió por filtración en Celite, seguido por lavado con acetato de etilo. El disolvente se removió por destilación bajo presión reducida.

El residuo resultante se disolvió en acetonitrilo (60 mL) y se le agregó una solución de diamonio nitrato de cerio (IV) (2.03 g, 3.70 mmol) en agua (30 mL), gota a gota a 0°C. Después de agitar a temperatura ambiente durante 17 horas bajo una atmósfera de nitrógeno, se le agregó una solución acuosa saturada de carbonato ácido de sodio (30 mL) y se extrajo dos veces con acetato de etilo (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente

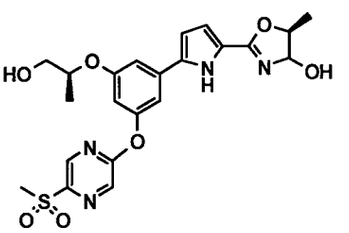
de elución: acetato de etilo/hexano = 70%-100%), para producir el producto deseado como un sólido blanco (645 mg, rendimiento de 52%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 1.37 (6/3H, d, J = 6.7 Hz), 1.47 (3/3H, d, J = 6.7 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 4.3, 10.2 Hz), 3.60 (1H, dd, J = 5.9, 10.2 Hz), 4.50-4.66 (2H, m), 5.39 (2/3H, d, J = 3.1 Hz), 5.66 (1/3H, d, J = 6.7 Hz), 6.50 (1H, brd, J = 3.9 Hz), 6.65 (1H, t, J = 2.4 Hz), 6.82 (1H, brd, J = 3.9 Hz), 6.94 (1H, t, J = 2.0 Hz), 7.08 (1H, t, J = 2.0 Hz), 8.48 (2H, d, J = 1.2 Hz), 8.80 (2H, d, J = 1.2 Hz).

MS (ESI) m/z: 503.16004 $(M+H)^+$.

EJEMPLO 104

(5S)-2-[5-(3-[(1S)-2-Hidroxi-1-metiletoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-ol



El (5S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-ol (410 mg, 0.816 mmol) sintetizado en el ejemplo (103d) se disolvió en cloruro de metileno (20 mL) y se enfrió a -78°C. Se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 2.04 mL, 2.04 mmol) y se agitó durante 2 horas, aumentando la temperatura gradualmente a la temperatura

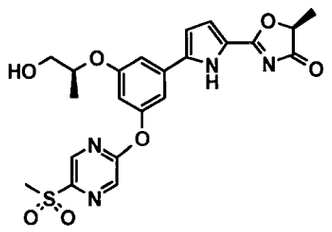
ambiente. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (20 mL) y se extrajo dos veces con cloruro de metileno (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 2%-10%), para producir el producto deseado como un sólido blanco (362 mg, rendimiento de 91%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.30 (3H, d, J = 6.3 Hz), 1.38 (6/3H, d, J = 6.7 Hz), 1.49 (3/3H, d, J = 6.7 Hz), 3.23 (3H, s), 3.76 (2H, brd, J = 5.5 Hz), 4.51-4.57 (2H, m), 5.39 (2/3H, d, J = 3.5 Hz), 5.66 (1/3H, d, J = 6.7 Hz), 6.49 (1H, d, J = 3.9 Hz), 6.61 (1H, t, J = 2.4 Hz), 6.81 (1H, d, J = 3.9 Hz), 6.94 (1H, t, J = 2.0 Hz), 7.06 (1H, t, J = 2.0 Hz), 8.47 (2H, d, J = 1.2 Hz), 8.78 (2H, d, J = 1.2 Hz).

MS (ESI) m/z: 489.14439 $(M+H)^+$.

EJEMPLO 105

(5S)-2-[5-(3-[(1S)-2-Hidroxi-1-metiletoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4(5H)-ona



(105a) (5S)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4(5H)-ona

El (5S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-ol (80.0 mg, 0.159 mmol) sintetizado en el ejemplo (103d) se disolvió en cloruro de metileno (10 mL), y se les agregó dicromato de piridinio (240 mg, 0.638 mmol) y tamices moleculares de 4A (200mg), seguido por agitación a temperatura ambiente durante 2 horas bajo una atmósfera de nitrógeno. Después de filtración en Celite, el disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-70%), para producir el producto deseado como un sólido blanco (44.1 mg, rendimiento de 55%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.36 (3H, d, J = 6.3 Hz), 1.62 (3H, d, J = 7.0 Hz), 3.25 (3H, s), 3.42 (3H, s), 3.52 (1H, dd, J = 3.9, 10.2 Hz), 3.62

(1H, dd, J = 5.9, 10.2 Hz), 4.62 (1H, m), 4.81 (1H, q, J = 7.0 Hz), 6.68 (1H, d, J = 3.9 Hz), 6.76 (1H, t, J = 2.4 Hz), 7.03 (1H, t, J = 2.0 Hz), 7.17 (1H, t, J = 2.0 Hz), 7.26 (1H, d, J = 3.9 Hz), 8.52 (2H, d, J = 1.2 Hz), 8.82 (2H, d, J = 1.2 Hz).

(105b) (5S)-2-[5-(3-[(1S)-2-Hidroxi-1-metiletoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4(5H)-ona

La (5S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4(5H)-ona (100 mg, 0.200 mmol) sintetizada en el ejemplo (105a) se disolvió en cloruro de metileno (10 mL) y se enfrió a -78°C. Se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 0.260 mL, 0.260 mmol) y se agitó durante 2 horas, aumentando la temperatura gradualmente a la temperatura ambiente. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (10 mL) y se extrajo dos veces con cloruro de metileno (10 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-10%), para producir el producto deseado como un sólido blanco (98.0 mg, rendimiento de ~100%).

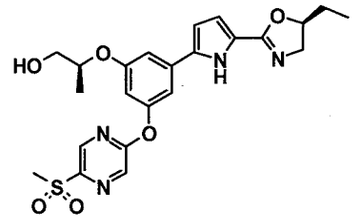
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 1.63 (3H, dd, J = 2.7, 7.0 Hz), 3.26 (3H, s), 3.80-3.84 (2H, m), 4.62 (1H, m), 4.84 (1H, q, J = 7.0 Hz), 6.66 (1H, d, J = 3.9 Hz), 6.69 (1H, m), 7.03 (1H, m), 7.20 (1H, m),

7.26 (1H, brd, J = 3.9 Hz), 8.51 (2H, d, J = 1.2 Hz), 8.81 (2H, d, J = 1.2 Hz).

MS (ESI) m/z: 487.12874 $(M+H)^+$.

EJEMPLO 106

(2S)-2-(3-{5-[(5S)-5-Etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol



(106a) 5-{3-Hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-carboxilato de bencilo

El 3-[(1S)-2-metoxi-1-metiletoxi]-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenol (26.79 g, 86.9 mmol) sintetizado en el ejemplo (78d), y el 5-bromo-1H-pirrol-1,2-dicarboxilato de 2-bencilo-1-t-butilo (32.32 g, 85.0 mmol) sintetizado en el ejemplo (78f), se disolvieron en 1,4-dioxano (360 mL) + agua (90 mL), y se les agregó complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano (2.34 g, 2.87 mmol) y carbonato de potasio (30.40 g, 220 mmol), seguido por agitación a 60°C durante 3 horas bajo una atmósfera de nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente, se le agregó agua (1000 mL) y se extrajo con acetato de etilo (700 mL). La capa orgánica se lavó con salmuera saturada; subsiguientemente se secó sobre sulfato de sodio anhidro

y el disolvente se removió por destilación bajo presión reducida.

El residuo resultante se disolvió en cloruro de metileno (100 mL) y se le agregó ácido trifluoroacético (120 mL), seguido por agitación a temperatura ambiente durante 1 hora. Después de que la solución de reacción se concentró bajo presión reducida, se diluyó con acetato de etilo (500 mL), se lavó con solución acuosa saturada de carbonato ácido de sodio y salmuera saturada; subsiguientemente se secó sobre sulfato de sodio anhidro y el disolvente se removió por destilación bajo presión reducida. El residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-50%), para producir el compuesto deseado como un aceite pardo (17.40 g, rendimiento de 54%).

^{1}H -RMN ($CDCl_3$, 400 Hz): δ 1.31 (3H, d, J = 6.3 Hz), 3.42 (3H, s), 3.49 (1H, dd, J = 9.8, 4.3 Hz), 3.59 (1H, dd, J = 10.2, 6.3 Hz), 4.52-4.59 (1H, m), 5.35 (2H, s), 6.42 (1H, t, J = 2.0 Hz), 6.47 (1H, dd, J = 3.9, 2.7 Hz), 6.72 (1H, s), 6.77 (1H, br s), 6.80 (1H, s), 6.98 (1H, dd, J = 3.9, 2.7 Hz), 7.45-7.33 (5H, m), 9.94 (1H, br s).

MS (FAB) m/z: 382 $(M+H)^+$.

(106b) 5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]-fenil}-1H-pirrol-2-carboxilato de bencilo

El 5-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-carboxilato de bencilo (27.35 g, 71.7 mmol) sintetizado en el ejemplo (106a) se disolvió en cloruro de metileno (350 mL), y se le agregó cloruro de triisopropilsililo (18.4 mL, 86.0 mmol), trietilamina (30.0 mL, 215 mmol) y 4-

dimetilaminopiridina (10.53 g, 86.2 mmol), seguido por agitación a temperatura ambiente durante 4 horas bajo una atmósfera de nitrógeno. Se le agregó agua (400 mL) para separar la solución y la capa orgánica se lavó con salmuera saturada, seguido por secado sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 3%-20%), para producir el producto deseado como un aceite amarillo pálido (34.41 g, rendimiento de 89%).

^{1}H-RMN ($CDCl_3$, 400 Hz): δ 1.11 (18H, d, J = 7.0 Hz), 1.22-1.30 (3H, m), 1.32 (3H, d, J = 6.3 Hz), 3.41 (3H, s), 3.49 (1H, dd, J = 10.2, 4.3 Hz), 3.58 (1H, dd, J = 10.2, 5.9 Hz), 4.49-4.56 (1H, m), 5.33 (2H, s), 6.43 (1H, t, J = 2.3 Hz), 6.47 (1H, dd, J = 3.9, 2.7 Hz), 6.66 (1H, t, J = 2.0 Hz), 6.71 (1H, t, J = 1.8 Hz), 6.98 (1H, dd, J = 3.9, 2.7 Hz), 7.32-7.45 (5H, m), 9.19 (1H, br s).

MS (FAB) m/z: 538 $(M+H)^+$.

(106c) Acido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)-oxi]fenil}-1H-pirrol-2-carboxílico

El 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]fenil}-1H-pirrol-2-carboxilato de bencilo (34.40 g, 64.0 mmol) sintetizado en el ejemplo (106b) se disolvió en etanol (320 mL), y se le agregó un catalizador de paladio al 10% en carbón (3.54 g), seguido por agitación durante 2 horas bajo una atmósfera de hidrógeno. El catalizador de paladio en carbón se removió por filtración en Celite y el disolvente se removió por destilación bajo presión reducida, para producir el compuesto deseado como un sólido blanco

(27.31 g, rendimiento de 95%).

^{1}H-RMN ($CDCl_3$, 400 Hz): δ 1.11 (18H, d, J = 7.4 Hz), 1.22-1.30 (3H, m), 1.33 (3H, d, J = 6.3 Hz), 3.46 (1H, s), 3.51 (1H, dd, J = 10.2, 4.7 Hz), 3.66 (1H, dd, J = 10.2, 5.9 Hz), 4.61-4.69 (1H, m), 6.43 (1H, t, J = 2.0 Hz), 6.51 (1H, dd, J = 3.7, 2.2 Hz), 6.74 (1H, t, J = 1.6 Hz), 6.98 (1H, t, J = 1.6 Hz), 7.05 (1H, dd, J = 3.9, 2.3 Hz), 10.02 (1H, br s).

MS (FAB) m/z: 448 $(M+H)^+$.

(106d) N-[(2R)-2-Hidroxibutil]-5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-carboxamida

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]-fenil}-1H-pirrol-2-carboxílico (1.03 g, 2.30 mmol) sintetizado en el ejemplo (106c) se disolvió en cloruro de metileno (20 mL), y se le agregó (2R)-1-aminobutan-2-ol (0.40 g, 4.49 mmol), sintetizado de acuerdo con un método conocido (*Angew. Chem. Int. Ed.* 2007, 46, 2245), WSC·HCl (1.15 g, 6.00 mmol) y 4-dimetilaminopiridina (280 mg, 2.29 mmol), seguido por agitación a temperatura ambiente durante la noche bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo con cloruro de metileno (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 60%-80%), para producir el compuesto deseado como un sólido blanco (1.01

g, rendimiento de 85%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 0.99 (3H, t, J = 7.4 Hz), 1.11 (18H, d, J = 7.0 Hz), 1.23-1.30 (3H, m), 1.31 (3H, d, J = 6.3 Hz), 1.49-1.60 (2H, m), 3.27-3.35 (1H, m), 3.42 (3H, s), 3.49 (1H, dd, J = 10.2, 4.3 Hz), 3.59 (1H, dd, J = 10.2, 5.9 Hz), 3.62-3.69 (1H, m), 3.70-3.76 (1H, m), 4.49-4.56 (1H, m), 6.33 (1H, t, J = 5.7 Hz), 6.41 (1H, t, J = 2.2 Hz), 6.45 (1H, dd, J = 3.5, 3.1 Hz), 6.61 (1H, dd, J = 3.7, 2.5 Hz), 6.67 (1H, t, J = 1.8 Hz), 6.73 (1H, t, J = 1.8 Hz), 9.58 (1H, s).

(106e) (5S)-5-Etil-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol

La N-[(2R)-2-hidroxibutil]-5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-carboxamida (1.01 g, 1.95 mmol) sintetizada en el ejemplo (106d) se disolvió en tetrahidrofurano (40 mL), y se le agregó ácido metanosulfónico anhidro (600 mg, 3.44 mmol) y trietilamina (1.60 mL, 11.48 mmol), seguido por agitación a 50°C durante 8 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con cloruro de metileno (80 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-70%), para producir el compuesto deseado como un sólido amarillo (980 mg, rendimiento de 100%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.01 (3H, t, J = 7.4 Hz), 1.09-1.14 (18H, m), 1.24-1.30 (3H, m), 1.32 (3H, d, J = 6.3 Hz), 1.71-1.82 (2H, m), 3.42 (3H, s), 3.49 (1H, dd, J = 10.2, 4.3 Hz), 3.57-3.63 (2H, m), 4.04 (2H, dd, J = 14.1,9.4 Hz), 4.51-4.56 (1H, m), 4.62-4.68 (1H, m), 6.39 (1H, t, J = 2.2 Hz), 6.46 (1H, d, J = 3.9 Hz), 6.71 (1H, s), 6.75 (1H, s), 6.76 (1H, s).

(106f) 2-(3-{5-[(5S)-5-Etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[(2S)-1-metoxipropan-2-il]oxi}fenoxi)-5-(metilsulfonil)pirazina

El (5S)-5-etil-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol (980 mg, 1.95 mmol) sintetizado en el ejemplo (106e) se disolvió en tetrahidrofurano (20 mL), y se le agregó fluoruro de tetrabutilamonio (solución en tetrahidrofurano 1.0 mol/L, 4.00 mL, 4.00 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante 1.5 horas bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo con cloruro de metileno (40 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida para producir un sólido amarillo.

Este se disolvió en acetonitrilo (20 mL) y se le agregó 2-cloro-5-(metilsulfonil)pirazina (420 mg, 2.18 mmol), sintetizada en el ejemplo (97c), y carbonato de cesio (1.42 g, 4.36 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante 2 horas bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó agua (30 mL) y se extrajo

con cloruro de metileno (40 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo = 100%), para producir el compuesto deseado como un sólido amarillo (860 mg, rendimiento de 88%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.08 (3H, t, J = 7.4 Hz), 1.38 (3H, d, J = 6.3 Hz), 1.81-1.94 (2H, m), 3.24 (3H, s), 3.42 (3H, s), 3.56 (1H, dd, J = 10.6, 3.9 Hz), 3.62 (1H, dd, J = 10.6, 5.9 Hz), 3.74 (1H, dd, J = 12.7, 7.6 Hz), 4.17 (1H, dd, J = 12.1,9.8 Hz), 4.74 (1H, br s), 4.99 (1H, br s), 6.61 (1H, d, J = 4.3 Hz), 6.74 (1H, s), 7.06 (1H, s), 7.20 (1H, s), 7.40 (1H, s), 8.50 (1H, d, J = 1.2 Hz), 8.82 (1H, d, J = 1.2 Hz).

(106g) (2S)-2-(3-{5-[(5S)-5-Etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol

La 2-(3-{5-[(5S)-5-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[(2S)-1-metoxipropan-2-il]oxi}fenoxi)-5-(metilsulfonil)pirazina (860 mg, 1.72 mmol) sintetizada en el ejemplo (106f) se disolvió en cloruro de metileno (20 mL), y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 2.50 mL, 2.50 mmol), gota a gota a -78°C, seguido por agitación a temperatura ambiente durante 2 horas bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio (20 mL) y se extrajo con cloruro de metileno (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se

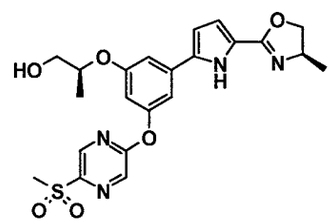
secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 2%-4%), para producir el compuesto deseado como un sólido amarillo (764 mg, rendimiento de 91%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.02 (3H, t, J = 7.4 Hz), 1.33 (3H, d, J = 6.3 Hz), 1.67-1.85 (2H, m), 3.23 (3H, s), 3.63 (1H, dd, J = 13.7, 7.8 Hz), 3.73-3.83 (2H, m), 4.07 (1H, dd, J = 13.7, 9.4 Hz), 4.60 (1H, br s), 4.72 (1H, br s), 6.51 (1H, d, J = 3.9 Hz), 6.60 (1H, s), 6.81 (1H, d, J = 3.5 Hz), 6.96 (1H, s), 7.12 (1H, s), 8.48 (1H, d, J = 1.2 Hz), 8.80 (1H, d, J = 1.2 Hz).

MS (ESI) m/z: 487.16397 $(M+H)^+$.

EJEMPLO 107

(2S)-2-(3-{5-[(4R)-4-Metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol



(107a) N-[(2R)-1-Hidroxipropan-2-il]-5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-carboxamida

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]-fenil}-1H-pirrol-2-carboxílico (2.25 g, 5.03 mmol) sintetizado en el ejemplo

(106c) se disolvió en metanol (50 mL), y se le agregó D-alaninol (0.70 mL, 8.97 mmol) y cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio n-hidratado (3.05 g, 11.02 mmol), seguido por agitación a temperatura ambiente durante 1 día, bajo una atmósfera de nitrógeno. Después de que el disolvente se removió por destilación bajo presión reducida, se le agregó una solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con acetato de etilo (80 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 80%-100%), para producir el compuesto deseado como un sólido blanco (1.95 g, rendimiento de 75%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.11 (18H, d, J = 7.4 Hz), 1.23-1.28 (3H, m), 1.28 (3H, d, J = 7.0 Hz), 1.32 (3H, d, J = 5.9 Hz), 3.42 (3H, s), 3.49 (1H, dd, J = 10.2, 4.3 Hz), 3.59 (1H, dd, J = 10.2, 5.9 Hz), 3.64 (1H, dd, J = 11.1, 6.1 Hz), 3.77 (1H, dd, J = 10.9, 3.5 Hz), 4.24 (1H, br s), 4.53 (1H, br s), 6.05 (1H, s), 6.41 (1H, t, J = 2.0 Hz), 6.45 (1H, t, J = 3.3 Hz), 6.60 (1H, dd, J = 3.7, 2.5 Hz), 6.67 (1H, t, J = 1.8 Hz), 6.74 (1H, t, J = 1.8 Hz), 9.60 (1H, s).

(107b) (4R)-2-[5-(3-{[(2S)-1-Metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-il]-4-metil-4,5-dihidro-1,3-oxazol

La N-[(2R)-1-hidroxipropan-2-il]-5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-carboxamida (1.95 g, 3.76 mmol) sintetizada en el ejemplo (107a) se disolvió en tetrahidrofurano (30 mL), y se le agregó ácido metanosulfónico anhidro (1.25 g, 7.18 mmol) y

trietilamina (2.80 mL, 20.09 mmol), seguido por agitación a 50°C durante 1 día, bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (80 mL) y se extrajo con cloruro de metileno (120 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-80%), para producir el compuesto deseado como un sólido amarillo (1.18 g, rendimiento de 64%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.12 (18H, d, J = 7.4 Hz), 1.23-1.31 (3H, m), 1.31-1.35 (6H, m), 3.42 (3H, s), 3.49 (1H, dd, J = 10.2, 4.7 Hz), 3.59 (1H, dd, J = 10.2, 5.9 Hz), 3.93 (1H, t, J = 7.8 Hz), 4.33 (1H, br s), 4.49 (1H, dd, J = 9.0, 8.2 Hz), 4.54 (1H, br s), 6.40 (1H, t, J = 2.2 Hz), 6.46 (1H, d, J = 3.5 Hz), 6.72 (1H, t, J = 1.8 Hz), 6.74 (1H, d, J = 3.9 Hz), 6.77 (1H, t, J = 1.8 Hz).

(107c) 3-{[(2S)-1-Metoxipropan-2-il]oxi}-5-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenol

El (4R)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-il]-4-metil-4,5-dihidro-1,3-oxazol (1.18 g, 2.42 mmol) sintetizado en el ejemplo (107b) se disolvió en tetrahidrofurano (10 mL), y se le agregó fluoruro de tetrabutilamonio (solución en tetrahidrofurano 1.0 mol/L, 3.00 mL, 3.00 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante 30 minutos bajo una atmósfera de nitrógeno. A

esta solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo con cloruro de metileno (40 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 1%-3%), para producir el compuesto deseado como un sólido amarillo (720 mg, rendimiento de 90%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 1.49 (3H, d, J = 6.3 Hz), 3.42 (3H, s), 3.48 (1H, dd, J = 10.2, 4.7 Hz), 3.59 (1H, dd, J = 10.2, 5.9 Hz), 4.02 (1H, t, J = 7.6 Hz), 4.47-4.61 (3H, m), 6.38 (1H, t, J = 2.2 Hz), 6.48 (1H, d, J = 3.9 Hz), 6.73 (1H, t, J = 1.8 Hz), 6.76 (1H, d, J = 3.9 Hz), 7.09 (1H, s), 11.09 (1H, s).

(107d) 2-Bromo-5-(metilsulfonil)pirazina

Se disolvió 2,5-dibromopirazina (270 mg, 1.14 mmol) en tetrahidrofurano (10 mL) y se le agregó tiometóxido de sodio (320 mg, 4.57 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante 2.5 horas bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó agua (10 mL) y se extrajo con éter dietílico (10 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 5%-

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10%) para producir un sólido amarillo.

Este se disolvió en cloruro de metileno (10 mL) y se le agregó ácido m-cloroperbenzoico (aproximadamente 65%, 580 mg, aproximadamente 2.2 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante 1 hora bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio (10 mL) y se extrajo con cloruro de metileno (10 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 15%-25%), para producir el compuesto deseado como un sólido blanco (190 mg, rendimiento de 70%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 3.26 (3H, s), 8.80 (1H, d, J = 1.2 Hz), 9.06 (1H, d, J = 1.2 Hz).

(107e) 2-(3-{[(2S)-1-Metoxipropan-2-il]oxi}-5-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-5-(metilsulfonil)pirazina

El 3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenol (340 mg, 1.03 mmol) sintetizado en el ejemplo (107c) se disolvió en acetonitrilo (10 mL) y se le agregó 2-bromo-5-(metilsulfonil)pirazina (300 mg, 1.27 mmol), sintetizada en el ejemplo (107d), y carbonato de cesio (850 mg, 2.61 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante 4.5 horas bajo una atmósfera de

nitrógeno. A esta solución de reacción, se le agregó agua (20 mL) y se extrajo con cloruro de metileno (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo = 100%), para producir el compuesto deseado como un sólido blanco (456 mg, rendimiento de 91%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 4.3 Hz), 1.35 (3H, d, J = 3.9 Hz), 3.24 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 10.2, 3.9 Hz), 3.60 (1H, dd, J = 10.4, 6.1 Hz), 3.93 (1H, t, J = 7.8 Hz), 4.33 (1H, br s), 4.51 (1H, t, J = 8.6 Hz), 4.58 (1H, br s), 6.52 (1H, d, J = 3.9 Hz), 6.66 (1H, t, J = 2.2 Hz), 6.76 (1H, d, J = 3.9 Hz), 6.92 (1H, t, J = 1.8 Hz), 7.07 (1H, d, J = 1.6 Hz), 8.49 (1H, d, J = 1.2 Hz), 8.81 (1H, d, J = 1.6 Hz).

(107f) (2S)-2-(3-{5-[(4R)-4-Metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol

La 2-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-5-(metilsulfonil)pirazina (456 mg, 0.94 mmol) sintetizada en el ejemplo (107e) se disolvió en cloruro de metileno (5.0 mL), y se le agregó a gotas a -78°C tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 1.50 mL, 1.50 mmol), seguido por agitación a temperatura ambiente durante 3 horas bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio (10 mL) y se extrajo con cloruro de metileno (20

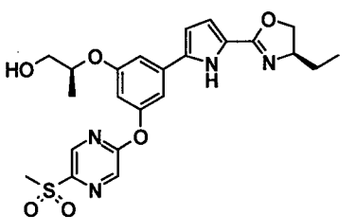
mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 4%-6%), para producir el compuesto deseado como un sólido blanco (330 mg, rendimiento de 74%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 1.40 (3H, d, J = 6.6 Hz), 3.22 (3H, s), 3.71 (1H, dd, J = 11.7, 4.3 Hz), 3.81 (1H, dd, J = 11.7, 6.6 Hz), 4.05-4.14 (1H, m), 4.38-4.45 (1H, m), 4.59-4.67 (2H, m), 6.53 (1H, d, J = 3.9 Hz), 6.62 (1H, t, J = 2.2 Hz), 6.87 (1H, d, J = 3.9 Hz), 6.98 (1H, s), 7.27 (1H, s), 8.47 (1H, d, J = 1.2 Hz), 8.79 (1H, d, J = 1.2 Hz).

MS (ESI) m/z: 473.14930 $(M+H)^+$.

EJEMPLO 108

(2S)-2-(3-{5-[(4R)-4-Etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol



(108a) (4R)-4-Etil-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)-

oxi]fenil}-1H-pirrol-2-carboxílico (1.40 g, 3.13 mmol) sintetizado en el ejemplo (106c) se disolvió en metanol (20 mL), y se le agregó (R)-(-)-2-amino-1-butanol (0.65 g, 7.29 mmol) y cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio n-hidratado (1.75 g, 6.32 mmol), seguido por agitación a temperatura ambiente durante 2 días bajo una atmósfera de nitrógeno. Después de que el disolvente se removió por destilación bajo presión reducida, se le agregó una solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con cloruro de metileno (100 mL). La capa orgánica se lavó con solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-80%), para producir el compuesto como una espuma blanca.

Esta se disolvió en tetrahidrofurano (20 mL) y se le agregó ácido metanosulfónico anhidro (0.80 g, 4.59 mmol) y trietilamina (1.20 mL, 8.61 mmol), seguido por agitación a 50°C durante la noche bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (60 mL) y se extrajo con cloruro de metileno (100 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 70%-90%), para producir el compuesto deseado

como un sólido blanco (965 mg, rendimiento de 62%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.00 (3H, t, J = 7.6 Hz), 1.07-1.14 (18H, m), 1.23-1.31 (3H, m), 1.32 (3H, d, J = 6.3 Hz), 1.56-1.65 (1H, m), 1.68-1.77 (1H, m), 3.41 (3H, s), 3.48 (1H, dd, J = 10.0, 4.6 Hz), 3.59 (1H, dd, J = 10.0, 5.6 Hz), 4.01 (1H, t, J = 7.8 Hz), 4.15-4.21 (1H, m), 4.44 (1H, t, J = 8.8 Hz), 4.49-4.54 (1H, m), 6.39 (1H, t, J = 2.0 Hz), 6.46 (1H, d, J = 3.9 Hz), 6.71 (1H, t, J = 1.7 Hz), 6.74 (1H, d, J = 3.4 Hz), 6.76 (1H, t, J = 1.7 Hz).

(108b) 3-{5-[(4R)-4-Etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[(2S)-1-metoxipropan-2-il]oxi}fenol

El (4R)-4-etil-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol (965 mg, 1.93 mmol) sintetizado en el ejemplo (108a) se disolvió en tetrahidrofurano (10 mL) y se le agregó fluoruro de tetrabutilamonio (solución en tetrahidrofurano 1.0 mol/L, 2.50 mL, 2.50 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante 1 hora bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo con cloruro de metileno (40 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 2%-4%), para producir el compuesto deseado como un sólido blanco (550 mg, rendimiento de 83%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.10 (3H, t, J = 7.4 Hz), 1.32 (3H, d, J = 6.3 Hz), 1.73 (1H, td, J = 14.1,7.0 Hz), 1.85 (1H, td, J = 14.0, 7.0 Hz), 3.41 (3H, s), 3.48 (1H, dd, J = 10.2, 4.7 Hz), 3.59 (1H, dd, J = 10.2, 5.9 Hz), 4.09-4.15 (1H, m), 4.32-4.40 (1H, m), 4.48-4.57 (2H, m), 6.36 (1H, t, J = 2.2 Hz), 6.47 (1H, d, J = 3.5 Hz), 6.72 (1H, t, J = 1.8 Hz), 6.76 (1H, d, J = 3.9 Hz), 7.10 (1H, t, J = 1.8 Hz), 11.12 (1H, br s).

(108c) 2-(3-{5-[(4R)-4-Etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[(2S)-1-metoxipropan-2-il]oxi}fenoxi)-5-(metilsulfonil)pirazina

El 3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[(2S)-1-metoxipropan-2-il]oxi}fenol (272 mg, 0.79 mmol) sintetizado en el ejemplo (108b) se disolvió en acetonitrilo (5.0 mL) y se le agregó 2-cloro-5-(metilsulfonil)pirazina (220 mg, 1.14 mmol), sintetizada en el ejemplo (97c), y carbonato de cesio (640 mg, 1.96 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante 3.5 horas bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó agua (20 mL) y se extrajo con cloruro de metileno (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 2%-3%), para producir el compuesto deseado como un sólido amarillo pálido (417 mg, rendimiento de ~100%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 0.96 (3H, t, J = 7.4 Hz), 1.34 (3H, d, J = 6.3 Hz), 1.53-1.60 (1H, m), 1.65-1.72 (1H, m), 3.23 (3H, s), 3.41 (3H, s),

3.50 (1H, dd, J = 10.2, 4.3 Hz), 3.59 (1H, dd, J = 10.6, 5.9 Hz), 4.01 (1H, t, J = 7.8 Hz), 4.11-4.19 (1H, m), 4.41-4.46 (1H, m), 4.57 (1H, br s), 6.50 (1H, d, J = 3.9 Hz), 6.64 (1H, t, J = 2.2 Hz), 6.73 (1H, d, J = 3.5 Hz), 6.94 (1H, d, J = 1.6 Hz), 7.09 (1H, d, J = 1.6 Hz), 8.47 (1H, d, J = 0.8 Hz), 8.80 (1H, d, J = 0.8 Hz).

(108d) (2S)-2-(3-{5-[(4R)-4-Etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol

La 2-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[(2S)-1-metoxipropan-2-il]oxi}fenoxi)-5-(metilsulfonil)pirazina (417 mg, 0.83 mmol) sintetizada en el ejemplo (108c) se disolvió en cloruro de metileno (10 mL) y se le agregó a gotas a -78°C tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 1.00 mL, 1.00 mmol), seguido por agitación a temperatura ambiente durante 1 hora bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa de hidróxido de sodio 1N (20 mL) y se extrajo con cloruro de metileno (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 3%-4%), para producir el compuesto deseado como un sólido blanco (325 mg, rendimiento de 80%).

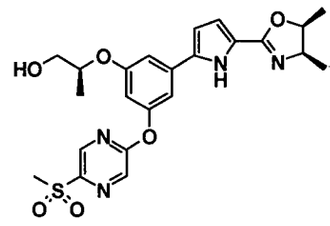
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.01 (3H, t, J = 7.4 Hz), 1.30 (3H, d, J = 6.3 Hz), 1.57-1.64 (1H, m), 1.68-1.75 (1H, m), 3.23 (3H, s), 3.78-3.80 (2H, m), 4.02 (1H, t, J = 8.0 Hz), 4.16-4.22 (1H, m), 4.47 (1H, t, J = 8.8 Hz), 4.57-4.63 (1H, m), 6.45 (1H, d, J = 3.5 Hz), 6.49 (1H, s), 6.73 (1H, d, J = 3.9

Hz), 6.90 (1H, s), 7.01 (1H, s), 8.44 (1H, s), 8.79 (1H, s).

MS (ESI) m/z: 487.16468 $(M+H)^+$.

EJEMPLO 109

(2S)-2-(3-{5-[(4R,5S)-4,5-Dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol



(109a) N-[(2R,3R)-3-Hidroxibutan-2-il]-5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-carboxamida

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]-fenil}-1H-pirrol-2-carboxílico (0.89 g, 1.99 mmol) sintetizado en el ejemplo (106c) se disolvió en metanol (20 mL) y se le agregó (2R,3R)-3-aminobutan-2-ol (0.41 g, 4.60 mmol), sintetizado en el ejemplo (88a), y cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio n-hidratado (1.20 g, 4.34 mmol), seguido por agitación a temperatura ambiente durante 3 días bajo una atmósfera de nitrógeno. Después de que el disolvente se removió por destilación bajo presión reducida, se le agregó una solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con cloruro de metileno (80 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El residuo resultante se purificó por

cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 60%-80%), para producir el compuesto deseado como una espuma blanca (722 mg, rendimiento de 70%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.11 (18H, d, J = 7.0 Hz), 1.22-1.29 (3H, m), 1.24 (3H, d, J = 6.3 Hz), 1.28 (3H, d, J = 7.0 Hz), 1.32 (3H, d, J = 6.3 Hz), 2.34 (1H, br s), 3.42 (3H, s), 3.49 (1H, dd, J = 10.2, 4.3 Hz), 3.59 (1H, dd, J = 10.2, 5.5 Hz), 3.84 (1H, br s), 4.03-4.13 (1H, m), 4.49-4.56 (1H, m), 6.06 (1H, d, J = 8.6 Hz), 6.41 (1H, t, J = 2.2 Hz), 6.45 (1H, dd, J = 3.7, 2.9 Hz), 6.61 (1H, dd, J = 3.9, 2.3 Hz), 6.67 (1H, t, J = 1.8 Hz), 6.73 (1H, t, J = 2.0 Hz), 9.49 (1H, br s).

(109b) (4R,5S)-2-[5-(3-{[(2S)-1-Metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-il]-4,5-dimetil-4,5-dihidro-1,3-oxazol

La N-[(2R,3R)-3-hidroxibutan-2-il]-5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-carboxamida (722 mg, 1.39 mmol) sintetizada en el ejemplo (109a) se disolvió en tetrahidrofurano (30 mL), se le agregó ácido metanosulfónico anhidro (430 mg, 2.47 mmol) y trietilamina (1.20 mL, 8.61 mmol), y se agitó a 50°C durante la noche bajo una atmósfera de nitrógeno. La solución de reacción se llevó de vuelta a la temperatura ambiente y se le agregó una solución acuosa saturada de cloruro de amonio (50 mL), seguido por extracción con cloruro de metileno (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en

columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 40%-70%), para producir el compuesto deseado como un líquido amarillo (700 mg, rendimiento de 100%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.11 (18H, d, J = 7.0 Hz), 1.21 (3H, d, J = 7.0 Hz), 1.23-1.30 (3H, m), 1.31 (3H, d, J = 6.3 Hz), 1.33 (3H, d, J = 6.6 Hz), 3.42 (3H, s), 3.48 (1H, dd, J = 10.2, 4.3 Hz), 3.58 (1H, dd, J = 10.2, 5.9 Hz), 4.24-4.32 (1H, m), 4.48-4.56 (1H, m), 4.78-4.85 (1H, m), 6.39 (1H, t, J = 2.2 Hz), 6.46 (1H, d, J = 3.5 Hz), 6.70 (1H, s), 6.73-6.75 (2H, m).

(109c) 3-{5-[(4R,5S)-4,5-Dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[(2S)-1-metoxipropan-2-il]oxi}fenol

El (4R,5S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-il]-4,5-dimetil-4,5-dihidro-1,3-oxazol (700 mg, 1.39 mmol) sintetizado en el ejemplo (109b) se disolvió en tetrahidrofurano (10 mL), y se le agregó fluoruro de tetrabutilamonio (solución en tetrahidrofurano 1.0 mol/L, 2.00 mL, 2.00 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante 30 minutos bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo con cloruro de metileno (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 2%-3%), para producir el compuesto deseado como un líquido amarillo (420

mg, rendimiento de 88%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 1.35-1.40 (6H, m), 3.41 (3H, s), 3.48 (1H, dd, J = 10.0, 4.5 Hz), 3.59 (1H, dd, J = 10.2, 5.5 Hz), 4.40-4.48 (1H, m), 4.48-4.56 (1H, m), 4.86-4.94 (1H, m), 6.38 (1H, t, J = 2.0 Hz), 6.47 (1H, d, J = 3.9 Hz), 6.72 (1H, s), 6.75 (1H, d, J = 3.9 Hz), 7.09 (1H, s).

(109d) 2-(3-{5-[(4R,5S)-4,5-Dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[(2S)-1-metoxipropan-2-il]oxi}fenoxi)-5-(metilsulfonil)pirazina

El 3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[(2S)-1-metoxipropan-2-il]oxi}fenol (420 mg, 1.22 mmol) sintetizado en el ejemplo (109c) se disolvió en acetonitrilo (20 mL), y se le agregó 2-cloro-5-(metilsulfonil)pirazina (345 mg, 1.46 mmol), sintetizada en el ejemplo (97c), y carbonato de cesio (1.02 g, 3.13 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante la noche bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó agua (30 mL) y se extrajo con cloruro de metileno (40 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 2%-3%), para producir el compuesto deseado como un sólido blanco (513 mg, rendimiento de 84%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.19-1.28 (6H, m), 1.35 (3H, d, J = 6.6 Hz), 3.24 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 10.2, 4.3 Hz), 3.61 (1H,

dd, J = 10.4,5.7 Hz), 4.25-4.35 (1H, m), 4.57-4.63 (1H, m), 4.81-4.91 (1H, m), 6.52 (1H, d, J = 3.9 Hz), 6.76 (1H, s), 6.96 (1H, s), 7.12 (1H, s), 8.49 (1H, d, J = 1.2 Hz), 8.81 (1H, d, J = 1.6 Hz).

(109e) ((2S)-2-(3-{5-[(4R,5S)-4,5-Dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol

La 2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[(2S)-1-metoxipropan-2-il]oxi}fenoxi)-5-(metilsulfonil)pirazina (513 mg, 1.02 mmol) sintetizada en el ejemplo (109d) se disolvió en cloruro de metileno (10 mL), y se le agregó a gotas a -78°C tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 1.50 mL, 1.50 mmol), seguido por agitación a temperatura ambiente durante 2 horas bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio (20 mL) y se extrajo con cloruro de metileno (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 4%-5%), para producir el compuesto deseado como un sólido amarillo pálido (390 mg, rendimiento de 79%).

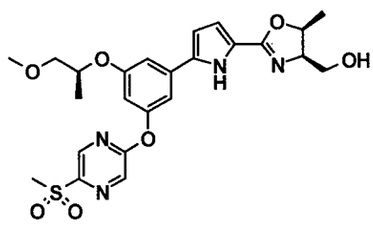
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.22 (3H, d, J = 7.0 Hz), 1.32 (3H, d, J = 6.3 Hz), 1.34 (3H, d, J = 6.6 Hz), 3.23 (3H, s), 3.76-3.79 (2H, m), 4.25-4.33 (1H, m), 4.54-4.60 (1H, m), 4.81-4.88 (1H, m), 6.49 (1H, d, J = 3.9 Hz), 6.59 (1H, s), 6.75 (1H, d, J = 3.9 Hz), 6.95 (1H, s), 7.09 (1H, s), 8.47 (1H, s),

8.80 (1H, d, J = 1.2 Hz).

MS (ESI) m/z: 487.16580 $(M+H)^+$.

EJEMPLO 110

{(4R,5S)-2-[5-(3-{[(2S)-1-Metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol



(110a) N-[(2R,3R)-1,3-Dihidroxibutan-2-il]-5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-carboxamida

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]-fenil}-1H-pirrol-2-carboxílico (2.05 g, 4.58 mmol) sintetizado en el ejemplo (106c) se disolvió en metanol (20 mL), y se le agregó L-treoninol (1.50 g, 14.27 mmol), disponible comercialmente, y cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio n-hidratado (2.85 g, 10.30 mmol), seguido por agitación a temperatura ambiente durante 3 días bajo una atmósfera de nitrógeno. Después de que el disolvente se removió por destilación bajo presión reducida, se le agregó una solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con cloruro de metileno (80 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El residuo resultante se purificó por

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cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 3%-7%), para producir el compuesto deseado como una espuma blanca (2.10 g, rendimiento de 86%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.11 (18H, d, J = 7.4 Hz), 1.21-1.33 (6H, m), 1.22 (3H, d, J = 6.3 Hz), 3.44 (3H, s), 3.49 (1H, dd, J = 10.2, 3.9 Hz), 3.57 (1H, dd, J = 10.2, 6.3 Hz), 3.83 (2H, br s), 3.96 (1H, br s), 4.26 (1H, ddd, J = 12.5,6.3,2.0 Hz), 4.45-4.53 (1H, m), 6.41 (1H, t, J = 2.2 Hz), 6.44 (1H, dd, J = 3.5, 2.7 Hz), 6.68-6.72 (3H, m), 6.72-6.77 (1H, m), 10.36 (1H, s).

(110b) N-{(2R,3R)-3-Hidroxi-1-[(tripropan-2-ilsilil)oxi]butan-2-il}-5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-carboxamida

La N-[(2R,3R)-1,3-dihidroxibutan-2-il]-5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-carboxamida (2.10 g, 3.93 mmol) sintetizada en el ejemplo (110a) se disolvió en cloruro de metileno (50 mL), y se le agregó triisopropilclorosilano (1.50 mL, 7.01 mmol), 4-dimetilaminopiridina (1.50 g, 12.27 mmol) y trietilamina (5.00 mL, 35.87 mmol), seguido por agitación a temperatura ambiente durante 1 día bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con cloruro de metileno (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución:

acetato de etilo/hexano = 25-40%), para producir el compuesto deseado como un sólido blanco (2.52 g, rendimiento de 93%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.07 (18H, d, J = 6.8 Hz), 1.12 (18H, d, J = 7.3 Hz), 1.21-1.31 (9H, m), 1.32 (3H, d, J = 6.3 Hz), 3.42 (3H, s), 3.49 (1H, dd, J = 10.3, 4.4 Hz), 3.55 (1H, br s), 3.59 (1H, dd, J = 10.3, 5.9 Hz), 4.00-4.04 (1H, m), 4.04-4.06 (2H, m), 4.29-4.34 (1H, m), 4.49-4.55 (1H, m), 6.41 (1H, t, J = 2.2 Hz), 6.46 (1H, dd, J = 3.9, 2.9 Hz), 6.60 (1H, s), 6.61 (1H, dd, J = 3.4, 2.4 Hz), 6.67 (1H, t, J = 2.0 Hz), 6.72 (1H, t, J = 2.0 Hz), 9.34 (1H, s).

(110c) {(4R,5S)-2-[5-(3-{[(2S)-1-Metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-il]-5-metil-4-{[(tripropan-2-ilsilil)oxi]-metil}-4,5-dihidro-1,3-oxazol

La N-{(2R,3R)-3-hidroxi-1-[(tripropan-2-ilsilil)oxi]butan-2-il}-5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-carboxamida (2.52 g, 3.65 mmol) sintetizada en el ejemplo (110b) se disolvió en tetrahidrofurano (20 mL), y se le agregó ácido metanosulfónico anhidro (1.05 g, 6.03 mmol) y trietilamina (2.00 mL, 14.35 mmol), seguido por agitación a 50°C durante 1 día bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con cloruro de metileno (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de

gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-30%), para producir el compuesto deseado como un líquido amarillo pálido (2.30 g, rendimiento de 94%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.06 (18H, d, J = 5.1 Hz), 1.11 (18H, d, J = 7.4 Hz), 1.22-1.30 (6H, m), 1.31 (3H, d, J = 6.3 Hz), 1.52 (3H, d, J = 6.3 Hz), 3.42 (3H, s), 3.48 (1H, dd, J = 10.2, 4.7 Hz), 3.59 (1H, dd, J = 10.4,5.7 Hz), 3.82 (1H, dd, J = 10.2, 9.0 Hz), 3.98 (1H, dd, J = 10.2, 3.9 Hz), 4.24 (1H, td, J = 8.7, 3.9 Hz), 4.48-4.55 (1H, m), 4.86-4.96 (1H, m), 6.39 (1H, t, J = 2.2 Hz), 6.45 (1H, d, J = 3.9 Hz), 6.67 (1H, s), 6.71 (1H, s), 6.75 (1H, d, J = 3.9 Hz).

(110d) {(4R,5S)-2-[5-(3-{[(2S)-1-Metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol

El {(4R,5S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-il]-5-metil-4-{[(tripropan-2-ilsilil)oxi]metil}-4,5-dihidro-1,3-oxazol (2.30 g, 3.42 mmol) sintetizado en el ejemplo (110c) se disolvió en tetrahidrofurano (20 mL), y se le agregó fluoruro de tetrabutilamonio (solución en tetrahidrofurano 1.0 mol/L, 8.00 mL, 8.00 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante 30 minutos bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (60 mL) y se extrajo con cloruro de metileno (80 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El

disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/acetato de etilo = 5%-10%), para producir un sólido blanco (2.10 g).

Se disolvieron 1.20 g del compuesto resultante en acetonitrilo (15 mL), y se le agregó a 0°C 2-cloro-5-(metilsulfonil)pirazina (410 mg, 2.13 mmol), sintetizada en el ejemplo (97c), y carbonato de potasio (0.85 g, 6.15 mmol), seguido por agitación bajo una atmósfera de nitrógeno a 0°C durante 5 horas y luego a temperatura ambiente durante 3 horas. A esta solución de reacción se le agregó agua (30 mL) y se extrajo con cloruro de metileno (40 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/acetato de etilo = 4%-6%), para producir el compuesto deseado como un sólido blanco (964 mg, rendimiento de 95%).

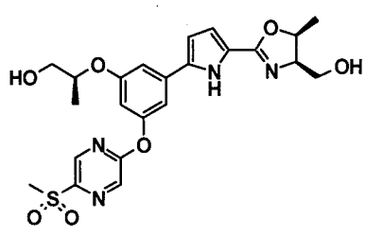
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.35 (3H, d, J = 6.3 Hz), 1.40 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 10.2, 4.3 Hz), 3.60 (1H, dd, J = 10.2, 5.9 Hz), 3.77 (1H, dd, J = 11.5, 6.1 Hz), 3.85 (1H, dd, J = 11.7, 3.5 Hz), 4.22-4.28 (1H, m), 4.54-4.60 (1H, m), 4.82-4.88 (1H, m), 6.45 (1H, d, J = 3.5 Hz), 6.65 (1H, t, J = 2.2 Hz), 6.67 (1H, d, J = 2.3 Hz), 6.94 (1H, t, J = 1.8 Hz), 7.10 (1H, t, J = 1.8 Hz), 8.48 (1H, d, J = 1.2 Hz), 8.80 (1H, d, J = 1.2 Hz).

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MS (ESI) m/z: 517.17452 $(M+H)^+$.

EJEMPLO 111

(2S)-2-(3-{5-[(4R,5S)-4-(Hidroximetil)-5-metil-4,5-dihidro-1,3-oxazol-2-il)]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol



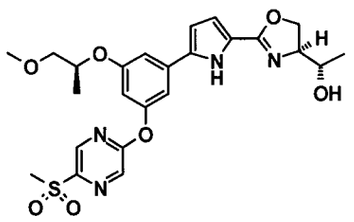
El {(4R,5S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol (209 mg, 0.40 mmol) sintetizado en el ejemplo (110d) se disolvió en cloruro de metileno (5.0 mL), y se le agregó a gotas a -78°C tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 0.80 mL, 0.80 mmol), seguido por agitación a temperatura ambiente durante 40 minutos bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa de hidróxido de sodio 1N (10 mL) y se extrajo con cloruro de metileno (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 4%-6%), para producir el compuesto deseado como un sólido blanco (169 mg, rendimiento de 83%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J = 6.3 Hz), 1.41 (3H, d, J = 6.6 Hz), 3.23 (3H, s), 3.76 (2H, d, J = 4.7 Hz), 3.70-3.80 (1H, m), 3.85 (1H, dd, J = 11.7, 3.9 Hz), 4.21-4.25 (1H, m), 4.49-4.60 (1H, m), 4.82-4.89 (1H, m), 6.43 (1H, d, J = 2.7 Hz), 6.59 (1H, s), 6.67 (1H, d, J = 2.7 Hz), 6.95 (1H, s), 7.07 (1H, s), 8.47 (1H, s), 8.78 (1H, s).

MS (ESI) m/z: 503.15957 $(M+H)^+$.

EJEMPLO 112

(1S)-1-{(4S)-2-[5-(3-{[(2S)-1-Metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol



(112a) N-[(2S,3S)-1,3-Dihidroxibutan-2-il]-5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-carboxamida

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]-fenil}-1H-pirrol-2-carboxílico (1.75 g, 3.91 mmol) sintetizado en el ejemplo (106c) se disolvió en metanol (30 mL), y se le agregó D-treoninol (1.00 g, 9.51 mmol) y cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio n-hidratado (2.85 g, 10.30 mmol), seguido por agitación a temperatura ambiente durante 5 días bajo una atmósfera de nitrógeno. Después de que el disolvente se removió por destilación bajo presión reducida, se le agregó una

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solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con cloruro de metileno (80 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 3%-7%), para producir el compuesto deseado como un sólido blanco (1.76 g, rendimiento de 84%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.08 (18H, d, J = 7.4 Hz), 1.18-1.25 (6H, m), 1.27 (3H, d, J = 6.3 Hz), 2.83 (2H, br s), 3.38 (3H, s), 3.45 (1H, dd, J = 10.2, 4.3 Hz), 3.55 (1H, dd, J = 10.2, 5.9 Hz), 3.87 (2H, s), 3.94-4.01 (2H, m), 4.22 (1H, br s), 4.46-4.52 (1H, m), 6.37 (1H, br s), 6.40-6.43 (1H, m), 6.59-6.66 (3H, m), 6.70 (1H, s), 9.78 (1H, br s).

(112b) (1S)-1-{(4S)-2-[5-(3-{[(2S)-1-Metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol

La N-[(2S,3S)-1,3-dihidroxibutan-2-il]-5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-carboxamida (1.76 g, 3.29 mmol) sintetizada en el ejemplo (112a) se disolvió en tetrahidrofurano (20 mL), y se le agregó ácido metanosulfónico anhidro (0.54 g, 3.10 mmol) y trietilamina (1.00 mL, 7.17 mmol) a -40°C, seguido por agitación a la misma temperatura durante 4 horas bajo una atmósfera de nitrógeno, y luego a 50°C durante la noche. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con cloruro de metileno (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente

se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 2%-5%), para producir el compuesto deseado como una espuma blanca (880 mg, rendimiento de 52%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.12 (18H, d, J = 7.0 Hz), 1.22-1.30 (6H, m), 1.32 (3H, d, J = 6.3 Hz), 3.42 (3H, s), 3.48 (1H, dd, J = 10.2, 4.3 Hz), 3.59 (1H, dd, J = 10.2, 5.9 Hz), 3.69-3.75 (1H, m), 4.10-4.20 (2H, m), 4.45 (1H, br s), 4.53 (1H, br s), 6.40 (1H, t, J = 1.6 Hz), 6.47 (1H, d, J = 3.9 Hz), 6.70 (1H, s), 6.75 (1H, s), 6.77 (1H, d, J = 3.9 Hz).

(112c) 3-(5-{(4S)-4-[(1S)-1-Hidroxietil]-4,5-dihidro-1,3-oxazol-2-il}-1H-pirrol-2-il)-5-{[(2S)-1-metoxipropan-2-il]oxi}fenol

El (1S)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol (1.48 g, 2.88 mmol) sintetizado en el ejemplo (112b) se disolvió en tetrahidrofurano (20 mL), y se le agregó fluoruro de tetrabutilamonio (solución en tetrahidrofurano 1.0 mol/L, 3.50 mL, 3.50 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante 1.5 horas bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con cloruro de metileno (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente

de elución: metanol/cloruro de metileno = 3%-6%), para producir el compuesto deseado como un sólido blanco (880 mg, rendimiento de 85%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 1.37 (3H, d, J = 6.3 Hz), 3.42 (3H, s), 3.46 (1H, dd, J = 10.2, 4.7 Hz), 3.61 (1H, dd, J = 10.0, 5.7 Hz), 3.85-3.92 (1H, m), 4.25-4.36 (2H, m), 4.49-4.56 (2H, m), 6.48 (1H, d, J = 3.9 Hz), 6.54 (1H, t, J = 2.0 Hz), 6.73 (1H, t, J = 1.8 Hz), 6.79 (1H, d, J = 3.5 Hz), 7.06 (1H, s).

(112d) (1S)-1-{(4S)-2-[5-(3-{[(2S)-1-Metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol

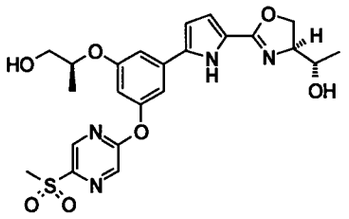
El 3-(5-{(4S)-4-[(1S)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-il}-1H-pirrol-2-il)-5-{[(2S)-1-metoxipropan-2-il]oxi}fenol (880 mg, 2.44 mmol) sintetizado en el ejemplo (112c) se disolvió en acetonitrilo (20 mL), y se le agregó 2-cloro-5-(metilsulfonil)pirazina (630 mg, 3.27 mmol), sintetizada en el ejemplo (97c), y carbonato de potasio (1.20 g, 8.68 mmol), seguido por agitación a temperatura ambiente durante 4 horas bajo una atmósfera de nitrógeno. Se le agregó agua (50 mL) y se extrajo con cloruro de metileno (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 1%-3%), para producir el compuesto deseado como un sólido blanco (1.00 g, rendimiento de 79%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.28 (3H, d, J = 6.3 Hz), 1.35 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.51 (1H, dd, J = 10.2, 4.3 Hz), 3.60 (1H, dd, J = 10.2, 6.3 Hz), 3.73 (1H, br s), 4.11-4.22 (2H, m), 4.46 (1H, br s), 4.60 (1H, br s), 6.52 (1H, d, J = 3.9 Hz), 6.67 (1H, t, J = 2.0 Hz), 6.78 (1H, d, J = 3.9 Hz), 6.96 (1H, s), 7.12 (1H, s), 8.49 (1H, s), 8.81 (1H, s).

MS (ESI) m/z: 517.17608 $(M+H)^+$.

EJEMPLO 113

(2S)-2-[3-(5-{(4S)-4-[(1S)-1-Hidroxietil]-4,5-dihidro-1,3-oxazol-2-il}-1H-pirrol-2-il)-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi]propan-1-ol



El (1S)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol (204 mg, 0.395 mmol) sintetizado en el ejemplo (112d) se disolvió en cloruro de metileno (5.0 mL), y se le agregó a gotas a -78°C tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 0.80 mL, 0.80 mmol), seguido por agitación a temperatura ambiente durante 1.5 horas bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa de hidróxido de sodio 1N (10 mL) y se extrajo con cloruro de metileno (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó

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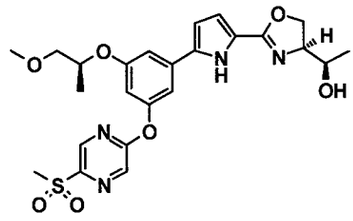
sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 3%-5%), para producir el compuesto deseado como un sólido blanco (159 mg, rendimiento de 80%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.28 (3H, d, J = 6.3 Hz), 1.32 (3H, d, J = 6.3 Hz), 3.24 (3H, s), 3.73-3.78 (3H, m), 4.12-4.23 (2H, m), 4.46 (1H, br s), 4.52-4.59 (1H, m), 6.50 (1H, d, J = 3.9 Hz), 6.62 (1H, t, J = 2.0 Hz), 6.76 (1H, d, J = 3.9 Hz), 6.94 (1H, t, J = 1.8 Hz), 7.08 (1H, s), 8.49 (1H, d, J = 1.2 Hz), 8.80 (1H, d, J = 1.2 Hz).

MS (ESI) m/z: 503.15930 $(M+H)^+$.

EJEMPLO 114

(1R)-1-{(4S)-2-[5-(3-{[(2S)-1-Metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol



(114a) N-[(2S,3R)-1,3-Dihidroxibutan-2-il]-5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-carboxamida

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]-fenil}-1H-pirrol-2-carboxílico (1.63 g, 3.64 mmol) sintetizado en el ejemplo

(106c) se disolvió en metanol (20 mL), y se le agregó D-alo-treoninol (1.05 g, 9.99 mmol) y cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio n-hidratado (2.00 g, 7.23 mmol), seguido por agitación a temperatura ambiente durante 1 día bajo una atmósfera de nitrógeno. Después de que el disolvente se removió por destilación bajo presión reducida, se le agregó una solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con cloruro de metileno (80 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 3%-7%), para producir el compuesto deseado como una espuma blanca (1.70 g, rendimiento de 87%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.07 (18H, d, J = 7.0 Hz), 1.17-1.27 (9H, m), 2.01 (1H, br s), 3.37 (3H, s), 3.44 (1H, dd, J = 10.0, 4.1 Hz), 3.44 (1H, s), 3.53 (1H, dd, J = 10.4, 6.1 Hz), 3.72-3.78 (1H, m), 3.88-3.93 (1H, m), 3.93-3.95 (1H, m), 3.96-4.04 (2H, m), 4.44-4.52 (1H, m), 6.35 (1H, t, J = 2.0 Hz), 6.39 (1H, t, J = 3.1 Hz), 6.67 (1H, t, J = 1.8 Hz), 6.70 (1H, s), 6.72 (1H, s), 6.99 (1H, d, J = 7.8 Hz), 10.34 (1H, br s).

(114b) (1R)-1-{(4S)-2-[5-(3-{[(2S)-1-Metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol

La N-[(2S,3R)-1,3-dihidroxibutan-2-il]-5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-carboxamida (1.70 g, 3.18 mmol) sintetizada en el ejemplo (114a) se disolvió en tetrahidrofurano (20 mL), y se le agregó ácido metanosulfónico anhidro (0.78 g, 4.48 mmol) y

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trietilamina (1.50 mL, 10.76 mmol) a 0°C, seguido por agitación a la misma temperatura durante 1.5 horas bajo una atmósfera de nitrógeno, seguido por agitación a 50°C durante la noche. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con cloruro de metileno (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 2%-4%), para producir el compuesto deseado como una espuma blanca (1.30 g, rendimiento de 79%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.10-1.14 (18H, m), 1.20 (3H, d, J = 6.6 Hz), 1.23-1.32 (3H, m), 1.34 (3H, d, J = 6.3 Hz), 3.41 (3H, s), 3.48 (1H, dd, J = 10.2, 4.3 Hz), 3.59 (1H, dd, J = 10.2, 5.9 Hz), 4.20-4.34 (4H, m), 4.53 (1H, br s), 6.33 (1H, d, J = 3.9 Hz), 6.40 (1H, t, J = 2.0 Hz), 6.44 (1H, br s), 6.74 (1H, t, J = 1.8 Hz), 6.78 (1H, t, J = 1.8 Hz).

(114c) 3-(5-{(4S)-4-[(1R)-1-Hidroxietil]-4,5-dihidro-1,3-oxazol-2-il}-1H-pirrol-2-il)-5-{[(2S)-1-metoxipropan-2-il]oxi}fenol

El (1R)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol (1.30 g, 2.52 mmol) sintetizado en el ejemplo (114b) se disolvió en tetrahidrofurano (15 mL), y se le agregó fluoruro de tetrabutilamonio (solución en tetrahidrofurano 1.0 mol/L, 4.00 mL, 4.00 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante 1 hora bajo una

atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con cloruro de metileno (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/acetato de etilo = 8%-12%), para producir el compuesto deseado como una espuma blanca (766 mg, rendimiento de 85%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (6H, d, J = 6.3 Hz), 3.28 (1H, br s), 3.42 (3H, s), 3.47 (1H, dd, J = 10.2, 4.3 Hz), 3.61 (1H, dd, J = 10.2, 5.9 Hz), 4.23 (1H, br s), 4.35-4.43 (1H, m), 4.47-4.56 (3H, m), 6.46-6.49 (2H, m), 6.72 (1H, s), 6.78 (1H, d, J = 3.5 Hz), 7.04 (1H, t, J = 1.8 Hz), 11.07 (1H, s).

(114d) (1R)-1-{(4S)-2-[5-(3-{[(2S)-1-Metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol

El 3-(5-{(4S)-4-[(1R)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-il}-1H-pirrol-2-il)-5-{[(2S)-1-metoxipropan-2-il]oxi}fenol (766 mg, 2.13 mmol) sintetizado en el ejemplo (114c) se disolvió en acetonitrilo (15 mL), y se le agregó 2-cloro-5-(metilsulfonil)pirazina (590 mg, 3.06 mmol), sintetizada en el ejemplo (97c), y carbonato de potasio (870 mg, 6.29 mmol), seguido por agitación a temperatura ambiente durante 4 horas bajo una atmósfera de nitrógeno. Se le agregó agua (50 mL) y se extrajo con cloruro de metileno (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se

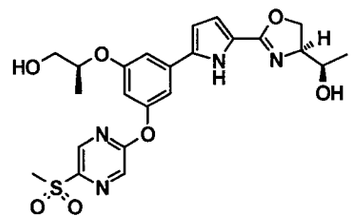
secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/acetato de etilo = 5%-8%), para producir el compuesto deseado como un sólido blanco (890 mg, rendimiento de 81%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.17 (3H, d, J = 6.6 Hz), 1.36 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 10.4, 4.1 Hz), 3.60 (1H, dd, J = 10.2, 5.9 Hz), 4.10-4.26 (2H, m), 4.28-4.35 (2H, m), 4.58 (1H, br s), 6.42 (1H, d, J = 3.9 Hz), 6.56 (1H, d, J = 3.5 Hz), 6.66 (1H, t, J = 2.2 Hz), 6.96 (1H, d, J = 1.6 Hz), 7.11 (1H, s), 8.49 (1H, d, J = 1.2 Hz), 8.81 (1H, d, J = 1.2 Hz).

MS (ESI) m/z: 517.17565 $(M+H)^+$.

EJEMPLO 115

(2S)-2-[3-(5-{(4S)-4-[(1R)-1-Hidroxietil]-4,5-dihidro-1,3-oxazol-2-il}-1H-pirrol-2-il)-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi]propan-1-ol



El (1R)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol (213 mg, 0.412 mmol) sintetizado en el ejemplo (114d) se disolvió en

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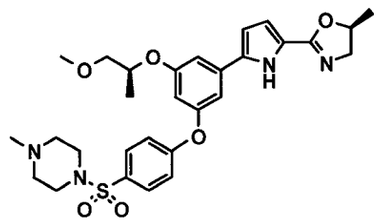
cloruro de metileno (5.0 mL), y se le agregó a gotas a -78°C tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 0.80 mL, 0.80 mmol), seguido por agitación a temperatura ambiente durante 1.5 horas bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio (10 mL) y se extrajo con cloruro de metileno (20 mL). La capa orgánica se lavó con una solución acuosa de hidróxido de sodio 1N (10 mL) y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 4%-5%), para producir el compuesto deseado como un sólido blanco (147 mg, rendimiento de 71%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.18 (3H, d, J = 6.3 Hz), 1.33 (3H, d, J = 6.3 Hz), 1.61 (2H, br s), 3.23 (3H, s), 3.73-3.82 (2H, m), 4.16-4.26 (2H, m), 4.30-4.36 (2H, m), 4.54-4.61 (1H, m), 6.39 (1H, d, J = 3.9 Hz), 6.53 (1H, d, J = 3.5 Hz), 6.61 (1H, s), 6.95 (1H, s), 7.07 (1H, s), 8.48 (1H, d, J = 1.2 Hz), 8.80 (1H, d, J = 1.6 Hz).

MS (ESI) m/z: 503.15973 $(M+H)^+$.

EJEMPLO 116

1-{[4-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)fenil]sulfonil}-4-metilpiperazina



(116a) 1-[(4-Fluorofenil)sulfonil]-4-metilpiperazina

Se suspendió en agua (15 mL) cloruro de 4-fluorobencenosulfonilo (1.00 g, 5.14 mmol), disponible comercialmente, y se le agregó N-metilpiperazina (0.68 mL, 6.17 mmol) y carbonato de potasio (1.56 g, 11.3 mmol), seguido por agitación a temperatura ambiente durante 14 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó agua (50 mL) seguido por extracción con acetato de etilo (50 mL); subsiguientemente la capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-90%), para producir el compuesto deseado como un sólido blanco (491 mg, rendimiento de 37%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.28 (3H, s), 2.49 (4H, t, J = 4.9 Hz), 3.04 (4H, br s), 7.21 (2H, dd, J = 9.4, 7.8 Hz), 7.76-7.79 (2H, m).

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(116b) N-[(2R)-2-Hidroxipropil]-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]fenil}-1H-pirrol-2-carboxamida

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]-fenil}-1H-pirrol-2-carboxílico (51.4 g, 115 mmol) sintetizado en el ejemplo (106c) se disolvió en metanol (600 mL), y se le agregó (R)-(-)-1-amino-2-propanol (19.9 mL, 253 mmol) y cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio n-hidratado (63.7 g, 230 mmol), seguido por agitación durante 15 horas bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y se le agregó agua (500 mL), seguido por extracción dos veces con acetato de etilo (500 mL). Subsiguientemente, la capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 25%-67%), para producir el compuesto deseado como un sólido blanco (48.7 g, rendimiento de 84%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.12 (18H, d, J = 7.8 Hz), 1.27 (3H, q, J = 8.3 Hz), 1.32 (3H, d, J = 6.3 Hz), 2.60 (1H, s), 3.27-3.33 (1H, m), 3.42 (3H, s), 3.49 (1H, dd, J = 10.3, 4.4 Hz), 3.56-3.65 (2H, m), 4.03 (1H, s), 4.53 (1H, td, J = 6.1,4.4 Hz), 6.31 (1H, br s), 6.41 (1H, t, J = 2.2 Hz), 6.46 (1H, t, J = 3.2 Hz), 6.61 (1H, t, J = 3.2 Hz), 6.67 (1H, t, J = 1.7 Hz), 6.73 (1H, t, J = 2.0 Hz), 9.51 (1H, br s).

(116c) (5S)-2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol

La N-[(2R)-2-hidroxipropil]-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]fenil}-1H-pirrol-2-carboxamida (48.7 g, 96.5 mmol) sintetizada en el ejemplo (116b) se disolvió en tetrahidrofurano (600 mL), y se le agregó ácido metanosulfónico anhidro (33.6 g, 193 mmol) y trietilamina (40.4 mL, 289 mmol), seguido por agitación a 50°C durante 3 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (500 mL) y se extrajo dos veces con acetato de etilo (500 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y al residuo resultante se le agregó éter diisopropílico (300 mL); la suspensión se agitó para producir un sólido blanco que se separó por filtración. El disolvente del licor madre se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-50%). Este se secó al vacío junto con el producto filtrado para producir el compuesto deseado como un sólido blanco (34.8 g, rendimiento de 74%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.11 (18H, d, J = 7.8 Hz), 1.25-1.34 (3H, m), 1.38 (3H, d, J = 6.3 Hz), 1.65 (3H, d, J = 5.9 Hz), 3.43 (3H, s), 3.58-3.65 (2H, m), 3.76 (1H, dd, J = 10.9, 7.8 Hz), 4.28 (1H, dd, J = 11.3, 9.8 Hz), 4.81-4.87 (1H, m), 5.28-5.37 (1H, m), 6.51 (1H, t, J = 2.2 Hz), 6.62 (1H, d, J =

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2.0 Hz), 6.91 (1H, s), 7.19 (1H, s), 7.35 (1H, s).

(116d) 3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenol

El (5S)-2-(5-{3-[(1*S*)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]-fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol (29.5 g, 60.7 mmol) sintetizado en el ejemplo (116c) se disolvió en tetrahidrofurano (400 mL), y se le agregó fluoruro de tetrabutilamonio (solución en tetrahidrofurano 1.0 mol/L, 66 mL, 66 mmol), seguido por agitación durante 1 hora bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y al residuo se le agregó agua (400 mL) y se extrajo dos veces con acetato de etilo (400 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-50%), para producir el compuesto deseado como un sólido blanco (16.7 g, rendimiento de 83%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 1.49 (4H, d, J = 6.3 Hz), 3.42 (3H, s), 3.49 (1H, dd, J = 10.2, 4.7 Hz), 3.59 (1H, dd, J = 10.2, 5.5 Hz), 3.68 (1H, dd, J = 13.3, 7.4 Hz), 4.22 (1H, dd, J = 13.5, 9.2 Hz), 4.52-4.57 (1H, m), 4.97-4.88 (1H, m), 6.34 (1H, t, J = 2.0 Hz), 6.47 (1H, d, J = 3.5 Hz), 6.72 (1H, s), 6.76 (1H, d, J = 3.5 Hz), 7.10 (1H, s).

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(116e) 1-{[4-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)fenil]sulfonil}-4-metilpiperazina

El 3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenol (40 mg, 0.12 mmol) sintetizado en el ejemplo (116d), y la 1-[(4-fluorofenil)sulfonil]-4-metilpiperazina (25 mg, 0.15 mmol) sintetizada en el ejemplo (116a), se disolvieron en N,N-dimetilformamida (2 mL) y se les agregó carbonato de potasio (51 mg, 0.37 mmol), seguido por agitación a 100°C durante 1 hora bajo una atmósfera de nitrógeno. Se le agregó nuevamente 1-[(4-fluorofenil)sulfonil]-4-metilpiperazina (30 mg), y la mezcla se agitó a 90°C durante la noche. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (10 mL) y se extrajo dos veces con acetato de etilo (10 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido blanco (25 mg, rendimiento de 35%).

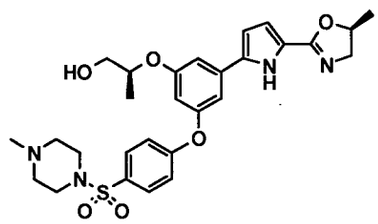
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 5.9 Hz), 1.43 (3H, d, J = 6.3 Hz), 2.29 (3H, s), 2.50 (4H, br s), 3.06 (4H, br s), 3.43 (3H, d, J = 2.4 Hz), 3.50-3.61 (3H, m), 4.10 (1H, dd, J = 14.2, 9.3 Hz), 4.58 (1H, dd, J = 10.5, 6.1 Hz), 4.82-4.86 (1H, m), 6.52 (1H, d, J = 3.4 Hz), 6.55 (1H, t, J = 2.2 Hz), 6.77 (1H, d, J = 3.9 Hz), 6.84 (1H, d, J = 2.0 Hz), 6.98 (1H, s), 7.09 (2H, d, J =

6.8 Hz), 7.71 (2H, d, J = 9.3 Hz).

MS (FAB) m/z: 569.2418 $(M+H)^+$.

EJEMPLO 117

(2S)-2-{3-{5-[(5S)-5-Metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{4-[(4-metilpiperazin-1-il)sulfonil]fenoxi}fenoxi)propan-1-ol



(117a) 3-[(1S)-2-Hidroxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenol

El 3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenol (60 mg, 0.18 mmol) sintetizado en el ejemplo (116d) se disolvió en cloruro de metileno (4 mL), y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 0.38 mL, 0.38 mmol) a -78°C y bajo una atmósfera de nitrógeno. Subsiguientemente, la temperatura se regresó a la temperatura ambiente, seguido por agitación durante 1 hora. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de

gel de sílice (disolvente de elución: hexano/acetato de etilo = 50%-70%), para producir el compuesto deseado como un sólido blanco (41 mg, rendimiento de 72%).

^{1}H-RMN ($CDCl_3$, 400 MHz) δ 1.29 (3H, d, J = 6.3 Hz), 1.49 (3H, d, J = 5.9 Hz), 3.66-3.78 (3H, m), 4.23 (1H, dd, J = 13.7, 9.3 Hz), 4.52 (1H, ddd, J = 14.4, 8.1,4.6 Hz), 4.93 (1H, dq, J = 17.7, 5.0 Hz), 6.32 (1H, t, J = 2.0 Hz), 6.48 (1H, d, J = 3.9 Hz), 6.71 (1H, s), 6.77 (1H, d, J = 3.4 Hz), 7.11 (1H, s), 11.09 (1H, s).

(117b) (2S)-2-(3-{5-[(5S)-5-Metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{4-[(4-metilpiperazin-1-il)sulfonil]fenoxi}fenoxi)propan-1-ol

El 3-[(1S)-2-hidroxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenol (40 mg, 0.13 mmol) sintetizado en el ejemplo (117a), y la 1-[(4-fluorofenil)sulfonil]-4-metilpiperazina (49 mg, 0.19 mmol) sintetizada en el ejemplo (116a), se disolvieron en N,N-dimetilformamida (2 mL) y se les agregó carbonato de potasio (52 mg, 0.38 mmol), seguido por agitación a 100°C durante 4 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (10 mL) y se extrajo dos veces con acetato de etilo (10 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido blanco (17 mg,

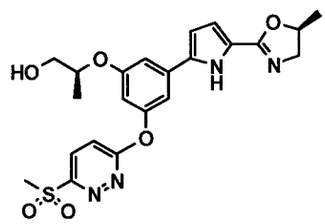
rendimiento de 25%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.29 (3H, d, J = 6.3 Hz), 1.43 (3H, d, J = 6.3 Hz), 2.28 (3H, s), 2.48-2.51 (4H, br m), 3.03 (4H, br s), 3.55 (1H, dd, J = 13.9, 7.2 Hz), 3.77 (2H, d, J = 5.1 Hz), 4.09 (1H, dd, J = 14.1, 9.4 Hz), 4.55-4.60 (1H, m), 4.87-4.81 (1H, m), 6.42 (1H, s), 6.50 (1H, d, J = 3.9 Hz), 6.76 (1H, d, J = 3.5 Hz), 6.83 (1H, s), 6.95 (1H, s), 7.07 (2H, d, J = 8.6 Hz), 7.70 (2H, d, J = 8.6 Hz).

MS (FAB) m/z: 555.2271 $(M+H)^+$.

EJEMPLO 118

(2S)-2-(3-{5-[(5S)-5-Metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridazin-3-il]oxi}fenoxi)propan-1-ol



(118a) 6-Cloropiridazin-3-tiol

Bajo una atmósfera de nitrógeno, se disolvió dicloropiridazina (1.00 g, 6.71 mmol) en metanol (20 mL) y se le agregó una solución acuosa de sulfuro ácido de potasio al 10-20% (20 mL), seguido por calentamiento a reflujo durante 2 horas. El disolvente se removió por destilación bajo presión reducida y el residuo se diluyó con agua, seguido por neutralización con ácido clorhídrico 1N. El precipitado amarillo resultante se separó por filtración, se

lavó con agua y hexano, y subsiguientemente se secó al vacío para producir el compuesto deseado como un sólido amarillo (500 mg, rendimiento de 51%).

^{1}H-RMN ($CDCl_3$, 400 MHz) δ 7.00 (1H, d, J = 9.4 Hz), 7.60 (1H, d, J = 9.4 Hz), 11.68 (1H, br s).

(118b) 3-Cloro-6-(metiltio)piridazina

El 6-cloropiridazin-3-tiol (500 mg, 3.41 mmol) sintetizado en el ejemplo (118a) se disolvió en metanol (20 mL), y se le agregó metóxido de sodio (203 mg, 3.75 mmol) y yodometano (234 mL, 3.75 mmol), seguido por agitación a 60°C durante 30 minutos bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (50 mL) y se extrajo dos veces con acetato de etilo (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-50%), para producir el compuesto deseado como un sólido amarillo (515 mg, rendimiento de 94%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.71 (3H, s), 7.25 (1H, d, J = 9.6 Hz), 7.30 (1H, d, J = 9.0 Hz).

(118c) 3-Cloro-6-(metilsulfonil)piridazina

La 3-cloro-6-(metiltio)piridazina (90 mg, 0.50 mmol) sintetizada en el ejemplo (118b) se disolvió en cloruro de metileno (10 mL) y se le agregó ácido m-cloroperbenzoico (220 mg, 1.00 mmol), seguido por agitación a 0°C

durante 30 minutos bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó agua (20 mL) y se extrajo dos veces con cloruro de metileno (10 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-100%), para producir el compuesto deseado como un sólido blanco (77 mg, rendimiento de 71%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 3.45 (3H, s), 7.81 (1H, d, J = 8.2 Hz), 8.16 (1H, d, J = 8.4 Hz).

(118d) 3-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-6-(metilsulfonil)piridazina

La 3-cloro-6-(metilsulfonil)piridazina (41 mg, 0.27 mmol) sintetizada en el ejemplo (118c), y el 3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenol (80 mg, 0.24 mmol) sintetizado en el ejemplo (116d), se disolvieron en acetonitrilo (2 mL) y se les agregó carbonato de cesio (158 mg, 0.48 mmol), seguido por agitación durante 1 hora bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó agua (10 mL) y se extrajo con acetato de etilo (10 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno =

0%-4%), para producir el compuesto deseado como un sólido blanco (116 mg, rendimiento de 98%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 1.42 (3H, d, J = 6.3 Hz), 3.40 (3H, s), 3.42 (3H, s), 3.48-3.62 (3H, m), 4.07 (1H, dd, J = 13.9, 9.2 Hz), 4.58 (1H, td, J = 6.2, 4.4 Hz), 4.82 (1H, dt, J = 11.7, 4.6 Hz), 6.50 (1H, d, J = 3.5 Hz), 6.69 (1H, t, J = 2.2 Hz), 6.74 (1H, d, J = 3.9 Hz), 6.99 (1H, q, J = 2.0 Hz), 7.09 (1H, t, J = 1.8 Hz), 7.40 (1H, d, J = 9.0 Hz), 8.17 (1H, d, J = 9.0 Hz).

(118e) (2S)-2-(3-{5-[(5S)-5-Metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridazin-3-il]oxi}fenoxi)propan-1-ol

La 3-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-6-(metilsulfonil)piridazina (116 mg, 0.24 mmol) sintetizada en el ejemplo (118d) se disolvió en cloruro de metileno (5 mL), y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 0.26 mL, 0.26 mmol), a -78°C y bajo una atmósfera de nitrógeno. Subsiguientemente la temperatura se regresó a la temperatura ambiente, seguido por agitación durante 4 horas. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado

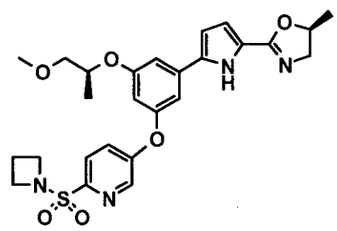
como un sólido blanco (100 mg, rendimiento de 89%).

^{1}H-RMN ($CDCl_3$, 400 MHz) δ 1.30 (3H, d, J = 6.3 Hz), 1.41 (3H, d, J = 6.3 Hz), 3.39 (3H, s), 3.53 (1H, dd, J = 13.7, 7.4 Hz), 3.76-3.77 (2H, m), 4.07 (1H, dd, J = 13.9, 9.2 Hz), 4.56 (1H, dd, J = 10.8, 6.1 Hz), 4.82 (1H, dt, J = 12.0, 4.6 Hz), 6.47 (1H, d, J = 3.5 Hz), 6.61 (1H, t, J = 2.2 Hz), 6.74 (1H, d, J = 3.9 Hz), 6.99 (1H, t, J = 1.6 Hz), 7.03 (1H, t, J = 1.6 Hz), 7.39 (1H, d, J = 9.4 Hz), 8.16 (1H, d, J = 9.4 Hz).

MS (ESI) m/z: 473.15056 $(M+H)^+$.

EJEMPLO 119

2-(Azetidin-1-ilsulfonil)-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-piridina



(119a) 5-Cloropiridin-2-tiol

Bajo una atmósfera de nitrógeno, se disolvió 2,5-dicloropiridina (5.00 g, 33.8 mmol) en sulfóxido de dimetilo (35 mL) y se le agregó disulfuro de sodio nonahidratado (9.00 g, 37.2 mmol), seguido por agitación a 120°C durante 2 horas. La solución de reacción se enfrió a temperatura ambiente y se le agregó agua (50 mL), seguido por neutralización con ácido clorhídrico 5N. El precipitado resultante se separó por filtración, seguido por lavado con

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agua y hexano, y subsiguientemente el sólido resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-10%), para producir el compuesto deseado como un sólido amarillo (2.28 g, rendimiento de 46%).

^{1}H-RMN ($CDCl_3$, 400 MHz) δ 2.63 (1H, s), 7.34 (1H, dd, J = 9.0, 2.2 Hz), 7.41 (1H, d, J = 9.3 Hz), 7.70 (1H, s).

(119b) 2-(Azetidin-1-ilsulfonil)-5-cloropiridina

El 5-cloropiridin-2-tiol (1.00 g, 6.87 mmol) sintetizado en el ejemplo (119a) se disolvió en cloruro de metileno (30 mL)/ácido clorhídrico 1N (30 mL), y se enfrió a -5°C. A la solución de reacción se le agregó a gotas una solución acuosa de perclorato de sodio al 7% (30 mL) enfriada con hielo, manteniéndola a 0°C o menos, y se agitó así durante 15 minutos. La capa orgánica se extrajo en un embudo de separación previamente enfriado con hielo, se enfrió a -78°C y se le agregó una solución de clorhidrato de azetidina (2.24 mg, 17.7 mmol), disponible comercialmente, en cloruro de metileno (10 mL), y trietilamina (1.8 mL, 12.9 mmol), y la temperatura se elevó a 0°C, seguido por agitación durante 30 minutos. A la solución de reacción se le agregó agua (50 mL) y se extrajo dos veces con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 5%-

857

60%), para producir el compuesto deseado como un sólido blanco (735 mg, rendimiento de 46%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.19-2.25 (2H, m), 4.10 (4H, t, J = 7.8 Hz), 7.91 (1H, dd, J = 8.3, 2.0 Hz), 7.95 (1H, d, J = 7.8 Hz), 8.72 (1H, d, J = 2.0 Hz).

(119c) 2-(Azetidin-1-ilsulfonil)-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-piridina

La 2-(azetidin-1-ilsulfonil)-5-cloropiridina (170 mg, 0.73 mmol) sintetizada en el ejemplo (119b), y el 3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenol (230 mg, 0.70 mmol) sintetizado en el ejemplo (116d), se disolvieron en N,N-dimetilformamida (3.5 mL) y se les agregó carbonato de cesio (454 mg, 1.39 mmol), seguido por agitación a 100°C durante 2 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) y se extrajo dos veces con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 5%-50%), para producir el compuesto deseado como un sólido blanco (273 mg, rendimiento de 75%).

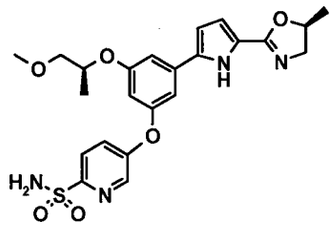
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 1.43 (3H, d, J = 6.3 Hz), 2.18-2.24 (2H, m), 3.42 (3H, s), 3.49-3.61 (3H, m), 4.10 (4H, t, J

= 7.6 Hz), 4.56-4.62 (1H, m), 4.82-4.86 (1H, m), 6.51 (1H, d, J = 3.9 Hz), 6.58 (1H, t, J = 2.0 Hz), 6.76 (1H, d, J = 3.9 Hz), 6.88 (1H, s), 7.04 (1H, s), 7.43 (1H, dd, J = 8.8, 2.9 Hz), 7.94 (1H, d, J = 8.8 Hz), 8.53 (1H, d, J = 2.9 Hz).

MS (ESI) m/z: 527.20527 $(M+H)^+$.

EJEMPLO 120

5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)piridin-2-sulfonamida



(120a) 5-Cloro-N-(4-metoxibencil)piridin-2-sulfonamida

El 5-cloropiridin-2-tiol (1.00 g, 6.87 mmol) sintetizado en el ejemplo (119a) se disolvió en cloruro de metileno (30 mL)/ácido clorhídrico 1N (30 mL) y se enfrió a -5°C. A la solución de reacción se le agregó una solución acuosa de perclorato de sodio al 7% (35 mL) enfriada con hielo, gota a gota, manteniendo la temperatura a 0°C o menos, y se agitó así durante 15 minutos. La capa orgánica se extrajo en un embudo de separación previamente enfriado con hielo y se enfrió a -78°C; se le agregó 4-metoxibencilamina (2.24 mL, 17.7 mmol), disponible comercialmente, y la temperatura se elevó a 0°C, seguido por agitación durante 30 minutos. A la

solución de reacción se le agregó ácido clorhídrico 0.1N (30 mL) y se extrajo dos veces con cloruro de metileno (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 5%-100%), para producir el compuesto deseado como un sólido blanco (983 mg, rendimiento de 46%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 3.78 (3H, s), 4.20 (2H, d, J = 6.3 Hz), 5.07 (1H, s), 6.79 (2H, dt, J = 9.4, 2.5 Hz), 7.14 (2H, d, J = 8.6 Hz), 7.83 (1H, dd, J = 8.6, 2.3 Hz), 7.90 (1H, d, J = 7.8 Hz), 8.60 (1H, dd, J = 2.3, 0.8 Hz).

(120b) 5-Cloro-N,N-bis(4-metoxibencil)piridin-2-sulfonamida

La 5-cloro-N-(4-metoxibencil)piridin-2-sulfonamida (983 mg, 3.14 mmol) sintetizada en el ejemplo (120a) se disolvió en N,N-dimetilformamida (5 mL), y se le agregó hidruro de sodio (132 mg, 3.30 mmol). Después de enfriar con hielo, se le agregó cloruro de p-metoxibencilo (1.02 mL, 3.37 mmol) y la temperatura se elevó a la temperatura ambiente, seguido por agitación durante 2 horas. A la solución de reacción se le agregó agua (20 mL) y se extrajo dos veces con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-100%), para producir el

compuesto deseado como un sólido blanco (1.14 g, rendimiento de 84%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 3.78 (6H, s), 4.40 (4H, s), 6.75 (4H, dt, J = 9.3,2.5 Hz), 7.05 (4H, dt, J = 8.2, 2.0 Hz), 7.78 (1H, dd, J = 8.2, 2.3 Hz), 7.84 (1H, d, J = 7.8 Hz), 8.55 (1H, d, J = 2.7 Hz).

(120c) N,N-Bis(4-metoxibencil)-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)piridin-2-sulfonamida

La 5-cloro-N,N-bis(4-metoxibencil)piridin-2-sulfonamida (288 mg, 0.67 mmol) sintetizada en el ejemplo (120b), y el 3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenol (220 mg, 0.67 mmol) sintetizado en el ejemplo (116d), se disolvieron en N,N-dimetilformamida (3 mL) y se les agregó carbonato de cesio (434 mg, 1.33 mmol), seguido por agitación a 100°C durante 1 hora bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) y se extrajo dos veces con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0.5%-5%), para producir el compuesto deseado como un sólido blanco (160 mg, rendimiento de 33%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 5.9 Hz), 1.43 (3H, d, J = 6.3 Hz), 3.42 (3H, s), 3.50-3.62 (3H, m), 3.77 (6H, s), 4.09 (1H, dd, J =

13.9, 9.0 Hz), 4.41 (4H, s), 4.56-4.63 (1H, m), 4.81-4.86 (1H, m), 6.52 (1H, d, J = 3.9 Hz), 6.56 (1H, t, J = 2.0 Hz), 6.76 (4H, d, J = 8.8 Hz), 7.07 (4H, d, J = 8.8 Hz), 7.33 (1H, dd, J = 8.5, 2.7 Hz), 7.88 (1H, d, J = 8.8 Hz), 8.39 (1H, d, J = 2.9 Hz).

(120d) 5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)piridin-2-sulfonamida

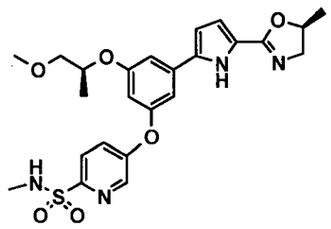
La N,N-bis(4-metoxibencil)-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)piridin-2-sulfonamida (160 mg, 0.24 mmol) sintetizada en el ejemplo (120c), se disolvió en ácido trifluoroacético (2 mL) y se agitó a 40°C durante 8 horas. El disolvente se removió por destilación bajo presión reducida; al residuo se le agregó cloruro de metileno y trietilamina en pequeñas porciones y nuevamente el disolvente se removió por destilación bajo presión reducida. El residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido blanco (106 mg, rendimiento de 99%).

^{1}H-RMN ($CDCl_3$, 400 MHz) δ 1.33 (3H, d, J = 6.3 Hz), 1.42 (3H, d, J = 5.9 Hz), 3.42 (3H, s), 3.49-3.53 (2H, m), 3.59 (1H, dd, J = 10.3, 5.9 Hz), 4.05 (1H, dd, J = 14.2, 9.3 Hz), 4.55-4.61 (1H, m), 4.79-4.86 (1H, m), 5.30 (2H, br s), 6.50 (1H, d, J = 3.9 Hz), 6.56 (1H, t, J = 2.2 Hz), 6.75 (1H, d, J = 3.9 Hz), 6.85 (1H, t, J = 1.7 Hz), 7.03 (1H, t, J = 1.7 Hz), 7.42 (1H, dd, J = 8.5, 2.7 Hz), 7.95 (1H, d, J = 8.8 Hz), 8.42 (1H, d, J = 2.4 Hz).

MS (ESI) m/z: 487.16619 $(M+H)^+$.

EJEMPLO 121

5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-N-metilpiridin-2-sulfonamida



(121a) 5-Cloro-N-metilpiridin-2-sulfonamida

El 5-cloropiridin-2-tiol (1.00 g, 6.87 mmol) sintetizado en el ejemplo (119a) se disolvió en cloruro de metileno (30 mL)/ácido clorhídrico 1N (30 mL), y se enfrió a -5°C. A la solución de reacción se le agregó una solución acuosa de perclorato de sodio al 7% (30 mL) enfriada con hielo, gota a gota, manteniendo la temperatura a 0°C o menos, y se agitó así durante 15 minutos. La capa orgánica se extrajo en un embudo de separación previamente enfriado con hielo, se enfrió a -78°C y se le agregó una solución de metilamina 40% /metanol (1.33 mL, 17.2 mmol), disponible comercialmente, en cloruro de metileno (10 mL), y la temperatura se elevó a 0°C, seguido por agitación durante 2 horas. A la solución de reacción se le agregó agua (50 mL) y se extrajo dos veces con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en

columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-80%), para producir el compuesto deseado como un sólido blanco (889 mg, rendimiento de 63%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.77 (3H, d, J = 4.9 Hz), 4.81 (1H, s), 7.90 (1H, dd, J = 8.3, 2.4 Hz), 7.97 (1H, d, J = 8.3 Hz), 8.65 (1H, d, J = 2.4 Hz).

(121b) 5-Cloro-N-(4-metoxibencil)-N-metilpiridin-2-sulfonamida

La 5-cloro-N-metilpiridin-2-sulfonamida (889 mg, 4.30 mmol) sintetizada en el ejemplo (121a) se disolvió en N,N-dimetilformamida (15 mL), y se le agregó hidruro de sodio (172 mg, 4.30 mmol). Después de enfriamiento con hielo, se le agregó cloruro de p-metoxibencilo (0.70 mL, 5.16 mmol) y la temperatura se elevó a temperatura ambiente, seguido por agitación durante 3 horas. A la solución de reacción se le agregó agua (20 mL) y se extrajo dos veces con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-20%), para producir el compuesto deseado como un aceite incoloro (817 mg, rendimiento de 58%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.79 (3H, s), 3.81 (3H, s), 4.36 (2H, s), 6.87 (2H, dt, J = 9.4, 2.4 Hz), 7.25 (2H, d, J = 7.3 Hz), 7.88 (1H, dd, J = 8.3,2.4 Hz), 7.94 (1H, d, J = 8.3 Hz), 8.66 (1H, d, J = 2.4 Hz).

(121c) N-(4-Metoxibencil)-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-N-metilpiridin-2-sulfonamida

La 5-cloro-N-(4-metoxibencil)-N-metilpiridin-2-sulfonamida (228 mg, 0.70 mmol) sintetizada en el ejemplo (121b), y el 3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenol (220 mg, 0.67 mmol) sintetizado en el ejemplo (116d), se disolvieron en N,N-dimetilformamida (3 mL) y se les agregó carbonato de cesio (434 mg, 1.33 mmol), seguido por agitación a 100°C durante 3 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) y se extrajo dos veces con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0.5%-5%), para producir el compuesto deseado como un sólido blanco (293 mg, rendimiento de 71%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 1.43 (3H, d, J = 5.9 Hz), 2.79 (3H, s), 3.42 (3H, s), 3.49-3.61 (3H, m), 3.81 (3H, s), 4.08 (1H, dd, J = 13.7, 9.3 Hz), 4.37 (2H, s), 4.55-4.62 (1H, m), 4.80-4.87 (1H, m), 6.51 (1H, d, J = 3.9 Hz), 6.57 (1H, t, J = 2.2 Hz), 6.75 (1H, d, J = 3.9 Hz), 6.87-6.89 (3H, m), 7.03 (1H, s), 7.28 (2H, d, J = 8.8 Hz), 7.41 (1H, dd, J = 8.5, 2.7 Hz), 7.94 (1H, d, J = 8.3 Hz), 8.47 (1H, d, J = 2.4 Hz).

(121d) 5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-N-metilpiridin-2-sulfonamida

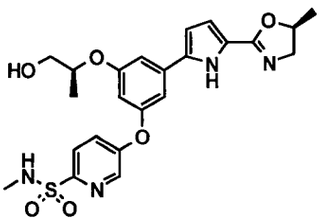
La N-(4-metoxibencil)-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-N-metilpiridin-2-sulfonamida (292 mg, 0.47 mmol) sintetizada en el ejemplo (121c) se disolvió en ácido trifluoroacético (2 mL) y se agitó a 45°C durante 1 hora. El disolvente se removió por destilación bajo presión reducida y al residuo se le agregó cloruro de metileno y trietilamina en pequeñas porciones, y nuevamente el disolvente se removió por destilación bajo presión reducida. El residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-4%), para producir el compuesto deseado como un sólido blanco (208 mg, rendimiento de 88%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 5.9 Hz), 1.43 (3H, d, J = 6.3 Hz), 2.76 (3H, s), 3.41 (3H, s), 3.49-3.61 (3H, m), 4.08 (1H, dd, J = 13.9, 9.0 Hz), 4.61-4.55 (1H, m), 4.84 (1H, dd, J = 15.1, 7.3 Hz), 6.50 (1H, d, J = 3.9 Hz), 6.56 (1H, t, J = 2.2 Hz), 6.76 (1H, d, J = 3.9 Hz), 6.86 (1H, s), 7.04 (1H, s), 7.41 (1H, dd, J = 8.5, 2.7 Hz), 7.96 (1H, d, J = 8.8 Hz), 8.45 (1H, d, J = 2.4 Hz).

MS (ESI) m/z: 501.18090 $(M+H)^+$.

EJEMPLO 122

5-(3-[(1S)-2-Hidroxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-N-metilpiridin-2-sulfonamida



La 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-N-metilpiridin-2-sulfonamida (166 mg, 0.32 mmol) sintetizada en el ejemplo (121d) se disolvió en cloruro de metileno (5 mL), y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 0.34 mL, 0.34 mmol), a -78°C y bajo una atmósfera de nitrógeno. Subsiguientemente, la temperatura se regresó a la temperatura ambiente, seguido por agitación durante 1.5 horas. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con cloruro de metileno. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-4%), para producir el compuesto deseado como un sólido blanco (119 mg, rendimiento de 78%).

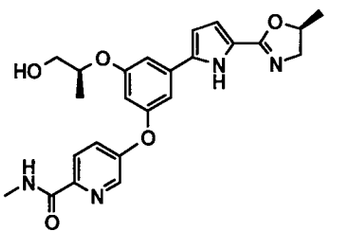
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.30 (3H, d, J = 6.3 Hz), 1.43 (3H, d, J = 6.8 Hz), 2.75 (3H, s), 3.54 (1H, dd, J = 13.7, 7.3 Hz), 3.75-3.77 (2H, m),

4.08 (1H, dd, J = 9.3, 13.7 Hz), 4.52-4.58 (1H, m), 4.81-4.88 (1H, m), 6.43 (1H, s), 6.47 (1H, d, J = 3.9 Hz), 6.75 (1H, d, J = 4.4 Hz), 6.83 (1H, s), 7.00 (1H, s), 7.39 (1H, dd, J = 8.8, 2.0 Hz), 7.95 (1H, d, J = 8.8 Hz), 8.39 (1H, s).

MS (ESI) m/z: 487.16369 $(M+H)^+$.

EJEMPLO 123

5-(3-[(1S)-2-Hidroxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-N-metilpiridin-2-carboxamida



(123a) 5-Fluoro-N-metilpiridin-2-carboxamida

Se disolvió ácido 5-fluoropiridin-2-carboxílico (495 mg, 3.51 mmol) en cloruro de metileno (10 mL), y se le agregó HOBt·H_2O (591 mg, 3.86 mmol), WSCI·HCl (1.35 g, 7.02 mmol), trietilamina (2.44 mL, 17.5 mmol) y solución de metilamina 40% /metanol (0.82 mL, 10.5 mmol), seguido por agitación durante 15 horas. A la solución de reacción se le agregó agua (30 mL) y se extrajo dos veces con cloruro de metileno (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-50%), para

producir el compuesto deseado como un sólido blanco (490 mg, rendimiento de 91%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 3.03 (3H, d, J = 5.5 Hz), 7.53 (1H, dt, J = 2.7, 8.6 Hz), 7.85 (1H, br s), 8.24 (1H, dd, J = 8.2, 4.7 Hz), 8.38 (1H, d, J = 2.7 Hz).

(123b) 5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-N-metilpiridin-2-carboxamida

La 5-fluoro-N-metilpiridin-2-carboxamida (122 mg, 0.79 mmol) sintetizada en el ejemplo (123a), y el 3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenol (275 mg, 0.83 mmol) sintetizado en el ejemplo (116d), se disolvieron en N,N-dimetilformamida (3 mL) y se les agregó carbonato de potasio (219 mg, 1.58 mmol), seguido por agitación a 100°C durante 3 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (30 mL) y se extrajo dos veces con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido blanco (283 mg, rendimiento de 77%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 1.42 (3H, d, J = 6.3 Hz), 3.03 (3H, d, J = 5.1 Hz), 3.41 (3H, s), 3.48-3.61 (3H, m), 4.08

(1H, dd, J = 13.9, 9.2 Hz), 4.53-4.60 (1H, m), 4.80-4.86 (1H, m), 6.49 (1H, d, J = 3.9 Hz), 6.53 (1H, t, J = 2.2 Hz), 6.74 (1H, d, J = 3.5 Hz), 6.83 (1H, d, J = 1.6 Hz), 7.00 (1H, s), 7.41 (1H, dd, J = 8.6, 2.7 Hz), 7.86 (1H, br s), 8.17 (1H, d, J = 8.6 Hz), 8.31 (1H, d, J = 2.7 Hz).

(123c) 5-(3-[(1S)-2-Hidroxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-N-metilpiridin-2-carboxamida

La 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-N-metilpiridin-2-carboxamida (176 mg, 0.38 mmol) sintetizada en el ejemplo (123b) se disolvió en cloruro de metileno (5 mL), y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 0.50 mL, 0.50 mmol) a -78°C. Subsiguientemente, la temperatura se regresó a la temperatura ambiente, seguido por agitación durante 1 hora. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con cloruro de metileno. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido blanco (118 mg, rendimiento de 69%).

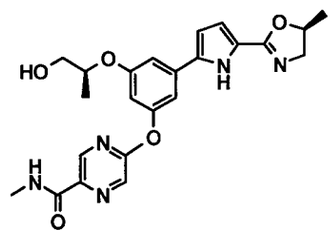
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.28 (3H, d, J = 5.9 Hz), 1.42 (3H, d, J = 6.3 Hz), 3.03 (3H, d, J = 5.1 Hz), 3.54 (1H, dd, J = 13.9, 7.2 Hz), 3.76 (2H, d, J = 4.7 Hz), 4.07 (1H, dd, J = 13.9, 9.2 Hz), 4.57 (1H, dd, J = 11.1, 6.1 Hz), 4.83 (1H, dt, J = 11.7, 4.6 Hz), 6.38 (1H, s), 6.45 (1H, d, J = 3.5 Hz), 6.73

(1H, d, J = 3.9 Hz), 6.80 (1H, s), 6.93 (1H, s), 7.35 (1H, dd, J = 8.6, 2.7 Hz), 7.87 (1H, d, J = 5.5 Hz), 8.15 (1H, d, J = 8.6 Hz), 8.27 (1H, d, J = 2.7 Hz).

MS (ESI) m/z: 451.19720 $(M+H)^+$.

EJEMPLO 124

5-(3-[(1S)-2-Hidroxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-N-metilpirazin-2-carboxamida



(124a) 5-Cloro-N-metilpirazin-2-carboxamida

Se disolvió ácido 5-cloropirazin-2-carboxílico (1.99 g, 12.6 mmol) en N,N-dimetilformamida (10 mL) y se le agregó HOBt·H_2O (591 mg, 3.86 mmol), WSCI·HCl (1.35 g, 7.02 mmol), N-metilmorfolina (2.76 mL, 25.1 mmol) y solución de metilamina 40% /metanol (2.92 mL, 37.6 mmol), seguido por agitación durante 18 horas. A la solución de reacción se le agregó agua (50 mL) y se extrajo dos veces con acetato de etilo (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-75%), para producir el compuesto deseado como un sólido blanco (585 mg, rendimiento

371

de 27%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 3.03 (3H, d, J = 4.9 Hz), 7.60 (1H, br s), 8.09 (1H, d, J = 1.5 Hz), 8.93 (1H, d, J = 1.0 Hz).

(124b) 5-(3-[(1S)-2-Hidroxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-N-metilpirazin-2-carboxamida

La 5-cloro-N-metilpirazin-2-carboxamida (171 mg, 1.00 mmol) sintetizada en el ejemplo (124a), y el 3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenol (300 mg, 0.91 mmol) sintetizado en el ejemplo (116d), se disolvieron en N,N-dimetilformamida (3 mL) y se les agregó carbonato de potasio (376 mg, 2.72 mmol), seguido por agitación a 100°C durante 5 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó 5-cloro-N-metilpirazin-2-carboxamida (110 mg, 0.64 mmol) y se agitó durante 3 horas. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (30 mL) y se extrajo dos veces con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir un sólido blanco (206 mg).

Este producto se disolvió en cloruro de metileno (5 mL) y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 0.57 mL, 0.57 mmol) a -78°C. Subsiguientemente, la temperatura se regresó a la

temperatura ambiente, seguido por agitación durante 1.5 horas. La solución de reacción se enfrió nuevamente a -78°C, se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 1.00 mL, 1.00 mmol), y la temperatura se regresó a la temperatura ambiente, seguido por agitación durante 3 horas. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con cloruro de metileno. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido blanco (87.8 mg, rendimiento de 21%).

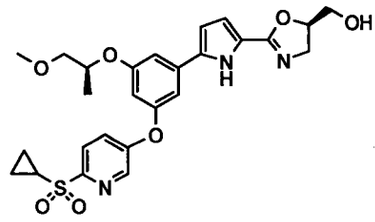
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J = 5.9 Hz), 1.43 (3H, d, J = 6.3 Hz), 3.05 (3H, d, J = 5.4 Hz), 3.55 (1H, dd, J = 13.9, 7.6 Hz), 3.77 (2H, d, J = 5.4 Hz), 4.09 (1H, dd, J = 13.9, 9.0 Hz), 4.56 (1H, dd, J = 11.2, 5.9 Hz), 4.87-4.80 (1H, m), 6.49 (1H, d, J = 3.4 Hz), 6.60 (1H, s), 6.75 (1H, d, J = 3.9 Hz), 6.93 (1H, s), 7.00 (1H, s), 7.62 (1H, d, J = 4.9 Hz), 8.29 (1H, s), 8.93 (1H, d, J = 1.0 Hz).

MS (ESI) m/z: 452.19252 $(M+H)^+$.

873

EJEMPLO 125

{(5R)-2-[5-(3-{[6-(Ciclopropilsulfonil)piridin-3-il]oxi}-5-[(1S)-2-metoxi-1-metiletoxi]fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol



(125a) {5-Cloro-2-[(3-cloropropil)tio]piridina

El 5-cloropiridin-2-tiol (600 mg, 4.12 mmol) sintetizado en el ejemplo (119a) se disolvió en metanol (15 mL), y se le agregó una solución de metóxido de sodio 28% /metanol (0.95 mL, 4.94 mmol) y 1-bromo-3-cloropropano (0.61 mL, 6.18 mmol), seguido por agitación a 60°C durante 1.5 horas. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (40 mL) y se extrajo dos veces con acetato de etilo (40 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida; se secó al vacío para producir el compuesto deseado como un aceite incoloro (849 mg, rendimiento de 92%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.26-2.31 (2H, m), 3.55-3.58 (2H, m), 3.67 (2H, t, J = 6.3 Hz), 7.96 (1H, dd, J = 8.3,2.0 Hz), 8.06 (1H, d, J = 7.8 Hz), 8.70 (1H, d, J = 2.4 Hz).

(125b) 5-Cloro-2-[(3-cloropropil)sulfonil]piridina

La 5-cloro-2-[(3-cloropropil)tio]piridina (846 mg, 3.80 mmol)

sintetizada en el ejemplo (125a) se disolvió en cloruro de metileno (20 mL) y subsiguientemente se le agregó ácido m-cloroperbenzoico (2.02 g, 7.62 mmol) enfriando con hielo, seguido por agitación así durante 1 hora. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio (40 mL) y se extrajo dos veces con cloruro de metileno (40 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-20%), para producir el compuesto deseado como un aceite incoloro (733 mg, rendimiento de 76%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.21-2.14 (2H, m), 3.30 (2H, t, J = 6.8 Hz), 3.67 (2H, t, J = 6.3 Hz), 7.13 (1H, dd, J = 8.6, 0.8 Hz), 7.45 (1H, dd, J = 8.6, 2.3 Hz), 8.37 (1H, dd, J = 5.1,3.1 Hz).

(125c) 5-Cloro-2-(ciclopropilsulfonil)piridina

La 5-cloro-2-[(3-cloropropil)sulfonil]piridina (732 mg, 3.05 mmol) sintetizada en el ejemplo (125b) se disolvió en tetrahidrofurano (10 mL) y se enfrió a -30°C; subsiguientemente se le agregó t-butóxido de potasio (582 mg, 5.18 mmol), seguido por agitación así durante 30 minutos. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (40 mL) y se extrajo dos veces con cloruro de metileno (40 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión

reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-25%), para producir el compuesto deseado (397 mg, rendimiento de 60%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.07-1.12 (2H, m), 1.37-1.41 (2H, m), 2.76-2.83 (1H, m), 7.91 (1H, dd, J = 8.2, 2.3 Hz), 7.98 (1H, d, J = 8.2 Hz), 8.71 (1H, dd, J = 2.3, 0.8 Hz).

(125d) N-[(2S)-2,3-Dihidroxipropil]-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]fenil}-1H-pirrol-2-carboxamida

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]-fenil}-1H-pirrol-2-carboxílico (9.32 g, 20.8 mmol) sintetizado en el ejemplo (106c) se disolvió en metanol (200 mL), y se le agregó (S)-(-)-3-amino-1,2-propanodiol (5.01 g, 55.0 mmol) y cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio n-hidratado (10.13 g, 32.3 mmol), seguido por agitación a temperatura ambiente durante la noche bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y al residuo resultante se le agregó agua (300 mL) y acetato de etilo (200 mL), y la solución se separó. La capa orgánica se lavó con salmuera saturada; subsiguientemente se secó sobre sulfato de magnesio anhidro y el disolvente se removió por destilación bajo presión reducida. El residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 70%-100%), para producir el producto deseado como un aceite incoloro (9.32 g, rendimiento de 86%).

^{1}H-RMN ($CDCl_3$, 400 Hz): δ 1.11 (18H, d, J = 7.0 Hz), 1.22-1.29

(3H, m), 1.31 (3H, d, J = 6.3 Hz), 3.07-3.14 (2H, m), 3.42 (3H, s), 3.50 (1H, dd, J = 10.2, 4.3 Hz), 3.54-3.66 (5H, m), 3.83-3.90 (1H, m), 4.49-4.57 (1H, m), 6.34 (1H, t, J = 6.5 Hz), 6.42 (1H, t, J = 2.3 Hz), 6.46 (1H, dd, J = 3.9, 2.7 Hz), 6.63 (1H, dd, J = 3.9, 2.3 Hz), 6.67 (1H, t, J = 1.6 Hz), 6.73 (1H, t, J = 1.6 Hz), 9.55 (1H, br s).

(125e) N-{(2S)-2-Hidroxi-3-[(triisopropilsilil)oxi]propil}-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]fenil}-1H-pirrol-2-carboxamida

La N-[(2S)-2,3-dihidroxipropil]-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]fenil}-1H-pirrol-2-carboxamida (9.30 g, 17.9 mmol) sintetizada en el ejemplo (125d) se disolvió en cloruro de metileno (180 mL), y se le agregó cloruro de triisopropilsililo (4.25 mL, 19.9 mmol), trietilamina (7.45 mL, 53.5 mmol) y 4-dimetilaminopiridina (2.20 g, 18.0 mmol), seguido por agitación a temperatura ambiente durante 2.5 horas bajo una atmósfera de nitrógeno. Se le agregó agua (300 mL) para separar la solución, y la capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-35%), para producir el compuesto deseado como un aceite incoloro (10.56 g, rendimiento de 87%).

^{1}H-RMN ($CDCl_3$, 400 Hz): δ 1.18-1.06 (39H, m), 1.22-1.30 (3H, m), 1.32 (3H, d, J = 6.3 Hz), 3.20 (1H, d, J = 4.3 Hz), 3.38-3.44 (1H, m), 3.42 (3H, s), 3.49 (1H, dd, J = 10.2, 4.3 Hz), 3.59 (1H, dd, J = 10.2, 5.5 Hz), 3.66-

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3.79 (3H, m), 3.85-3.91 (1H, m), 4.49-4.56 (1H, m), 6.30 (1H, t, J = 5.9 Hz), 6.41 (1H, t, J = 2.0 Hz), 6.45 (1H, dd, J = 3.9, 2.7 Hz), 6.59 (1H, dd, J = 3.9, 2.3 Hz), 6.66 (1H, t, J = 2.0 Hz), 6.72 (1H, t, J = 2.0 Hz), 9.34 (1H, br s).

(125f) (5R)-2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[(triisopropilsilil)-oxi]fenil}-1H-pirrol-2-il)-5{[(triisopropilsilil)oxi]metil}-4,5-dihidro-1,3-oxazol

La N-{(2S)-2-hidroxi-3-[(triisopropilsilil)oxi]propil}-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]fenil}-1H-pirrol-2-carboxamida (10.54 g, 15.6 mmol) sintetizada en el ejemplo (125e) se disolvió en tetrahidrofurano (160 mL), y se le agregó ácido metanosulfónico anhidro (5.51 g, 31.6 mmol) y trietilamina (8.70 mL, 62.4 mmol), seguido por agitación a temperatura ambiente durante 3 horas bajo una atmósfera de nitrógeno; subsiguientemente la temperatura se elevó a 60°C, seguido por agitación durante 3 horas. A la solución de reacción se le agregó agua (200 mL) y se extrajo con acetato de etilo (300 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 5%-30%), para producir el compuesto deseado como un aceite pardo (9.72 g, rendimiento de 95%).

^{1}H-RMN ($CDCl_3$, 400 Hz): δ 1.04-1.14 (39H, m), 1.22-1.29 (3H, m), 1.32 (3H, d, J = 6.3 Hz), 3.42 (3H, s), 3.48 (1H, dd, J = 10.2, 4.3 Hz), 3.59 (1H, dd, J = 10.2, 5.9 Hz), 3.85-3.90 (3H, m), 4.02 (1H, dd, J = 14.1,9.8 Hz), 4.48-4.54 (1H, m), 4.72-4.78 (1H, m), 6.39 (1H, t, J = 2.0 Hz), 6.45 (1H, d, J =

3.9 Hz), 6.67 (1H, t, J = 2.0 Hz), 6.71 (1H, t, J = 2.0 Hz), 6.73 (1H, d, J = 3.9 Hz).

(125g) 3-{5-[(5R)-5-(Hidroxilmetil)-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenol

El (5R)-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]-fenil}-1H-pirrol-2-il)-5{[(triisopropilsilil)oxi]metil}-4,5-dihidro-1,3-oxazol (9.69 g, 14.7 mmol) sintetizado en el ejemplo (125f) se disolvió en tetrahidrofurano (150 mL), y se le agregó a gotas fluoruro de tetrabutilamonio (solución en tetrahidrofurano 1 mol/L, 30.0 mL, 30 mmol), a 0°C, seguido por agitación a 0°C durante 30 minutos. Se le agregó una solución acuosa saturada de cloruro de amonio (200 mL) y se extrajo con acetato de etilo (200 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 3%-7%), para producir el compuesto deseado como un sólido amarillo pálido (6.50 g, rendimiento de ~100%).

^{1}H-RMN ($CDCl_3$, 400 Hz): δ 1.31 (3H, d, J = 6.3 Hz), 3.41 (3H, s), 3.48 (1H, dd, J = 10.2, 4.3 Hz), 3.58 (1H, dd, J = 10.2, 5.9 Hz), 3.78 (1H, dd, J = 12.5,5.5 Hz), 3.92-3.97 (2H, m), 4.12 (1H, dd, J = 13.7, 9.8 Hz), 4.51-4.59 (1H, m), 4.88-4.94 (1H, m), 6.39 (1H, t, J = 2.0 Hz), 6.47 (1H, d, J = 3.5 Hz), 6.72 (1H, s), 6.82 (1H, d, J = 3.9 Hz), 7.06 (1H, s), 11.05 (1H, br s).

(125h) {(5R)-2-[5-(3-{[6-(Ciclopropilsulfonil)piridin-3-il]oxi}-5-[(1S)-2-metoxi-1-metiletoxi]fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol

La 5-cloro-2-(ciclopropilsulfonil)piridina (168 mg, 0.77 mmol) sintetizada en el ejemplo (125c), y el 3-{5-[(5R)-5-(hidroxilmetil)-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenol (401 mg, 1.16 mmol) sintetizado en el ejemplo (125g), se disolvieron en N,N-dimetilformamida (2 mL) y se les agregó carbonato de potasio (213 mg, 154 mmol), seguido por agitación a 100°C durante 3 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (30 mL) y se extrajo dos veces con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0.5%-5%), para producir el compuesto deseado como un sólido blanco (139 mg, rendimiento de 34%).

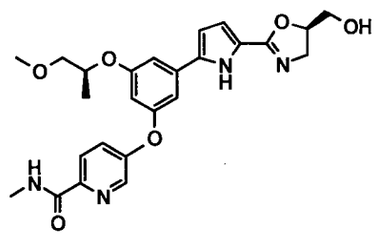
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.06-1.11 (2H, m), 1.31 (3H, d, J = 6.3 Hz), 1.37-1.41 (2H, m), 2.76-2.83 (1H, m), 3.42 (3H, d, J = 2.3 Hz), 3.50 (1H, dd, J = 10.2, 3.9 Hz), 3.59 (1H, dd, J = 10.2, 6.3 Hz), 3.68-3.79 (2H, m), 3.87 (1H, dd, J = 12.3, 2.9 Hz), 4.03 (1H, dd, J = 14.1, 9.8 Hz), 4.60-4.53 (1H, m), 4.84-4.77 (1H, m), 6.49 (1H, d, J = 3.9 Hz), 6.57 (1H, t, J = 2.2 Hz), 6.75 (1H, d, J = 3.9 Hz), 6.86 (1H, t, J = 1.8 Hz), 7.03 (1H, s), 7.42 (1H, dd, J = 8.6, 2.7 Hz), 7.97 (1H, d, J = 8.6 Hz), 8.51 (1H, d, J = 2.7 Hz).

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MS (ESI) m/z: 528.17975 $(M+H)^+$.

EJEMPLO 126

5-(3-{5-[(5R)-5-(Hidroximetil)-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)-N-metilpiridin-2-carboxamida



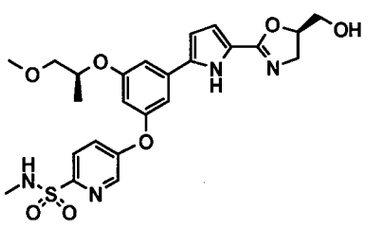
La 5-fluoro-N-metilpiridin-2-carboxamida (150 mg, 0.97 mmol) sintetizada en el ejemplo (123a), y el 3-{5-[(5R)-5-(hidroxilmetil)-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenol (438 mg, 1.27 mmol) sintetizado en el ejemplo (125 g), se disolvieron en N,N-dimetilformamida (3 mL) y se les agregó carbonato de potasio (269 mg, 1.95 mmol), seguido por agitación a 100°C durante 3 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (30 mL) y se extrajo dos veces con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido blanco (281 mg, rendimiento de 60%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.30 (3H, d, J = 6.3 Hz), 3.03 (3H, d, J = 4.9 Hz), 3.41 (3H, s), 3.49 (1H, dd, J = 10.3, 3.9 Hz), 3.58 (1H, dd, J = 10.3, 6.3 Hz), 3.69 (1H, dd, J = 11.7, 5.4 Hz), 3.76 (1H, dd, J = 13.9, 7.1 Hz), 3.85 (1H, d, J = 12.2 Hz), 4.02 (1H, dd, J = 14.2, 9.3 Hz), 4.58-4.52 (1H, m), 4.78 (1H, s), 6.47 (1H, d, J = 3.9 Hz), 6.54 (1H, t, J = 2.2 Hz), 6.73 (1H, d, J = 3.4 Hz), 6.83 (1H, t, J = 1.7 Hz), 6.98 (1H, s), 7.40 (1H, dd, J = 8.8, 2.9 Hz), 7.86 (1H, d, J = 4.4 Hz), 8.16 (1H, d, J = 8.3 Hz), 8.30 (1H, d, J = 2.4 Hz).

MS (ESI) m/z: 481.20954 $(M+H)^+$.

EJEMPLO 127

5-(3-{5-[(5R)-5-(Hidroximetil)-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)-N-metilpiridin-2-sulfonamida



(127a) 5-(3-{5-[(5R)-5-Hidroximetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)-N-(4-metoxibencil)-N-metilpiridin-2-sulfonamida

La 5-cloro-N-(4-metoxibencil)-N-metilpiridin-2-sulfonamida (427 mg, 1.31 mmol) sintetizada en el ejemplo (121b), y el 3-{5-[(5R)-5-(hidroxilmetil)-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenol (568 mg, 1.64 mmol) sintetizado en el ejemplo (125g), se

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disolvieron en N,N-dimetilformamida (5 mL) y se les agregó carbonato de potasio (361 mg, 2.61 mmol), seguido por agitación a 100°C durante 2 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (40 mL) y se extrajo dos veces con acetato de etilo (40 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-3.5%), para producir el compuesto deseado como un sólido blanco (228 mg, rendimiento de 27%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J = 5.9 Hz), 2.79 (3H, s), 3.43 (3H, s), 3.51 (1H, dd, J = 10.3, 3.9 Hz), 3.59 (1H, dd, J = 10.3, 6.3 Hz), 3.69-3.73 (1H, m), 3.75-3.81 (4H, m), 3.87 (1H, d, J = 12.2 Hz), 4.04 (1H, dd, J = 14.2, 9.8 Hz), 4.37 (2H, s), 4.55-4.58 (1H, m), 4.79-4.84 (1H, m), 6.50 (1H, d, J = 3.9 Hz), 6.58 (1H, t, J = 2.2 Hz), 6.76 (1H, d, J = 3.9 Hz), 6.85 (1H, s), 6.88 (2H, d, J = 8.8 Hz), 6.99 (1H, s), 7.28 (3H, d, J = 8.8 Hz), 7.42 (1H, dd, J = 8.8, 2.9 Hz), 7.94 (1H, d, J = 8.8 Hz), 8.47 (1H, d, J = 2.4 Hz).

(127b) 5-(3-{5-[(5R)-5-(Hidroximetil)-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)-N-metilpiridin-2-sulfonamida

La 5-(3-{5-[(5R)-5-hidroximetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)-N-(4-metoxibencil)-N-metilpiridin-2-sulfonamida (292 mg, 0.47 mmol) sintetizada en el ejemplo (127a) se disolvió en ácido trifluoroacético (2 mL) y se agitó a 45°C durante 6

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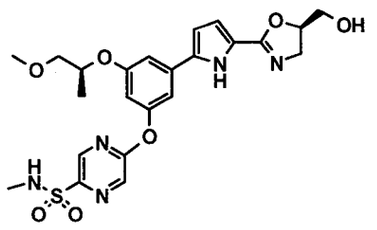
horas. El disolvente se removió por destilación bajo presión reducida y al residuo se le agregó cloruro de metileno y trietilamina en pequeñas porciones, y nuevamente el disolvente se removió por destilación bajo presión reducida. El residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-4%), para producir el compuesto deseado como un sólido blanco (184 mg, rendimiento de 100%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 5.9 Hz), 1.43 (3H, d, J = 6.3 Hz), 2.76 (3H, s), 3.41 (3H, s), 3.49-3.61 (3H, m), 4.08 (1H, dd, J = 13.9, 9.0 Hz), 4.61-4.55 (1H, m), 4.84 (1H, dd, J = 15.1, 7.3 Hz), 6.50 (1H, d, J = 3.9 Hz), 6.56 (1H, t, J = 2.2 Hz), 6.76 (1H, d, J = 3.9 Hz), 6.86 (1H, s), 7.04 (1H, s), 7.41 (1H, dd, J = 8.5, 2.7 Hz), 7.96 (1H, d, J = 8.8 Hz), 8.45 (1H, d, J = 2.4 Hz).

MS (ESI) m/z: 517.17549 $(M+H)^+$.

EJEMPLO 128

5-(3-{5-[(5R)-5-(Hidroximetil)-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)-N-metilpirazin-2-sulfonamida



(128a) 5-Bromopirazin-2-tiol

Bajo una atmósfera de nitrógeno, se disolvió 2,5-dibromopirazina

(300 mg, 1.26 mmol) en sulfóxido de dimetilo (3 mL), y se le agregó disulfuro de sodio nonahidratado (454 mg, 1.89 mmol), seguido por agitación a 100°C durante 1.5 horas. La solución de reacción se enfrió a temperatura ambiente y se le agregó agua (30 mL), seguido por neutralización con ácido clorhídrico 5N. Después, el precipitado resultante se separó por filtración y se lavó con agua; el sólido resultante se disolvió en éter dietílico/tetrahidrofurano y el material insoluble se separó por filtración. El disolvente se removió por destilación bajo presión reducida y el residuo se secó al vacío para producir el compuesto deseado como un sólido anaranjado (163 mg, rendimiento de 68%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 3.19 (1H, s), 7.97 (1H, d, J = 1.0 Hz), 8.34 (1H, d, J = 1.0 Hz).

(128b) 5-Bromo-N-metilpirazin-2-sulfonamida

El 5-bromopirazin-2-tiol (988 mg, 5.17 mmol) sintetizado en el ejemplo (128a) se disolvió en cloruro de metileno (15 mL) /ácido clorhídrico 1N (15 mL), y se enfrió a -10°C. A la solución de reacción se le agregó a gotas una solución acuosa de perclorato de sodio al 7% (15 mL) enfriada con hielo, manteniendo la temperatura a -5°C o menos, y se agitó así durante 1 hora. La capa orgánica se extrajo en un embudo de separación previamente enfriado con hielo y se enfrió a 0°C; se le agregó una solución de metilamina 40% /metanol (1.00 mL, 12.9 mmol), y la temperatura se regresó a la temperatura ambiente, seguido por agitación durante 17 horas. A la solución de reacción

se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo dos veces con cloruro de metileno (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-30%), para producir el compuesto deseado como un sólido blanco (147 mg, rendimiento de 11%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.83 (3H, d, J = 5.5 Hz), 4.80 (1H, s), 8.76 (1H, d, J = 1.6 Hz), 8.96 (1H, d, J = 1.2 Hz).

(128c) 5-(3-{5-[(5R)-5-(Hidroximetil)-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)-N-metilpirazin-2-sulfonamida

La 5-bromo-N-metilpirazin-2-sulfonamida (147 mg, 0.58 mmol) sintetizada en el ejemplo (128b), y el 3-{5-[(5R)-5-(hidroxilmetil)-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenol (262 mg, 0.76 mmol) sintetizado en el ejemplo (125g), se disolvieron en acetonitrilo (6 mL) y se les agregó carbonato de potasio (161 mg, 1.17 mmol), seguido por agitación durante 4 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó agua (20 mL) y se extrajo dos veces con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se

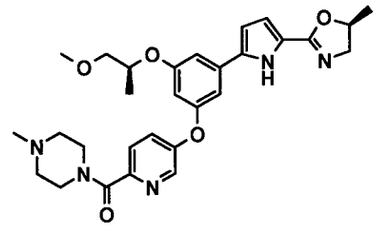
purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-3.5%), para producir el compuesto deseado como un sólido blanco (161 mg, rendimiento de 54%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 2.81 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 10.3, 3.9 Hz), 3.60 (1H, dd, J = 10.3, 5.9 Hz), 3.68-3.76 (2H, m), 3.85 (1H, dd, J = 12.2, 3.4 Hz), 4.00 (1H, dd, J = 14.2, 9.8 Hz), 4.60-4.54 (1H, m), 4.76-4.82 (1H, m), 5.23 (1H, s), 6.49 (1H, d, J = 3.9 Hz), 6.66 (1H, t, J = 2.0 Hz), 6.75 (1H, d, J = 3.4 Hz), 6.96 (1H, t, J = 1.7 Hz), 7.06 (1H, t, J = 2.0 Hz), 8.44 (1H, d, J = 1.5 Hz), 8.70 (1H, d, J = 1.0 Hz).

MS (ESI) m/z: 518.17036 $(M+H)^+$.

EJEMPLO 129

1-{[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)piridin-2-il]carbonil}-4-metilpiperazina



(129a) 5-~~Fluoro~~hidroxi-piridin-2-carboxilato de metilo

Se disolvió 2-bromo-5-fluoro-piridina (3.80 g, 21.6 mmol), disponible comercialmente, en metanol (50 mL), y se le agregó N,N-dimetilformamida (50 mL), acetato de paladio (484 mg, 2.16 mmol), 1,1-bis(difenilfosfino)ferroceno (2.39 g, 4.32 mmol) y trietilamina (6.0 mL, 43.2

mmol), seguido por agitación a temperatura ambiente durante 3 días bajo una atmósfera de monóxido de carbono; el material insoluble se separó de la solución de reacción por filtración. Se le agregó agua (100 mL), seguido por extracción con acetato de etilo (100 mL); la capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-50%), para producir el compuesto deseado como un sólido amarillo pálido (2.87 g, rendimiento de 86%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 4.01 (3H, s), 7.54 (1H, dt, J = 8.6, 3.9 Hz), 8.20 (1H, dd, J = 8.6, 4.7 Hz), 8.59 (1H, d, J = 2.7 Hz).

(129b) 5-(3-{5-[(Benciloxi)carbonil]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)piridin-2-carboxilato de metilo

El 5-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-1,2-dicarboxilato de 2-bencilo-1-t-butilo (4.08 g, 8.47 mmol) sintetizado en el ejemplo (78g), y el 5-fluoro piridin-2-carboxilato de metilo (1.45 g, 9.32 mmol) sintetizado en el ejemplo (129a), se disolvieron en N,N-dimetilformamida (30 mL) y se les agregó carbonato de potasio (3.51 g, 25.4 mmol), seguido por agitación a 100°C durante 3 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (100 mL) y se extrajo con acetato de etilo (100 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión

reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-35%).

El sólido amarillo resultante se disolvió en cloruro de metileno (5 mL) y se le agregó ácido trifluoroacético (7.5 mL), seguido por agitación a temperatura ambiente durante 1 hora. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio (50 mL) y se extrajo dos veces con acetato de etilo (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido amarillo pálido (3.26 g, rendimiento de 75%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 3.40 (3H, s), 3.50 (1H, dd, J = 10.2, 3.9 Hz), 3.58 (1H, dd, J = 10.4, 6.5 Hz), 4.00 (3H, s), 4.52-4.59 (1H, m), 5.32 (2H, s), 6.50 (1H, t, J = 2.9 Hz), 6.59 (1H, s), 6.83 (1H, s), 6.99-6.97 (2H, m), 7.34-7.44(5H, m), 8.12 (1H, d, J = 8.6 Hz), 8.52 (1H, d, J = 2.7 Hz), 9.22 (1H, s).

(129c) Acido 5-(3-{[6-(metoxicarbonil)]piridin-3-il]oxi}-5-[(1S)-2-metoxi-1-metiletoxi]fenil)-1H-pirrol-2-carboxílico

El 5-(3-{5-[(benciloxi)carbonil]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)piridin-2-carboxilato de metilo (3.18 g, 6.16 mmol) sintetizado en el ejemplo (129b) se disolvió en ácido fórmico 5% /etanol (200 mL), y se le

agregó un catalizador de paladio al 10% en carbón (2.00 g), seguido por agitación durante 2 horas bajo una atmósfera de hidrógeno. El catalizador de paladio en carbón se removió por filtración en Celite, seguido por lavado con tetrahidrofurano. El disolvente se removió por destilación bajo presión reducida, seguido por dilución con cloruro de metileno (100 mL), lavado con agua y secado sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida para producir el compuesto deseado como un sólido blanco (2.41 g, rendimiento de 92%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.46 (3H, s), 3.54 (1H, dd, J = 10.2, 3.9 Hz), 3.66 (1H, dd, J = 10.2, 6.6 Hz), 4.00 (3H, s), 4.71 (1H, td, J = 6.3, 4.3 Hz), 6.49 (1H, dd, J = 3.9, 2.7 Hz), 6.59 (1H, d, J = 2.0 Hz), 6.92 (1H, t, J = 1.6 Hz), 7.02 (1H, dd, J = 3.9, 2.3 Hz), 7.39 (1H, dd, J = 8.8, 2.9 Hz), 8.13 (1H, d, J = 8.6 Hz), 8.57 (1H, d, J = 2.7 Hz), 10.46 (1H, s).

(129d) 5-(3-{[(2R)-2-Hidroxipropil]carbamoil}-1H-pirrol-2-il)-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi}piridin-2-carboxilato de metilo

El ácido 5-(3-{[6-(metoxicarbonil)]piridin-3-il]oxi}-5-[(1S)-2-metoxi-1-metiletoxi]fenil)-1H-pirrol-2-carboxílico (800 mg, 1.87 mmol) sintetizado en el ejemplo (129c) se disolvió en metanol (20 mL), y se le agregó (R)-(-)-1-amino-2-propanol (339 μL, 4.30 mol) y cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio n-hidratado (829 mg, 2.99 mmol), seguido por agitación a temperatura ambiente durante 16 horas bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente

de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido blanco (726 mg, rendimiento de 80%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.25 (3H, d, J = 6.6 Hz), 1.32 (3H, d, J = 6.3 Hz), 3.25-3.32 (1H, m), 3.41 (3H, s), 3.51 (1H, dd, J = 10.2, 3.9 Hz), 3.57-3.65 (2H, m), 4.05 (3H, s), 4.58 (1H, td, J = 6.3, 4.0 Hz), 6.35 (1H, s), 6.48 (1H, dd, J = 3.9, 3.1 Hz), 6.57 (1H, t, J = 2.2 Hz), 6.61 (1H, dd, J = 3.9, 2.3 Hz), 6.85 (1H, t, J = 1.8 Hz), 7.00 (1H, t, J = 1.8 Hz), 7.36 (1H, dd, J = 8.8, 2.9 Hz), 8.12 (1H, d, J = 9.0 Hz), 8.53 (1H, d, J = 2.7 Hz), 9.66 (1H, s).

(129e) 5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)piridin-2-carboxilato de metilo

El 5-(3-{[(2R)-2-hidroxipropil]carbamoil}-1H-pirrol-2-il)-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi}piridin-2-carboxilato de metilo (726 mg, 1.50 mmol) sintetizado en el ejemplo (129d) se disolvió en tetrahidrofurano (20 mL), y se le agregó ácido metanosulfónico anhidro (523 mg, 3.00 mmol) y trietilamina (0.63 mL, 4.50 mmol), seguido por agitación a 50°C durante 5 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo con cloruro de metileno (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-7.5%), para producir el compuesto deseado como un sólido amarillo pálido (264 mg, rendimiento de 38%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 1.42 (3H, d, J = 6.3 Hz), 3.41 (3H, d, J = 3.1 Hz), 3.54 (3H, ddt, J = 26.4, 11.3, 4.4 Hz), 4.01 (3H, s), 4.04-4.11 (1H, m), 4.60-4.53 (1H, m), 4.87-4.78 (1H, m), 6.49 (1H, d, J = 3.9 Hz), 6.55 (1H, t, J = 2.0 Hz), 6.75 (1H, d, J = 3.9 Hz), 6.83 (1H, t, J = 1.8 Hz), 6.99 (1H, t, J = 2.0 Hz), 7.35 (1H, dd, J = 8.6, 2.7 Hz), 8.12 (1H, d, J = 9.0 Hz), 8.53 (1H, d, J = 2.7 Hz).

(129f) Acido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)piridin-2-carboxílico

El 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)piridin-2-carboxilato de metilo (264 mg, 0.57 mmol) sintetizado en el ejemplo (129e) se disolvió en metanol (20 mL), y se le agregó agua (3 mL) e hidróxido de litio monohidratado (71 mg, 1.70 mmol), seguido por agitación a 50°C durante 1 hora bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (50 mL), seguido por extracción dos veces con cloruro de metileno (40 mL), lavado con salmuera saturada y secado sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida; se secó al vacío para producir el compuesto deseado como un sólido amarillo pálido (256 mg, rendimiento de 100%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.40 (3H, d, J = 6.3 Hz), 1.67 (3H, d, J = 6.3 Hz), 3.43 (3H, s), 3.58-3.65 (2H, m), 3.78 (1H, dd, J = 11.2, 7.8 Hz), 4.29 (1H, t, J = 10.3 Hz), 4.84-4.90 (1H, m), 5.30-5.36 (1H, m), 6.65 (1H, d, J = 3.9 Hz), 6.69 (1H, t, J = 2.2 Hz), 7.21 (2H, s), 7.50 (1H, dd, J = 7.3, 3.4 Hz),

7.56 (1H, s), 8.18 (1H, s), 8.39 (1H, d, J = 2.4 Hz).

(129g) 1-{[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)piridin-2-il]carbonil}-4-metilpiperazina

El ácido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)piridin-2-carboxílico (270 mg, 0.60 mmol) sintetizado en el ejemplo (129f) se disolvió en tetrahidrofurano (5 mL), y se le agregó N-metilpiperazina (199 μl, 1.79 mmol), HATU (454 mg, 1.19 mmol) y N,N-diisopropiletilamina (624 μL, 3.58 mmol), seguido por agitación a temperatura ambiente durante 3 días bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó salmuera saturada (15 mL) y se extrajo dos veces con acetato de etilo (15 mL), seguido por secado sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido amarillo pálido (208 mg, rendimiento de 65%).

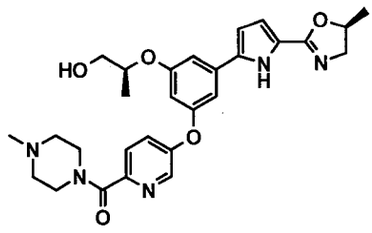
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 1.42 (3H, d, J = 5.9 Hz), 2.33 (3H, s), 2.44 (2H, t, J = 4.9 Hz), 2.52 (2H, t, J = 4.9 Hz), 3.41 (3H, d, J = 0.8 Hz), 3.48-3.60 (3H, m), 3.73 (2H, br s), 3.84 (2H, br s), 4.08 (1H, dd, J = 14.3, 9.2 Hz), 4.56 (1H, dd, J = 10.2, 6.3 Hz), 4.83 (1H, dd, J = 15.6, 6.6 Hz), 6.49 (1H, d, J = 4.3 Hz), 6.54 (1H, t, J = 2.0 Hz), 6.75 (1H, d, J = 3.9 Hz), 6.81 (1H, t, J = 1.8 Hz), 6.95 (1H, t, J = 1.8 Hz), 7.38 (1H, dd, J = 8.6, 2.7 Hz), 7.69 (1H, d, J = 8.6 Hz), 8.36 (1H, d, J = 2.7 Hz).

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MS (ESI) m/z: 534.27234 $(M+H)^+$.

EJEMPLO 130

(2S)-2-[3-{5-[(5S)-5-Metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-({6-[(4-metilpiperazin-1-il)carbonil] piridin-3-il}oxi)fenoxi]propan-1-ol



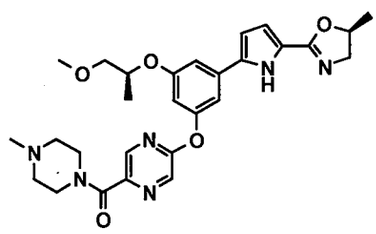
La 1-{[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)piriding-2-il]carbonil}-4-metilpiperazina (185 mg, 0.35 mmol) sintetizada en el ejemplo (129g) se disolvió en cloruro de metileno (10 mL), y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 694 μL, 0.694 mmol) a -78°C. Subsiguientemente, la temperatura se regresó a la temperatura ambiente, seguido por agitación durante 50 minutos. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-10%), para producir el compuesto deseado como un sólido blanco (51 mg, rendimiento de 28%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.28 (3H, d, J = 6.3 Hz), 1.43 (3H, d, J = 6.3 Hz), 2.34 (3H, s), 2.44 (2H, t, J = 4.9 Hz), 2.53 (2H, t, J = 4.9 Hz), 3.55 (1H, dd, J = 13.9, 7.2 Hz), 3.72 (2H, t, J = 4.7 Hz), 3.78 (2H, d, J = 5.5 Hz), 3.84 (2H, s), 4.09 (1H, dd, J = 13.9, 9.2 Hz), 4.60 (1H, dd, J = 11.3, 5.5 Hz), 4.85 (1H, dt, J = 11.6, 4.5 Hz), 6.35 (1H, s), 6.46 (1H, d, J = 3.9 Hz), 6.75 (1H, d, J = 3.9 Hz), 6.79 (1H, t, J = 1.8 Hz), 6.90 (1H, s), 7.33 (1H, dd, J = 8.6, 2.7 Hz), 7.67 (1H, dd, J = 8.6, 0.8 Hz), 8.33 (1H, t, J = 1.8 Hz).

MS (ESI) m/z: 520.25784 $(M+H)^+$.

EJEMPLO 131

2-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-5-[(4-metilpiperazin-1-il)carbonil]pirazina



(131a) 2-Cloro-5-[(4-metilpiperazin-1-il)carbonil]pirazina

Se disolvió ácido 5-hidroxipirazin-2-carboxílico (5.00 g, 39.0 mmol), disponible comercialmente, en cloruro de tionilo (64 mL), y se le agregaron unas gotas de N,N-dimetilformamida, seguido por calentamiento a reflujo durante 5 horas bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se diluyó con cloruro de metileno (50 mL). Enfriando en un baño de hielo se le agregó

diisopropiletilamina (18.7 mL, 107 mmol) y 1-metilpiperazina (4.37 mL, 39.2 mmol), y se agitó a temperatura ambiente durante 3 días bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó agua (100 mL) y se extrajo con cloruro de metileno (100 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 3%-5%), para producir el compuesto deseado como un sólido pardo (5.32 g, rendimiento de 62%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.34 (3H, s), 2.44 (2H, t, J = 5.1 Hz), 2.53 (2H, t, J = 5.1 Hz), 3.64 (2H, t, J = 5.1 Hz), 3.84 (2H, t, J = 4.9 Hz), 8.55 (1H, d, J = 1.2 Hz), 8.76 (1H, d, J = 1.6 Hz).

(131b) 5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-({5-[(4-metilpiperazin-1-il)carbonil]pirazin-2-il}oxi)fenil}-1H-pirrol-2-carboxilato de bencilo

El 5-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-1,2-dicarboxilato de 2-bencilo-1-t-butilo (2.00 g, 4.15 mmol) sintetizado en el ejemplo (78g), y la 2-cloro-5-[(4-metilpiperazin-1-il)carbonil]pirazina (1.10 g, 4.57 mmol) sintetizada en el ejemplo (131a), se disolvieron en N,N-dimetilformamida (20 mL) y se les agregó carbonato de potasio (1.72 g, 12.5 mmol), seguido por agitación a 80°C durante 4 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (80 mL) y se extrajo dos veces con acetato de etilo (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó

sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-7.5%) para producir un compuesto como un aceite pardo (2.88 g).

Este se disolvió en cloruro de metileno (5 mL) y se le agregó ácido trifluoroacético (5 mL), seguido por agitación a temperatura ambiente durante 2 horas. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio (50 mL) y se extrajo dos veces con cloruro de metileno (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-7.5%), para producir el compuesto deseado como un sólido amarillo pálido (1.96 g, rendimiento de 81%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ1.34 (3H, d, J = 6.3 Hz), 2.34 (3H, s), 2.45 (2H, t, J = 4.5 Hz), 2.53 (2H, t, J = 4.9 Hz), 3.41 (3H, s), 3.51 (1H, dd, J = 10.9, 3.7 Hz), 3.59 (1H, dd, J = 9.8, 5.5 Hz), 3.71 (2H, br s), 3.84 (2H, br s), 4.53-4.60 (1H, m), 5.33 (2H, s), 6.51 (1H, dd, J = 3.9, 2.7 Hz), 6.69 (1H, t, J = 2.0 Hz), 6.93 (1H, s), 6.98 (1H, dd, J = 3.7, 2.5 Hz), 7.02 (1H, s), 7.34-7.44(5H, m), 8.35 (1H, t, J = 1.4 Hz), 8.54 (1H, d, J = 0.8 Hz), 9.21 (1H, br s).

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(131c) N-[(2R)-2-Hidroxipropil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-({5-[(4-metilpiperazin-1-il)carbonil]pirazin-2-il}oxi)fenil}-1H-pirrol-2-carboxamida

El 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-({5-[(4-metilpiperazin-1-il)carbonil]pirazin-2-il}oxi)fenil}-1H-pirrol-2-carboxilato de bencilo (1.94 g, 3.32 mmol) sintetizado en el ejemplo (131b) se disolvió en metanol (100 mL), y se le agregó un catalizador de paladio al 10% en carbón (1.20 g), seguido por agitación a temperatura ambiente durante 2.5 horas bajo una atmósfera de hidrógeno. El catalizador de paladio en carbón se removió por filtración en Celite, seguido por lavado con tetrahidrofurano. El disolvente se removió por destilación bajo presión reducida para producir un sólido blanco (1.45 g).

Este sólido blanco (700 mg, 1.41 mmol) y 4-dimetilaminopiridina (86 mg, 0.71 mmol) se disolvieron en cloruro de metileno (30 mL), y se les agregó WSCI·HCl (625 mg, 2.26 mmol) y (R)-1-amino-2-propanol (256 μL, 3.25 mmol) a temperatura ambiente, seguido por agitación durante 3 días bajo una atmósfera de nitrógeno. La solución de reacción se diluyó con cloruro de metileno (60 mL), se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-10%), para producir el producto deseado como un sólido blanco (447 mg, 50%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.23 (3H, d, J = 6.3 Hz), 1.33 (3H, d, J = 8.0 Hz), 2.34 (3H, s), 2.45 (2H, t, J = 4.7 Hz), 2.53 (2H, t, J = 4.7 Hz), 3.23-3.30 (1H, m), 3.42 (3H, s), 3.51 (1H, dd, J = 10.2, 4.3 Hz), 3.58-3.63 (2H, m), 3.71 (2H, t, J = 4.7 Hz), 3.84 (2H, t, J = 5.5 Hz), 4.00 (1H, br s), 4.53-4.60 (1H, m), 6.37 (1H, s), 6.49 (1H, t, J = 3.3 Hz), 6.61 (1H, dd, J = 3.9, 2.3 Hz), 6.66 (1H, s), 6.93 (1H, t, J = 1.8 Hz), 7.02 (1H, t, J = 2.0 Hz), 8.34 (1H, s), 8.53 (1H, s), 9.66 (1H, br s).

(131d) 2-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-5-[(4-metilpiperazin-1-il)carbonil]-pirazina

La N-[(2R)-2-hidroxipropil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-({5-[(4-metilpiperazin-1-il)carbonil]pirazin-2-il}oxi)fenil}-1H-pirrol-2-carboxamida (447 mg, 0.81 mmol) sintetizada en el ejemplo (131c) se disolvió en tetrahidrofurano (20 mL), y se le agregó ácido metanosulfónico anhidro (282 mg, 1.62 mmol) y trietilamina (0.34 mL, 2.43 mmol), seguido por agitación a 50°C durante 4 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo dos veces con cloruro de metileno (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido amarillo pálido (279 mg,

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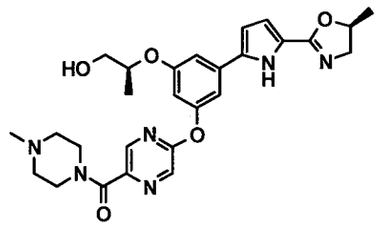
rendimiento de 65%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 1.42 (3H, d, J = 6.3 Hz), 2.34 (3H, s), 2.46 (2H, t, J = 4.7 Hz), 2.53 (2H, t, J = 4.7 Hz), 3.42 (3H, s), 3.49-3.62 (3H, m), 3.72 (2H, t, J = 4.3 Hz), 3.84 (2H, t, J = 5.1 Hz), 4.08 (1H, dd, J = 14.1, 9.0 Hz), 4.53-4.60 (1H, m), 4.87-4.78 (1H, m), 6.50 (1H, d, J = 3.9 Hz), 6.65 (1H, t, J = 2.2 Hz), 6.75 (1H, d, J = 3.9 Hz), 6.91 (1H, t, J = 1.8 Hz), 7.02 (1H, t, J = 2.0 Hz), 8.34 (1H, d, J = 1.2 Hz), 8.54 (1H, d, J = 1.2 Hz).

MS (ESI) m/z: 535.26585 $(M+H)^+$.

EJEMPLO 132

(2S)-2-[3-{5-[(5S)-5-Metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-({5-[(4-metilpiperazin-1-il)carbonil]pirazin-2-il}oxi)fenoxi]propan-1-ol



La 2-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-5-[(4-metilpiperazin-1-il)carbonil]pirazina (259 mg, 0.48 mmol) sintetizada en el ejemplo (131d) se disolvió en cloruro de metileno (15 mL), y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 0.81 mL, 0.81 mmol) a -78°C. Subsiguientemente, la temperatura se regresó a la temperatura ambiente, seguido por agitación

durante 3 horas. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 2%-8%), para producir el compuesto deseado como un sólido blanco (62.4 mg, rendimiento de 25%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.28 (4H, d, J = 6.3 Hz), 1.41 (3H, d, J = 6.3 Hz), 2.34 (3H, s), 2.45 (2H, t, J = 4.5 Hz), 2.52 (2H, t, J = 4.7 Hz), 3.53 (1H, dd, J = 13.7, 7.4 Hz), 3.71 (2H, t, J = 4.7 Hz), 3.77-3.79 (2H, m), 3.83 (2H, t, J = 4.7 Hz), 4.07 (1H, dd, J = 13.7, 9.4 Hz), 4.59 (1H, td, J = 11.5, 5.7 Hz), 4.83 (1H, dq, J = 17.8, 5.1 Hz), 6.44 (1H, d, J = 3.9 Hz), 6.47 (1H, s), 6.72 (1H, d, J = 3.9 Hz), 6.88 (1H, s), 6.94 (1H, s), 8.30 (1H, s), 8.52 (1H, d, J = 0.8 Hz).

MS (ESI) m/z: 521.25002 $(M+H)^+$.

EJEMPLO DE PRUEBA 1

(1) Preparación de GK

Por medio de una reacción en cadena de polimerasa (PCR) se clonó ADNc que codifica el polipéptido GK pancreático humano (No. de registro de GenBank NM_000162, variante de glucocinasa humana 1) de una

colección de ADNc humano, y se introdujo en un vector de expresión de proteína fusionado con glutatión S-transferasa (GST) (GEX4T, GE Healthcare Bioscience). El vector se introdujo en *Escherichia coli* (tal como BL21 o JM109, Invitrogen), y la *E. coli* transformada se cultivó durante la noche a 37 °C, seguido por recuperación de las células. Después de congelar y descongelar las células recuperadas, se suspendieron en amortiguador de fosfato que contenía Triton-X a una concentración final de 1%, seguido por lisis de las células con un homogeneizador ultrasónico. El sobrenadante obtenido por centrifugación del homogenato a baja velocidad (10,000 x g, 30 minutos) se sometió adicionalmente a centrifugación de alta velocidad (100,000 x g, 10 minutos), seguido por recuperación del sobrenadante y purificación de la proteína fusionada usando un sistema de purificación de proteína GST fusionada (Bulk GST Purification Module, GE Healthcare Bioscience). La proteína GK-fusionada se dividió en alícuotas más pequeñas y se guardó a -80 °C.

(2) Prueba de actividad de GK

La actividad de GK se midió usando la GK purificada del paso (1) anterior. Más específicamente, se preparó una solución de enzima agregando la GK purificada del paso (1) anterior y glucosa-6-fosfato deshidrogenasa (Sigma) a la solución 1 de un kit de prueba de glucosa (D-Glucose UV Method, Roche Diagnostics). La solución de enzima, un diluente del compuesto de prueba y glucosa (concentración final: 5 mM), se mezclaron en una placa de ELISA de 96 pocillos y se dejaron reaccionar 30 minutos a

temperatura ambiente. Después de terminarse la reacción se midió la absorbancia a una longitud de onda de 340 nm usando SpectraMax Plus (Molecular Probe). Además, se usó la absorbancia sin reacción (cuando no se agregó glucosa) como referencia.

Las proporciones de activación de GK se indican con los valores representados por la siguiente fórmula numérica: (absorbancia después de reaccionar durante 30 minutos con el compuesto de prueba) / (absorbancia después de reaccionar durante 30 minutos sin compuesto de prueba). En el cuadro 1 se muestran los resultados de las proporciones de activación de GK obtenidas a una concentración de compuesto de prueba de 1 μM.

CUADRO 1

Ejemplo	Proporción de activación de GK
1	2.0
2	1.9
3	1.9
15	1.6
20	2.0
21	2.0
25	2.0
26	2.3
29	2.0
31	2.0
32	2.0

CUADRO 1 (Continuación)

Ejemplo	Proporción de activación de GK
33	1.7
35	2.1
41	2.1
47	2.0
60	2.0
64	1.9
65	2.4
67	1.7
68	2.0
69	2.2
70	1.9
73	2.0
74	2.0
75	1.8
76	3.0
77	2.6
81	2.2
82	2.7
84	2.7
85	2.9
86	2.5
88	2.4
89	2.3
91	2.6
93	2.4
95	2.5

CUADRO 1 (Continuación)

Ejemplo	Proporción de activación de GK
98	1.9
100	1.9
101	1.9
103	2.1
107	2.0
108	2.0
109	2.2
110	2.4
112	2.4
114	2.2
122	2.5
123	2.6
126	2.6
127	2.4

Basándose en estos resultados, los compuestos de la presente invención tienen una actividad activadora de GK superior y son útiles como agentes terapéuticos o preventivos de una enfermedad seleccionada del conjunto que consiste en diabetes, deterioro de tolerancia a la glucosa, diabetes gestacional, complicaciones crónicas de la diabetes (que incluyen neuropatía periférica diabética, nefropatía diabética, retinopatía diabética y macroangiopatía diabética), y síndrome metabólico.

EJEMPLO DE PREPARACION 1

Cápsula

Compuesto del ejemplo 1 o 78	50 mg
Lactosa	128 mg
Almidón de maíz	70 mg
Estearato de magnesio	2 mg
	250 mg

Los polvos de esta formulación se mezclaron y se pasaron a través de un tamiz de malla 60, y después se vaciaron en una cápsula de gelatina de 250 mg para obtener una cápsula.

EJEMPLO DE PREPARACION 2

Tableta

Compuesto del ejemplo 1 o 78	50 mg
Lactosa	126 mg
Almidón de maíz	23 mg
Estearato de magnesio	1 mg
	200 mg

Los polvos de esta formulación se mezclaron, se granularon con una pasta de almidón de maíz y se secaron; después se comprimió en tableta con una máquina tableteadora para obtener una tableta de 200 mg. Esta

tableta se puede proveer con un recubrimiento de azúcar conforme sea necesario.

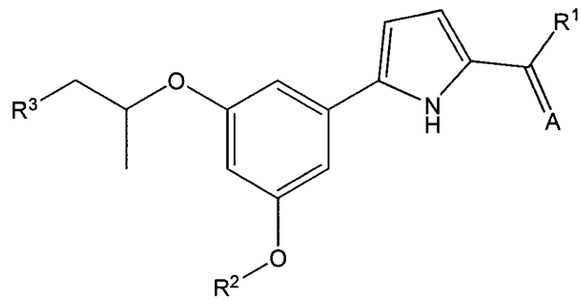
Aplicación industrial

Un compuesto representado por la fórmula general (I) de la presente invención, o una sal farmacológicamente aceptable del mismo, tiene una actividad activadora de GK superior y es útil como agente terapéutico o preventivo (particularmente terapéutico) para la diabetes, deterioro de tolerancia a la glucosa, diabetes gestacional, complicaciones crónicas de la diabetes (que incluyen neuropatía periférica diabética, nefropatía diabética, retinopatía diabética y macroangiopatía diabética), o síndrome metabólico (particularmente diabetes o deterioro de tolerancia a la glucosa), para usarse en animales de sangre caliente (particularmente en humanos).

NOVEDAD DE LA INVENCION

REIVINDICACIONES

1.- Un compuesto que tiene la fórmula general (I):



(I)

[en donde: A representa un grupo representado por la fórmula $=NOR^4$, un átomo de oxígeno o un átomo de azufre; R^4 representa un átomo de hidrógeno o un grupo alquilo de C_1-C_6; R^1 representa un grupo alquilo de C_1-C_6, un grupo alcoxi de C_1-C_6, un grupo alquilo de C_1-C_6 halogenado, un grupo alcoxi de C_1-C_6 halogenado, un grupo amino, un grupo mono-alquil(C_1-C_6)-amino, un grupo mono-alquilo halogenado (C_1-C_6)-amino, un grupo di-alquil(C_1-C_6)-amino, o un grupo di-alquilo halogenado (C_1-C_6)-amino, o A y R^1 junto con el átomo de carbono al que están unidos, forman un grupo heterocíclico que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α; R^2 representa un grupo fenilo que puede estar sustituido con 1 a 5 grupos seleccionados independientemente del conjunto de sustituyentes α, o un grupo heterocíclico

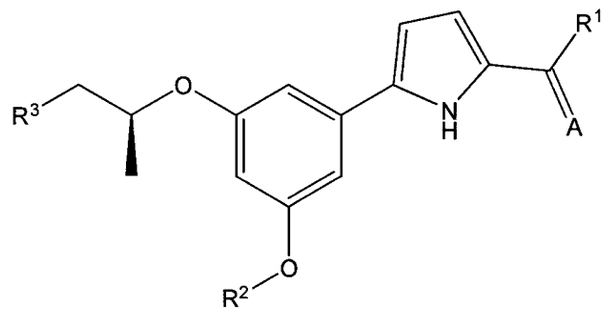
que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α; R^3 representa un grupo hidroxi o un grupo alcoxi de C_1-C_6; y el conjunto de sustituyentes α comprende un átomo de halógeno, un grupo alquilo de C_1-C_6, un grupo de alquilo de C_1-C_6 halogenado, un grupo alquenilo de C_2-C_6, un grupo alquinilo de C_2-C_6, un grupo hidroxi, un grupo alquilo de C_1-C_6 sustituido con 1 o 2 grupos hidroxi, un grupo alcoxi de C_1-C_6, un grupo alcoxi de C_1-C_6 halogenado, un grupo alcoxi(C_1-C_6)-alquilo(C_1-C_6), un grupo alcoxi(C_1-C_6)-alcoxi(C_1-C_6), un grupo formilo, un grupo carboxilo, un grupo alquilcarbonilo de C_2-C_7, un grupo alcoxicarbonilo de C_2-C_7, un grupo alquilcaboniloxi de C_2-C_7, un grupo alcoxicarboniloxi de C_2-C_7, un grupo nitro, un grupo amino, un grupo mono-alquil(C_1-C_6)-amino, un grupo di-alquil(C_1-C_6)-amino, un grupo alquiltio de C_1-C_6, un grupo alquilsulfonilo de C_1-C_6, un grupo cicloalquilsulfonilo de C_3-C_6, un grupo hidroxialquilsulfonilo de C_1-C_6, un grupo alcoxi(C_1-C_6)-alquilsulfonilo(C_1-C_6), un grupo representado por la fórmula -V-NR^5R^6 (en donde V representa un grupo carbonilo o un grupo sulfonilo, y R^5 y R^6 pueden ser iguales o diferentes y representan respectivamente un átomo de hidrógeno o un grupo alquilo de C_1-C_6, o R^5 y R^6, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros que puede estar sustituido con 1 o 2 grupos seleccionados independientemente de un grupo alquilo de C_1-C_6 y un grupo hidroxi, y el heterociclo saturado de 4 a 6 miembros puede contener también un átomo de oxígeno o un átomo de nitrógeno), un grupo mono-alquilcarbonilamino de C_2-C_7, un grupo mono-

alquil(C_1-C_6)-aminocarboniloxi, un grupo di-alquil(C_1-C_6)-aminocarboniloxi, un grupo mono-alcoxicarbonilamino de C_2-C_7, un grupo mono-alquilsulfonilamino de C_1-C_6, un grupo ciano, un grupo 1,3,4-oxadiazol-2-ilo sustituido opcionalmente con un grupo alquilo de C_1-C_6 en la posición 5, un grupo 1,3,4-tiadiazol-2-ilo sustituido opcionalmente con un grupo alquilo de C_1-C_6 en la posición 5, y un grupo oxo], o una sal farmacológicamente aceptable del mismo.

2.- El compuesto o sal farmacológicamente aceptable de conformidad con la reivindicación 1, caracterizado además porque el conjunto de sustituyentes α comprende un átomo de halógeno, un grupo alquilo de C_1-C_6, un grupo alquilo de C_1-C_6 halogenado, un grupo alquenilo de C_2-C_6, un grupo alquinilo de C_2-C_6, un grupo hidroxi, un grupo alquilo de C_1-C_6 sustituido con 1 o 2 grupos hidroxi, un grupo alcoxi de C_1-C_6, un grupo alcoxi de C_1-C_6 halogenado, un grupo alcoxi(C_1-C_6)-alquilo(C_1-C_6), un grupo alcoxi(C_1-C_6)-alcoxi(C_1-C_6), un grupo formilo, un grupo carboxilo, un grupo alquilcarbonilo de C_2-C_7, un grupo alcoxicarbonilo de C_2-C_7, un grupo alquilcaboniloxi de C_2-C_7, un grupo alcoxicarboniloxi de C_2-C_7, un grupo nitro, un grupo amino, un grupo mono-alquil(C_1-C_6)-amino, un grupo di-alquil(C_1-C_6)-amino, un grupo alquiltio de C_1-C_6, un grupo alquilsulfonilo de C_1-C_6, un grupo cicloalquilsulfonilo de C_3-C_6, un grupo hidroxialquilsulfonilo de C_1-C_6, un grupo alcoxi(C_1-C_6)-alquilsulfonilo(C_1-C_6), un grupo representado por la fórmula -V-NR^5R^6 (en donde V representa un grupo carbonilo o un grupo sulfonilo, y R^5 y R^6 pueden ser iguales o diferentes y representan respectivamente un átomo de hidrógeno

o un grupo alquilo de C_1-C_6, o R^5 y R^6, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros que puede estar sustituido con 1 o 2 grupos seleccionados independientemente de un grupo alquilo de C_1-C_6 y un grupo hidroxi, y el heterociclo saturado de 4 a 6 miembros puede contener también un átomo de oxígeno o un átomo de nitrógeno), un grupo mono-alquilcarbonilamino de C_2-C_7, un grupo mono-alquil(C_1-C_6)-aminocarboniloxi, un grupo di-alquil(C_1-C_6)-aminocarboniloxi, un grupo mono-alcoxicarbonilamino de C_2-C_7, un grupo mono-alquilsulfonilamino de C_1-C_6, un grupo ciano, un grupo 1,3,4-oxadiazol-2-ilo sustituido opcionalmente con un grupo alquilo de C_1-C_6 en la posición 5, y un grupo 1,3,4-tiadiazol-2-ilo sustituido opcionalmente con un grupo alquilo de C_1-C_6 en la posición 5.

3.- El compuesto o sal farmacológicamente aceptable de conformidad con la reivindicación 1 o 2, caracterizado además porque la fórmula general (I) es la fórmula general (Ia):



(Ia)

4.- El compuesto o sal farmacológicamente aceptable de conformidad con cualquiera de las reivindicaciones 1 a 3, caracterizado

además porque A es un átomo de oxígeno.

5.- El compuesto o sal farmacológicamente aceptable de conformidad con cualquiera de las reivindicaciones 1 a 4, caracterizado además porque R^1 es un grupo alquilo de C_1-C_6, un grupo alcoxi de C_1-C_6 o un grupo mono-alquilo halogenado (C_1-C_6)-amino.

6.- El compuesto o sal farmacológicamente aceptable de conformidad con cualquiera de las reivindicaciones 1 a 4, caracterizado además porque R^1 es un grupo metilo o un grupo 2-cloroetilamino.

7.- El compuesto o sal farmacológicamente aceptable de conformidad con cualquiera de las reivindicaciones 1 a 3, caracterizado además porque el grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están unidos, y que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, es un grupo 2-piridilo, un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo, un grupo 1,3-tiazol-2-ilo, un grupo 1,3-oxazol-2-ilo, un grupo 1,3,4-oxadiazol-2-ilo, un grupo 1,3,4-tiadiazol-2-ilo, un grupo 4,5-dihidro-1,3-tiazol-2-ilo, un grupo 4,5-dihidro-1,3-oxazol-2-ilo, o un grupo 4,5-dihidro-1,3-benzotiazol-2-ilo, que pueden estar sustituidos con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes γ, y el conjunto de sustituyentes γ comprende un átomo de halógeno, un grupo alquilo de C_1-C_6, un grupo alquilo de C_1-C_6 halogenado, un grupo alquilo de C_1-C_6 sustituido con 1 o 2 grupos hidroxi, un grupo alcoxi de C_1-C_6, un grupo carboxilo, un grupo mono-alquil(C_1-C_6)-aminocarbonilo, un grupo di-alquil(C_1-C_6)-aminocarbonilo y un grupo hidroxi.

8.- El compuesto o sal farmacológicamente aceptable de conformidad con cualquiera de las reivindicaciones 1 a 3, caracterizado además porque el grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están unidos, y que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, es un grupo 1,3-tiazol-2-ilo, un grupo 5-metil-1,3-tiazol-2-ilo, un grupo 5-metil-1,3,4-oxadiazol-2-ilo, un grupo 4,5-dihidro-1,3-tiazol-2-ilo, un grupo 4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo 5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-etil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1R)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1S)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-4-hidroxi-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4-hidroximetil-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5R)-5-hidroximetil-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo 5-carboxil-1,3-tiazol-2-ilo, un grupo 5-dimetilaminocarbonil-1,3-tiazol-2-ilo, un grupo 5-metil-1,3,4-tiadiazol-2-ilo, o un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo.

9.- El compuesto o sal farmacológicamente aceptable de conformidad con cualquiera de las reivindicaciones 1 a 3, caracterizado además porque el grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están unidos, y que puede estar sustituido con 1 a 3 grupos

seleccionados independientemente del conjunto de sustituyentes α, es un grupo 4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-etil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1R)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1S)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4-hidroximetil-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5R)-5-hidroximetil-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo 1,3-tiazol-2-ilo, un grupo 5-carboxil-1,3-tiazol-2-ilo, un grupo 5-dimetilaminocarbonil-1,3-tiazol-2-ilo, un grupo 5-metil-1,3,4-tiadiazol-2-ilo, un grupo 5-metil-1,3,4-oxadiazol-2-ilo, un grupo 4,5-dihidro-1,3-tiazol-2-ilo, o un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo.

10.- El compuesto o sal farmacológicamente aceptable de conformidad con cualquiera de las reivindicaciones 1 a 3, caracterizado además porque el grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están unidos, y que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, es un grupo 4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-etil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1R)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1S)-1-

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hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4-hidroximetil-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, o un grupo (4R,5R)-5-hidroximetil-4-metil-4,5-dihidro-1,3-oxazol-2-ilo.

11.- El compuesto o sal farmacológicamente aceptable de conformidad con cualquiera de las reivindicaciones 1 a 10, caracterizado además porque R^2 es un grupo fenilo que puede estar sustituido con 1 a 5 grupos seleccionados independientemente del conjunto de sustituyentes δ, o un grupo 2-piridilo, 3-piridilo o 2-pirazinilo que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes δ, y el conjunto de sustituyentes δ comprende un átomo de halógeno, un grupo alquilo de C_1-C_6, un grupo alquilo de C_1-C_6 halogenado, un grupo alquilo de C_1-C_6 sustituido con 1 o 2 grupos hidroxi, un grupo alquilcarbonilo de C_2-C_7, un grupo alcoxicarbonilo de C_2-C_7, un grupo alquilsulfonilo de C_1-C_6, un grupo representado por la fórmula –V-NR^5R^6 (en donde V representa un grupo carbonilo o un grupo sulfonilo, y R^5 y R^6 pueden ser iguales o diferentes y representan, respectivamente, un átomo de hidrógeno o un grupo alquilo de C_1-C_6, o R^5 y R^6, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros que puede estar sustituido con 1 o 2 grupos seleccionados independientemente de un grupo alquilo de C_1-C_6 y un grupo hidroxi, y el heterociclo saturado de 4 a 6 miembros puede contener también un átomo de oxígeno o un átomo de nitrógeno), un grupo 1,3,4-oxadiazol-2-ilo sustituido opcionalmente con un grupo alquilo de C_1-C_6 en la

posición 5, y un grupo 1,3,4-tiadiazol-2-ilo sustituido opcionalmente con un grupo alquilo de C_1-C_6 en la posición 5.

12.- El compuesto o sal farmacológicamente aceptable de conformidad con cualquiera de las reivindicaciones 1 a 10, caracterizado además porque R^2 es un grupo 4-metilsulfonilfenilo, un grupo 4-(1-azetidinil)carbonil-2-fluorofenilo, un grupo 2-fluoro-4-(1-pirrolidinil)-carbonilfenilo, un grupo 5-(1-azetidinil)carbonil-3-cloro-2-piridilo, un grupo 2-metilsulfonil-5-piridilo, un grupo 5-(4-metil-1-piperazinil)carbonil-2-pirazinilo, un grupo 2-metilaminocarbonil-5-piridilo, un grupo 2-metilaminosulfonil-5-piridilo, o un grupo 5-metilsulfonil-2-pirazinilo.

13.- El compuesto o sal farmacológicamente aceptable de conformidad con cualquiera de las reivindicaciones 1 a 10, caracterizado además porque R^2 es un grupo 4-metilsulfonilfenilo, un grupo 2-metilsulfonil-5-piridilo, un grupo 5-metilsulfonil-2-pirazinilo, o un grupo 5-(1-azetidinil)carbonil-3-cloro-2-piridilo.

14.- El compuesto o sal farmacológicamente aceptable de conformidad con cualquiera de las reivindicaciones 1 a 13, caracterizado además porque R^3 es un grupo hidroxi o un grupo metoxi.

15.- El compuesto o sal farmacológicamente aceptable de conformidad con la reivindicación 1, caracterizado además porque el compuesto representado por la fórmula general (I) es: (2S)-2-{3-[5-(4,5-dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[4-(metilsulfonil)fenoxi]fenoxi}propan-1-ol; (2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[4-

(metilsulfonil)fenoxi]fenoxi)propan-1-ol; (2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol; {(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}-metanol; (2S)-2-(3-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenoxi)propan-1-ol; (2S)-2-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol; {(4R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]-oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}metanol; (2S)-2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol; {(4R,5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4-metil-4,5-dihidro-1,3-oxazol-5-il}metanol; {(4R,5S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol; (1S)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol; (1R)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol; (2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenoxi)propan-1-ol; {(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol; (2S)-2-(3-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol; (2S)-2-(3-{5-[(4R)-4-etil-

4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}-fenoxi)propan-1-ol; (2S)-2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol; {(4R,5S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol; (1S)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol; o (1R)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol.

16.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque el compuesto representado por la fórmula general (I) es: (2S)-2-{3-[5-(4,5-dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[4-(metilsulfonil)fenoxi]fenoxi}propan-1-ol; (2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[4-(metilsulfonil)fenoxi]fenoxi)propan-1-ol; (2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol; {(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}-metanol; (2S)-2-(3-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol; (2S)-2-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol; {(4R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}metanol; (2S)-2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-

pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol; {(4R,5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4-metil-4,5-dihidro-1,3-oxazol-5-il}metanol; {(4R,5S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol; (1S)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol; (1R)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol; (2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol; {(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol; (2S)-2-(3-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol; (2S)-2-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol; (2S)-2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol; {(4R,5S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol; (1S)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol; o (1R)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol.

17.- Un activador de glucocinasa que contiene como ingrediente activo del mismo un compuesto o sal farmacológicamente aceptable del mismo de cualquiera de las reivindicaciones 1 a 16.

18.- Una composición farmacéutica que contiene como ingrediente activo de la misma un compuesto o sal farmacológicamente aceptable del mismo de cualquiera de las reivindicaciones 1 a 16.

19.- La composición farmacéutica de conformidad con la reivindicación 18, caracterizada además porque la composición farmacéutica tiene actividad activadora de la glucocinasa.

20.- La composición farmacéutica de conformidad con la reivindicación 18, caracterizada además porque la composición farmacéutica es para tratar y/o prevenir una enfermedad que se puede tratar y/o prevenir por actividad activadora de la glucocinasa.

21.- La composición farmacéutica de conformidad con la reivindicación 18, caracterizada además porque la composición farmacéutica es para tratar y/o prevenir una enfermedad cuyos síntomas se tratan, mejoran, disminuyen y/o se previenen por activación de la glucocinasa y mantenimiento de la homeostasis de la glucosa o regulación de la concentración de glucosa en la sangre.

22.- La composición farmacéutica de conformidad con la reivindicación 18, caracterizada además porque la composición farmacéutica es para tratar y/o prevenir la diabetes, deterioro de tolerancia a la glucosa, diabetes gestacional, complicaciones crónicas de la diabetes (que incluyen

neuropatía periférica diabética, nefropatía diabética, retinopatía diabética y macroangiopatía diabética), o síndrome metabólico.

23.- La composición farmacéutica de conformidad con la reivindicación 18, caracterizada además porque la composición farmacéutica es para tratar y/o prevenir la diabetes o el deterioro de tolerancia a la glucosa.

24.- El uso de un compuesto o sal farmacológicamente aceptable del mismo de cualquiera de las reivindicaciones 1 a 16, para producir una composición farmacéutica.

25.- El uso como el que se reclama en la reivindicación 24, en donde la composición farmacéutica es una composición para activar la glucocinasa.

26.- El uso como el que se reclama en la reivindicación 24, en donde la composición farmacéutica es una composición para tratar y/o prevenir la diabetes, deterioro de tolerancia a la glucosa, diabetes gestacional, complicaciones crónicas de la diabetes (que incluyen neuropatía periférica diabética, nefropatía diabética, retinopatía diabética y macroangiopatía diabética), o síndrome metabólico.

27.- El uso como el que se reclama en la reivindicación 24, en donde la composición farmacéutica es una composición para tratar y/o prevenir la diabetes o el deterioro de tolerancia a la glucosa.

28.- Un método de activación de la glucocinasa, que comprende administrar una cantidad farmacológicamente efectiva de un compuesto o sal farmacológicamente aceptable del mismo de cualquiera de las

reivindicaciones 1 a 16 a un animal de sangre caliente.

29.- Un método para tratar y/o prevenir una enfermedad, que comprende administrar una cantidad farmacológicamente efectiva de un compuesto o sal farmacológicamente aceptable del mismo de cualquiera de las reivindicaciones 1 a 16 a un animal de sangre caliente.

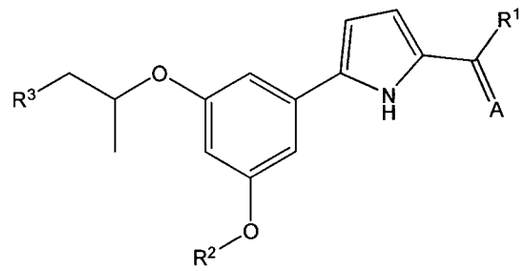
30.- El método de conformidad con la reivindicación 29, caracterizado además porque la enfermedad es la diabetes, deterioro de tolerancia a la glucosa, diabetes gestacional, complicaciones crónicas de la diabetes (que incluyen neuropatía periférica diabética, nefropatía diabética, retinopatía diabética y macroangiopatía diabética), o síndrome metabólico.

31.- El método de conformidad con la reivindicación 29, caracterizado además porque la enfermedad es la diabetes o el deterioro de tolerancia a la glucosa.

32.- El método de conformidad con cualquiera de las reivindicaciones 28 a 31, caracterizado además porque el animal de sangre caliente es un humano.

RESUMEN DE LA INVENCION

La presente invención se refiere a un compuesto que tiene una actividad activadora de glucocinasa superior y está representado por la fórmula general (I), y las sales farmacológicamente aceptables del mismo:



(I)

[en donde: A representa, por ejemplo, un átomo de oxígeno o un átomo de azufre, R^1 representa, por ejemplo, un grupo alquilo de C_1-C_6, un grupo alcoxi de C_1-C_6 o un grupo alquilo de C_1-C_6 halogenado, A y R^1 junto con el átomo de carbono al que están unidos forman un grupo heterocíclico que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, R^2 representa un grupo fenilo que puede estar sustituido con 1 a 5 grupos seleccionados independientemente del conjunto de sustituyentes α, o un grupo heterocíclico que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, R^3 representa un grupo hidroxi o un grupo alcoxi de C_1-C_6, y el conjunto de sustituyentes α consiste, por ejemplo, en un átomo de halógeno, un grupo alquilo de C_1-C_6, un grupo

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alquilo de C_1-C_6 sustituido con 1 o 2 grupos hidroxi, un grupo alquilsulfonilo de C_1-C_6 y un grupo representado por la fórmula –V-NR^5R^6 (en donde V representa un grupo carbonilo o un grupo sulfonilo, y R^5 y R^6 pueden ser iguales o diferentes entre sí y representan respectivamente un átomo de hidrógeno o un grupo alquilo de C_1-C_6, o R^5 y R^6, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros que puede estar sustituido con 1 o 2 grupos seleccionados independientemente de un grupo alquilo de C_1-C_6 y un grupo hidroxi, y el heterociclo saturado de 4 a 6 miembros también puede contener un átomo de oxígeno o un átomo de nitrógeno)].

EA

P10/797F

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2009/051834

A. CLASSIFICATION OF SUBJECT MATTER
See extra sheet.

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)
See extra sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Jitsuyo Shinan Koho 1922-1996 Jitsuyo Shinan Toroku Koho 1996-2009
Kokai Jitsuyo Shinan Koho 1971-2009 Toroku Jitsuyo Shinan Koho 1994-2009

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAplus(STN), REGISTRY(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 2007-536298 A (F. HOFFMANN-LA ROCHE AG.), 13 December, 2007 (13.12.07), & US 2005/0250769 A & EP 1749002 A & WO 2005/108393 A1 & KR 2007009686 A & CN 1950361 A	1-27
A	JP 2007-523142 A (Astra Zeneca AB.), 16 August, 2007 (16.08.07), & EP 1718624 A1 & WO 2005/080359 A1 & KR 2007007103 A & CN 1922159 A	1-27
A	WO 2004/076420 A1 (Banyu Pharmaceutical Co., Ltd.), 10 September, 2004 (10.09.04), & US 2006/0167053 A1 & EP 1600442 A1 & KR 2005105488 A & CN 1777589 A	1-27

☐ 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 application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 February, 2009 (20.02.09)	10 March, 2009 (10.03.09)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2009/051834

Continuation of A. CLASSIFICATION OF SUBJECT MATTER
(International Patent Classification (IPC))

C07D207/333(2006.01)i, *A61K31/40*(2006.01)i, *A61K31/4155*(2006.01)i, *A61K31/422*(2006.01)i, *A61K31/4245*(2006.01)i, *A61K31/427*(2006.01)i, *A61K31/428*(2006.01)i, *A61K31/433*(2006.01)i, *A61K31/4439*(2006.01)i, *A61K31/497*(2006.01)i, *A61K31/5355*(2006.01)i, *A61K31/5377*(2006.01)i, *A61P3/04*(2006.01)i, *A61P3/10*(2006.01)i, *A61P9/00*(2006.01)i, *A61P9/10*(2006.01)i, *A61P13/12*(2006.01)i, *A61P25/00*(2006.01)i, *A61P25/02*(2006.01)i, *A61P27/02*(2006.01)i, *A61P43/00*(2006.01)i, *C07D207/335*(2006.01)i, *C07D207/34*(2006.01)i, *C07D401/04*(2006.01)i, *C07D403/04*(2006.01)i, *C07D413/04*(2006.01)i, *C07D413/14*(2006.01)i, *C07D417/04*(2006.01)i, *C07D417/14*(2006.01)i

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

Continuation of B. FIELDS SEARCHED
Minimum documentation searched (International Patent Classification (IPC))

C07D207/333, A61K31/40, A61K31/4155, A61K31/422, A61K31/4245, A61K31/427, A61K31/428, A61K31/433, A61K31/4439, A61K31/497, A61K31/5355, A61K31/5377, A61P3/04, A61P3/10, A61P9/00, A61P9/10, A61P13/12, A61P25/00, A61P25/02, A61P27/02, A61P43/00, C07D207/335, C07D207/34, C07D401/04, C07D403/04, C07D413/04, C07D413/14, C07D417/04, C07D417/14

Minimum documentation searched (classification system followed by classification symbols)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2009/051834

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [×] Claims Nos.: 28-32
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 28 to 32 pertain to methods for treatment of the human body by therapy.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. [ ] As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

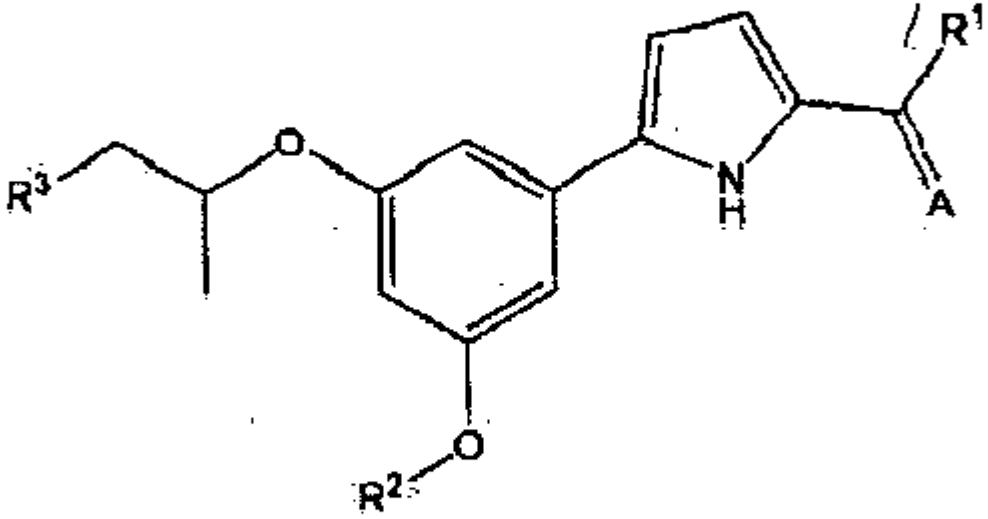
4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

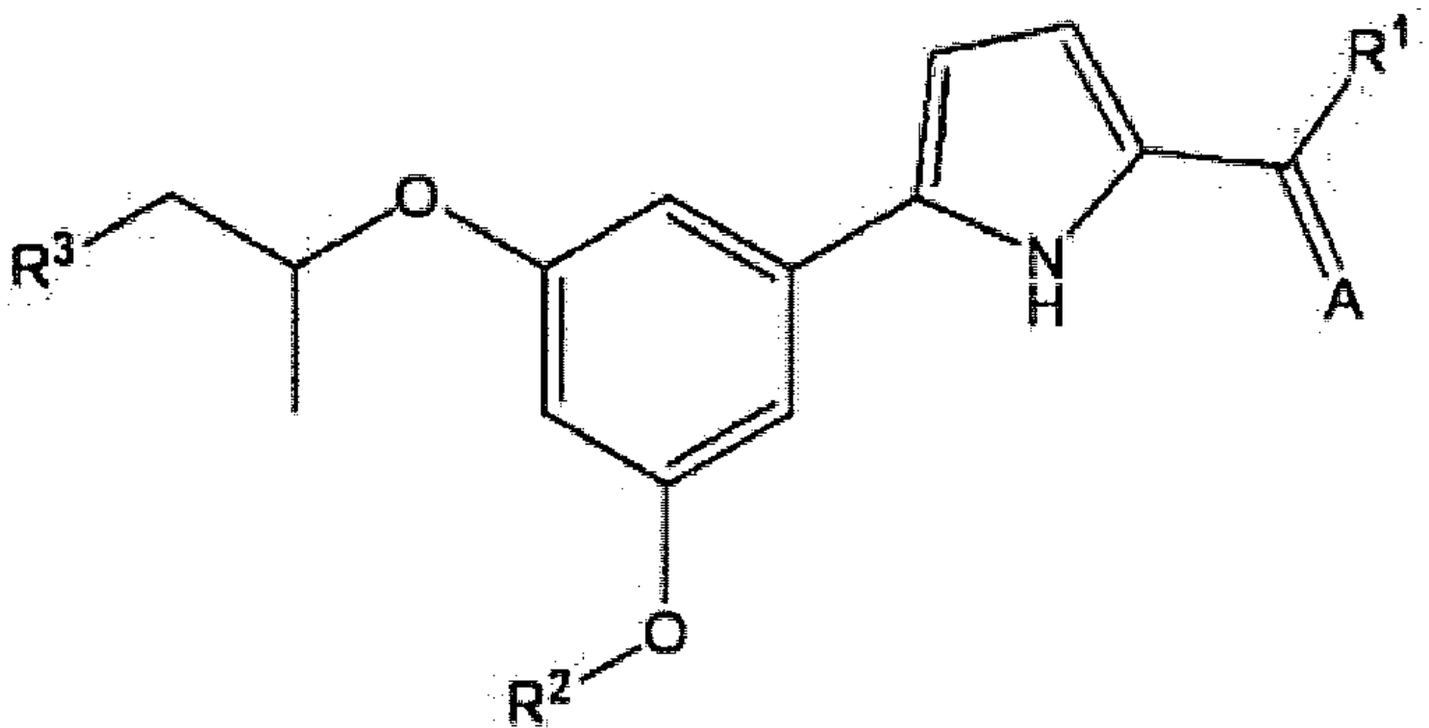
the

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, payment of a protest fee.

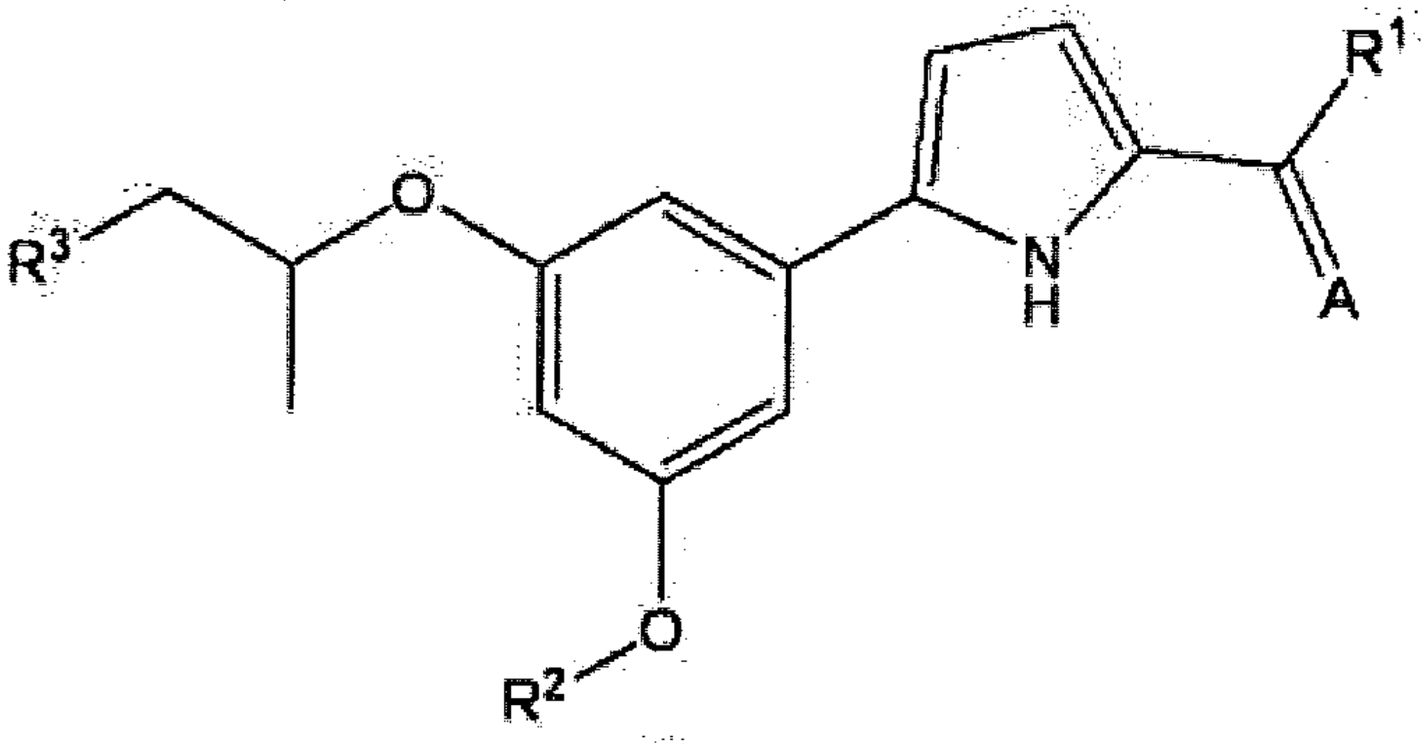
[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.



(I)



(I)



(I)

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 67,890
FECHA : AGOSTO 18 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-109309- -00000-0000
Fecha: 2010-09-03 16:34:02 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1441

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAG	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754327	354682860	17/08/2010	60,033,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	554,000.00
		TOTAL : $	554,000.00

SON: QUINIENTOS CINCUENTA Y CUATRO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

COLO: 35869- 841 - 022-8

929

Industria y Comercio
SUPERINTENDENCIA

Espacio reservado para el adhesivo de radicación

FORMULARIO UNICO DE CORRECCIONES Y MODIFICACIONES

1 **SOLICITUD DE:**

☐ Corrección de Error Material ☒ Modificación a una solicitud

2 **SOLICITANTE**

Nombre: DAIICHI SANKYO COMPANY, LIMITED
Sociedad constituida y existente bajo las leyes de Japón.

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Domicilio: Tokyo,
Japón

Teléfono: 546 09 70 **Fax:** 249 40 70
E-mail: clientes@cavelier.com

IDENTIFICACION

C.C. ☐ NIT ☐
C.E. ☐ Otro ☐

Número: _____

3 **REPRESENTANTE O APODERADO**

Nombre: Luz Clemencia de PAEZ
Dirección: Carrera 4ª No. 72-35
Teléfono: 347 36 11 **Fax:** 217 92 11
E-mail: cavelier@cavelier.com

IDENTIFICACION

C.C. ☒ NIT ☐
C.E. ☐ Otro ☐

Número: 35.456.344 TP 23.555

4 **Número de expediente:** _____

5 **Descripción de la corrección o modificación solicitada:**

Presento nuevos capítulos descriptivo y reivindicatorio compuesto por 17 reivindicaciones y pido respetuosamente que el examen de patentabilidad sea realizado sobre estas nuevas reivindicaciones presentadas.

Respetuosamente manifiesto que a pesar de eliminar materia del pliego reivindicatorio originalmente presentado, mi representada no renuncia a la protección que pueda obtener sobre dicha materia y se reserva el derecho de presentar una solicitud divisional que la contenga durante el trámite de la presente solicitud, beneficiándose de la fecha de prioridad inicialmente reivindicada.

6

Comprobante de pago No. 10-65,119 **Fecha:** 09 de agosto de 2010
Comprobante de pago No. 10-65,122 **Fecha:** 09 de agosto de 2010
Comprobante de pago No. 10-69,575 **Fecha:** 23 de agosto de 2010
Comprobante de pago No. 10-69,576 **Fecha:** 23 de agosto de 2010

930

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Anexos

- [x] Comprobante de pago de la tasa por $114.000, por concepto de modificaciones.
- [x] Comprobante de pago por 7 reivindicaciones adicionales después de la décima reivindicación por.
- [ ] Poderes, si fuere el caso
- [ ] Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

8

NOMBRE: LUZ CLEMENCIA DE PAEZ **FIRMA:** Luz Clemencia de Páez

C.C. 35.456.344 de Usaquén **T.P.A.** 23.555

SCT

DERIVADO DE FENILPIRROL NOVEDOSO

CAMPO TECNICO

La presente invención se refiere a un compuesto de fenilpirrol y las sales farmacológicamente aceptables del mismo, que tienen una actividad activadora de glucocinasa superior y son útiles como agentes terapéuticos para la diabetes y similares.

ANTECEDENTES DE LA INVENCION

La glucocinasa (abreviada como GK en la presente descripción, EC 2.7.1.1) es uno de los cuatro tipos de hexocinasas (hexocinasa IV) encontradas en los mamíferos. Las hexocinasas son enzimas que catalizan la conversión de glucosa a glucosa-6-fosfato en la primera etapa del sistema de glucólisis en las células, y la expresión de GK se localiza principalmente en el hígado y las células beta pancreáticas. En las células beta pancreáticas, la GK funciona como un mecanismo de detección de la concentración extracelular de glucosa, que regula la secreción de insulina estimulada por glucosa, mientras que en el hígado la reacción enzimática de GK sirve como el paso limitativo de velocidad para regular reacciones subsiguientes tales como glucólisis y síntesis de glucógeno. Aunque la GK encontrada en el hígado y la encontrada en las células beta pancreáticas difieren en su

secuencia que consiste en 15 aminoácidos desde el extremo N, debido a una diferencia de empalme, sus propiedades enzimáticas son idénticas. A diferencia de las actividades enzimáticas de los tres tipos de hexocinasas diferentes de GK (tipos I, II y III), que se saturan a una concentración de glucosa de 1 mM o menor, la GK presenta baja afinidad por la glucosa y su valor de Km es cercano al nivel fisiológico de la glucosa en la sangre de 8-15 mM. De esta manera, ocurre una aceleración del metabolismo de la glucosa intracelular mediada por GK en respuesta a cambios de concentración de la glucosa sanguínea que varían de las concentraciones normales (aproximadamente 5 mM) a concentraciones postprandiales (10 mM a 15 mM).

Durante mucho tiempo se ha afirmado la hipótesis de que la GK funciona como un sensor de glucosa en el hígado y las células beta pancreáticas (documentos no patentes 1 a 3). Recientes hallazgos de investigación han mostrado que la GK desempeña realmente una función importante en el mantenimiento de la homeostasis de la glucosa sistémica, verificando así esta hipótesis. Por ejemplo, unos ratones en los que se ha trastocado el gen de glucocinasa mostraron síntomas prominentes de hiperglucemia y murieron poco después del nacimiento, mientras que se observó que unos ratones heterodeficientes en GK tienen una tolerancia defectuosa a la glucosa y deterioro de la secreción de insulina estimulada por glucosa (documento no patente 4). Por otra parte, se observó que ratones normales que expresan excesivamente la GK muestran una disminución de la

concentración de glucosa en la sangre y un aumento del contenido de glucógeno en el hígado, y estos fenómenos fueron similares a los observados en ratones en los que se indujo artificialmente la diabetes (documento no patente 5).

Además, la GK también funciona como un sensor de glucosa en los humanos y una investigación reciente ha mostrado que desempeña una función importante en el mantenimiento de homeostasis de la glucosa. Se han descubierto anormalidades en los genes de GK de linajes de familia que muestran una forma de diabetes de aparición juvenil, llamada diabetes de tipo MODY 2 (*maturity onset diabetes of the young*), y se observó claramente una correlación entre estos casos y la actividad de GK (documento no patente 6). Por otra parte, también se han encontrado linajes de familia que tienen una mutación que aumenta la actividad de GK, y en dichos linajes de familia se han observado síntomas de hipoglucemia en ayunas acompañados por elevación de la concentración de la insulina plasmática (documento no patente 7). Basándose en estos reportes, la GK desempeña una función importante en la regulación de glucosa en la sangre, funcionando como un sensor de glucosa en los mamíferos incluyendo los humanos. De esta manera, las sustancias que tienen actividad activadora de GK se consideran útiles como fármacos para el tratamiento de enfermedades glucometabólicas que incluyen la diabetes mellitus de tipo II. Puesto que es de esperar que las sustancias activadoras de GK muestren simultáneamente actividad promotora de la captación de glucosa, actividad inhibitoria de la liberación de glucosa en el

hígado, y también actividad promotora de secreción de insulina, en particular en las células beta pancreáticas, se prevé que serán capaces de mostrar potentes efectos terapéuticos que no pueden ser obtenidos con los fármacos existentes.

Recientemente se ha determinado que la GK de tipo célula beta pancreática se expresa en el hipotálamo ventromedial (VMH) del cerebro de la rata. Convencionalmente se sabe que el VMH es el sitio de las neuronas que responden a la concentración de glucosa. En contraste con la disminución de la ingestión de alimento cuando se administra glucosa al ventrículo de la rata, cuando se inhibe el metabolismo de la glucosa por administración del análogo de glucosa glucosamina, la ingestión de alimento se acelera (documento no patente 8). Experimentos electrofisiológicos han mostrado que las neuronas sensibles a la glucosa se activan respondiendo a cambios fisiológicos de la concentración de glucosa (5 mM a 20 mM), y se ha determinado que la glucocinasa funciona similarmente como un sensor de glucosa en el tejido periférico (documento no patente 9). De esta manera, se puede esperar que las sustancias que activen la glucocinasa no solo en el hígado y las células beta pancreáticas, sino también en el VMH, muestren actividad reductora de glucosa en la sangre y también actividad que corrija la obesidad, que se considera un problema asociado con muchos pacientes de diabetes mellitus de tipo II.

Basándose en las descripciones anteriormente mencionadas, las sustancias que tienen actividad activadora de GK son útiles como agentes

terapéuticos y preventivos para la diabetes, o como agentes terapéuticos y preventivos para las complicaciones crónicas de la diabetes que incluyen retinopatía diabética, nefropatía diabética, neuropatía diabética, enfermedad isquémica cardiaca y arteriosclerosis.

Además, aunque en el pasado se ha reportado una pluralidad de compuestos que tiene actividad activadora de GK, todos estos tienen estructuras diferentes a las del compuesto de la presente invención. Por ejemplo, aunque el documento de patente 1 describe un compuesto que tiene una estructura de amida como constituyente esencial del mismo, el compuesto de la presente invención tiene una estructura de pirrol en lugar de una estructura de amida como constituyente esencial. Además, aunque el documento de patente 2 describe un compuesto que tiene un pirrol condensado, el compuesto de la presente invención tiene un pirrol no condensado como constituyente esencial. Además, aunque el documento de patente 3 describe un compuesto que tiene una porción de pirazol o 1,2,4-triazol 3,5-di-sustituidos, ésta difiere de la estructura de pirrol 2,5-di-sustituido de la presente invención. Aunque se ha reportado una pluralidad de compuestos que tienen actividad activadora de GK además de los descritos en las publicaciones anteriores, todos ellos tienen estructuras diferentes del compuesto de la presente invención (véanse por ejemplo los documentos de patente 4 a 15 y los documentos no patentes 10 y 11).

Documento de patente 1: Publicación internacional No. WO2005/080359

Documento de patente 2: Publicación internacional No. WO2007/031739

Documento de patente 3: Publicación internacional No. WO2007/061923

Documento de patente 4: Publicación internacional No. WO2000/058293

Documento de patente 5: Publicación internacional No. WO2003/080585

Documento de patente 6: Publicación internacional No. WO2005/066145

Documento de patente 7: Publicación internacional No. WO2005/090332

Documento de patente 8: Publicación internacional No. WO2006/112549

Documento de patente 9: Publicación internacional No. WO2007/007886

Documento de patente 10: Publicación internacional No. WO2007/037534

Documento de patente 11: Publicación internacional No. WO2007/053765

Documento de patente 12: Publicación internacional No. WO2007/117381

Documento de patente 13: Publicación internacional No.

WO2005/044801

Documento de patente 14: Publicación internacional No. WO2007/053662

Documento de patente 15: Publicación internacional No. WO2008/136428

Documento no patente 1: *Am J Physiol.*, septiembre de 1984; 247(3 Pt 2):R527-36.

Documento no patente 2: *Diabetes*, enero de 1986; 35(1):61-7.

Documento no patente 3: *Diabetes*, octubre de 1986; 35(10):1163-73.

Documento no patente 4: *Cell*, 6 de octubre de 1995; 83(1):69-78.

Documento no patente 5: *Proc Natl Acad Sci U S A*, 9 de julio de 1996; 93(14):7225-30.

Documento no patente 6: *Nature*, 23 de abril de 1992; 356(6371):721-2.

Documento no patente 7: *N Engl J Med.*, 22 de enero de 1998; 338(4):226-30.

Documento no patente 8: *Life Sci.*, 30 de diciembre de 1985; 37(26):2475-82.

Documento no patente 9: *Diabetes*, febrero de 2006; 55(2):412-20; fe de erratas en: *Diabetes*, marzo de 2006; 55(3):862.

Documento no patente 10: *Science*, 18 de julio de 2003;

301(5631):370-3.

Documento no patente 11: *J Biol Chem.*, 8 de diciembre de 2006; 281(49):37668-74. Epub 6 de octubre de 2006.

BREVE DESCRIPCION DE LA INVENCION

Problemas que intenta resolver la invención

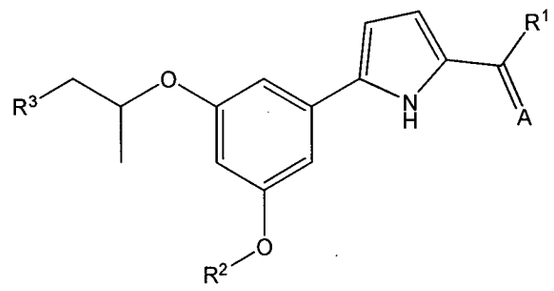
Un objeto de la presente invención es proveer un derivado de fenilpirrol novedoso y un activador de GK que utiliza este derivado de fenilpirrol novedoso, y particularmente proveer un agente terapéutico y preventivo para la diabetes y el deterioro de la tolerancia a la glucosa. Como resultado de la realización de extensos estudios sobre compuestos que tienen actividad activadora de GK, los inventores de la presente invención encontraron que un compuesto de fenilpirrol que tiene una estructura química específica tiene una actividad activadora de GK superior. Además, el compuesto de la presente invención tiene una selectividad de GK superior, baja toxicidad y pocos efectos secundarios adversos. Los inventores de la presente invención también encontraron que este compuesto de fenilpirrol es útil como ingrediente activo de una composición farmacéutica para el tratamiento o prevención de enfermedades seleccionadas del conjunto que consiste en diabetes, deterioro de tolerancia a la glucosa, diabetes gestacional, complicaciones crónicas de la diabetes (que incluyen neuropatía periférica diabética, nefropatía diabética, retinopatía diabética y

macroangiopatía diabética), y síndrome metabólico. La presente invención se cumplió basándose en los hallazgos anteriormente mencionados.

Medios para resolver los problemas

La presente invención se refiere a:

(1) un compuesto que tiene la fórmula general (I):



(I)

[en donde:

A representa un grupo representado por la fórmula $=NOR^4$, un átomo de oxígeno o un átomo de azufre,

R^4 representa un átomo de hidrógeno o un grupo alquilo de C_1-C_6,

R^1 representa un grupo alquilo de C_1-C_6, un grupo alcoxi de C_1-C_6, un grupo alquilo de C_1-C_6 halogenado, un grupo alcoxi de C_1-C_6 halogenado, un grupo amino, un grupo mono-alquil(C_1-C_6)-amino, un grupo mono-alquilo halogenado (C_1-C_6)-amino, un grupo di-alquil(C_1-C_6)-amino, o un grupo di-alquilo halogenado (C_1-C_6)-amino, o

A y R^1, junto con el átomo de carbono al que están unidos, forman un grupo heterocíclico que puede estar sustituido con 1 a 3 grupos

seleccionados independientemente del conjunto de sustituyentes α,

R^2 representa un grupo fenilo que puede estar sustituido con 1 a 5 grupos seleccionados independientemente del conjunto de sustituyentes α, o un grupo heterocíclico que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α,

R^3 representa un grupo hidroxi o un grupo alcoxi de C_1-C_6, y

el conjunto de sustituyentes α comprende un átomo de halógeno, un grupo alquilo de C_1-C_6, un grupo de alquilo de C_1-C_6 halogenado, un grupo alquenilo de C_2-C_6, un grupo alquinilo de C_2-C_6, un grupo hidroxi, un grupo alquilo de C_1-C_6 sustituido con 1 o 2 grupos hidroxi, un grupo alcoxi de C_1-C_6, un grupo alcoxi de C_1-C_6 halogenado, un grupo alcoxi(C_1-C_6)-alquilo(C_1-C_6), un grupo alcoxi(C_1-C_6)-alcoxi(C_1-C_6), un grupo formilo, un grupo carboxilo, un grupo alquilcarbonilo de C_2-C_7, un grupo alcoxicarbonilo de C_2-C_7, un grupo alquilcaboniloxi de C_2-C_7, un grupo alcoxicarboniloxi de C_2-C_7, un grupo nitro, un grupo amino, un grupo mono-alquil(C_1-C_6)-amino, un grupo di-alquil(C_1-C_6)-amino, un grupo alquiltio de C_1-C_6, un grupo alquilsulfonilo de C_1-C_6, un grupo cicloalquilsulfonilo de C_3-C_6, un grupo hidroxialquilsulfonilo de C_1-C_6, un grupo alcoxi(C_1-C_6)-alquilsulfonilo(C_1-C_6), un grupo representado por la fórmula -V-NR^5R^6 (en donde V representa un grupo carbonilo o un grupo sulfonilo, y R^5 y R^6 pueden ser iguales o diferentes y representan respectivamente un átomo de hidrógeno o un grupo alquilo de C_1-C_6, o R^5 y R^6, junto con el átomo de nitrógeno al que están

unidos, forman un heterociclo saturado de 4 a 6 miembros que puede estar sustituido con 1 o 2 grupos seleccionados independientemente de un grupo alquilo de C_1-C_6 y un grupo hidroxi, y el heterociclo saturado de 4 a 6 miembros puede contener también un átomo de oxígeno o un átomo de nitrógeno), un grupo mono-alquilcarbonilamino de C_2-C_7, un grupo mono-alquil(C_1-C_6)-aminocarboniloxi, un grupo di-alquil(C_1-C_6)-aminocarboniloxi, un grupo mono-alcoxicarbonilamino de C_2-C_7, un grupo mono-alquilsulfonilamino de C_1-C_6, un grupo ciano, un grupo 1,3,4-oxadiazol-2-ilo sustituido opcionalmente con un grupo alquilo de C_1-C_6 en la posición 5, un grupo 1,3,4-tiadiazol-2-ilo sustituido opcionalmente con un grupo alquilo de C_1-C_6 en la posición 5, y un grupo oxo],

y las sales farmacológicamente aceptables del mismo;

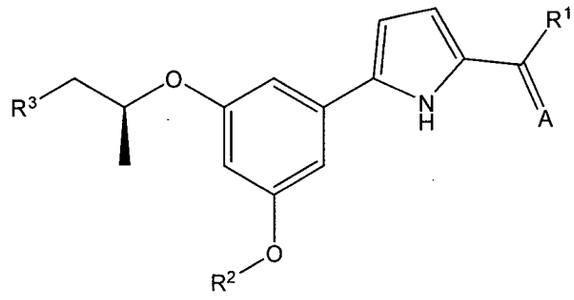
(2) el compuesto o sal farmacológicamente aceptable del inciso (1) anterior, en donde:

el conjunto de sustituyentes α comprende un átomo de halógeno, un grupo alquilo de C_1-C_6, un grupo alquilo de C_1-C_6 halogenado, un grupo alquenilo de C_2-C_6, un grupo alquinilo de C_2-C_6, un grupo hidroxi, un grupo alquilo de C_1-C_6 sustituido con 1 o 2 grupos hidroxi, un grupo alcoxi de C_1-C_6, un grupo alcoxi de C_1-C_6 halogenado, un grupo alcoxi(C_1-C_6)-alquilo(C_1-C_6), un grupo alcoxi(C_1-C_6)-alcoxi(C_1-C_6), un grupo formilo, un grupo carboxilo, un grupo alquilcarbonilo de C_2-C_7, un grupo alcoxicarbonilo de C_2-C_7, un grupo alquilcaboniloxi de C_2-C_7, un grupo alcoxicarboniloxi de C_2-C_7, un grupo nitro, un grupo amino, un grupo mono-alquil(C_1-C_6)-amino, un

grupo di-alquil(C_1-C_6)-amino, un grupo alquiltio de C_1-C_6, un grupo alquilsulfonilo de C_1-C_6, un grupo cicloalquilsulfonilo de C_3-C_6, un grupo hidroxialquilsulfonilo de C_1-C_6, un grupo alcoxi(C_1-C_6)-alquilsulfonilo(C_1-C_6), un grupo representado por la fórmula -V-NR^5R^6 (en donde V representa un grupo carbonilo o un grupo sulfonilo, y R^5 y R^6 pueden ser iguales o diferentes y representan respectivamente un átomo de hidrógeno o un grupo alquilo de C_1-C_6, o R^5 y R^6, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros que puede estar sustituido con 1 o 2 grupos seleccionados independientemente de un grupo alquilo de C_1-C_6 y un grupo hidroxi, y el heterociclo saturado de 4 a 6 miembros puede contener también un átomo de oxígeno o un átomo de nitrógeno), un grupo mono-alquilcarbonilamino de C_2-C_7, un grupo mono-alquil(C_1-C_6)-aminocarboniloxi, un grupo di-alquil(C_1-C_6)-aminocarboniloxi, un grupo mono-alcoxicarbonilamino de C_2-C_7, un grupo mono-alquilsulfonilamino de C_1-C_6, un grupo ciano, un grupo 1,3,4-oxadiazol-2-ilo sustituido opcionalmente con un grupo alquilo de C_1-C_6 en la posición 5, y un grupo 1,3,4-tiadiazol-2-ilo sustituido opcionalmente con un grupo alquilo de C_1-C_6 en la posición 5;

(3) el compuesto o sal farmacológicamente aceptable del inciso (1) o (2) anteriores, en donde:

la fórmula general (I) es la fórmula general (Ia):



(Ia)

(4) el compuesto o sal farmacológicamente aceptable de cualquiera de los incisos (1) a (3) anteriores, en donde A es un átomo de oxígeno;

(5) el compuesto o sal farmacológicamente aceptable de cualquiera de los incisos (1) a (4) anteriores, en donde R^1 es un grupo alquilo de C_1-C_6, un grupo alcoxi de C_1-C_6 o un grupo mono-alquilo halogenado (C_1-C_6)-amino;

(6) el compuesto o sal farmacológicamente aceptable de cualquiera de los incisos (1) a (4) anteriores, en donde R^1 es un grupo metilo o un grupo 2-cloroetilamino;

(7) el compuesto o sal farmacológicamente aceptable de cualquiera de los incisos (1) a (4) anteriores, en donde el grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están unidos, y que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, es un grupo 2-piridilo, un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo, un grupo 1,3-tiazol-2-ilo, un grupo 1,3-oxazol-2-ilo, un grupo 1,3,4-oxadiazol-2-ilo, un grupo 1,3,4-tiadiazol-2-ilo, un grupo 4,5-dihidro-

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1,3-tiazol-2-ilo, un grupo 4,5-dihidro-1,3-oxazol-2-ilo, o un grupo 1,3-benzotiazol-2-ilo, que pueden estar sustituidos con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes γ, y

el conjunto de sustituyentes γ comprende un átomo de halógeno, un grupo alquilo de C_1-C_6, un grupo alquilo de C_1-C_6 halogenado, un grupo alquilo de C_1-C_6 sustituido con 1 o 2 grupos hidroxi, un grupo alcoxi de C_1-C_6, un grupo carboxilo, un grupo mono-alquil(C_1-C_6)-aminocarbonilo, un grupo di-alquil(C_1-C_6)-aminocarbonilo y un grupo hidroxi;

(8) el compuesto o sal farmacológicamente aceptable de cualquiera de los incisos (1) a (3) anteriores, en donde el grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están unidos, y que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, es un grupo 1,3-tiazol-2-ilo, un grupo 5-metil-1,3-tiazol-2-ilo, un grupo 5-metil-1,3,4-oxadiazol-2-ilo, un grupo 4,5-dihidro-1,3-tiazol-2-ilo, un grupo 4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo 5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-etil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1R)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1S)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-4-hidroxi-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4-

hidroximetil-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5R)-5-hidroximetil-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo 5-carboxil-1,3-tiazol-2-ilo, un grupo 5-dimetilaminocarbonil-1,3-tiazol-2-ilo, un grupo 5-metil-1,3,4-tiadiazol-2-ilo, o un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo;

(9) el compuesto o sal farmacológicamente aceptable de cualquiera de los incisos (1) a (3) anteriores, en donde el grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están unidos, y que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, es un grupo 4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-etil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1R)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1S)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4-hidroximetil-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5R)-5-hidroximetil-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo 1,3-tiazol-2-ilo, un grupo 5-carboxil-1,3-tiazol-2-ilo, un grupo 5-dimetilaminocarbonil-1,3-tiazol-2-ilo, un grupo 5-metil-1,3,4-tiadiazol-2-ilo, un grupo 5-metil-1,3,4-oxadiazol-2-ilo, un grupo 4,5-dihidro-1,3-tiazol-2-ilo, o un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo;

(10) el compuesto o sal farmacológicamente aceptable de cualquiera de los incisos (1) a (3) anteriores, en donde el grupo heterocíclico

formado por A y R^1 junto con el átomo de carbono al que están unidos, y que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, es un grupo 4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-etil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1R)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1S)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4-hidroximetil-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, o un grupo (4R,5R)-5-hidroximetil-4-metil-4,5-dihidro-1,3-oxazol-2-ilo;

(11) el compuesto o sal farmacológicamente aceptable de cualquiera de los incisos (1) a (10) anteriores, en donde R^2 es un grupo fenilo que puede estar sustituido con 1 a 5 grupos seleccionados independientemente del conjunto de sustituyentes δ o un grupo 2-piridilo, 3-piridilo o 2-pirazinilo que pueden estar sustituidos con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes δ, y

el conjunto de sustituyentes δ comprende un átomo de halógeno, un grupo alquilo de C_1-C_6, un grupo alquilo de C_1-C_6 halogenado, un grupo alquilo de C_1-C_6 sustituido con 1 o 2 grupos hidroxi, un grupo alquilcarbonilo de C_2-C_7, un grupo alcoxicarbonilo de C_2-C_7, un grupo alquilsulfonilo de C_1-C_6, un grupo representado por la fórmula –V-NR^5R^6 (en donde V representa un

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grupo carbonilo o un grupo sulfonilo, y R^5 y R^6 pueden ser iguales o diferentes y representan, respectivamente, un átomo de hidrógeno o un grupo alquilo de C_1-C_6, o R^5 y R^6, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros que puede estar sustituido con 1 o 2 grupos seleccionados independientemente de un grupo alquilo de C_1-C_6 y un grupo hidroxi, y el heterociclo saturado de 4 a 6 miembros puede contener también un átomo de oxígeno o un átomo de nitrógeno), un grupo 1,3,4-oxadiazol-2-ilo sustituido opcionalmente con un grupo alquilo de C_1-C_6 en la posición 5, y un grupo 1,3,4-tiadiazol-2-ilo sustituido opcionalmente con un grupo alquilo de C_1-C_6 en la posición 5;

(12) el compuesto o sal farmacológicamente aceptable de cualquiera de los incisos (1) a (10) anteriores, en donde R^2 es un grupo 4-metilsulfonilfenilo, un grupo 4-(1-azetidinil)carbonil-2-fluorofenilo, un grupo 2-fluoro-4-(1-pirrolidinil)carbonilfenilo, un grupo 5-(1-azetidinil)carbonil-3-cloro-2-piridilo, un grupo 2-metilsulfonil-5-piridilo, un grupo 5-(4-metil-1-piperazinil)carbonil-2-pirazinilo, un grupo 2-metilaminocarbonil-5-piridilo, un grupo 2-metilaminosulfonil-5-piridilo, o un grupo 5-metilsulfonil-2-pirazinilo;

(13) el compuesto o sal farmacológicamente aceptable de cualquiera de los incisos (1) a (10) anteriores, en donde R^2 es un grupo 4-metilsulfonilfenilo, un grupo 2-metilsulfonil-5-piridilo, un grupo 5-metilsulfonil-2-pirazinilo, o un grupo 5-(1-azetidinil)carbonil-3-cloro-2-piridilo.

(14) el compuesto o sal farmacológicamente aceptable de cualquiera de los incisos (1) a (13) anteriores, en donde R^3 es un grupo hidroxi

o un grupo metoxi;

(15) el compuesto o sal farmacológicamente aceptable del inciso (1) anterior, en donde la fórmula general (I) es la fórmula general (Ia), A es un átomo de oxígeno, R^1 es un grupo alquilo de C_1-C_6, un grupo alcoxi de C_1-C_6 o un grupo mono-alquilo halogenado (C_1-C_6)-amino, R^2 es un grupo fenilo que puede estar sustituido con 1 a 5 grupos seleccionados independientemente del conjunto de sustituyentes δ o un grupo 2-piridilo, un grupo 3-piridilo o un grupo 2-pirazinilo, que pueden estar sustituidos con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes δ, y R^3 es un grupo hidroxi o un grupo metoxi;

(16) el compuesto o sal farmacológicamente aceptable del inciso (1) anterior, en donde la fórmula general (I) es la fórmula general (Ia), A es un átomo de oxígeno, R^1 es un grupo metilo o un grupo 2-cloroetilamino, R^2 es un grupo 4-metilsulfonilfenilo, un grupo 4-(1-azetidinil)carbonil-2-fluorofenilo, un grupo 2-fluoro-4-(1-pirrolidinil)carbonilfenilo, un grupo 5-(1-azetidinil)carbonil-3-cloro-2-piridilo, un grupo 2-metilsulfonil-5-piridilo, un grupo 5-(4-metil-1-piperazinil)carbonil-2-pirazinilo, un grupo 2-metilaminocarbonil-5-piridilo, un grupo 2-metilaminosulfonil-5-piridilo, o un grupo 5-metilsulfonil-2-pirazinilo, y R^3 es un grupo hidroxi o un grupo metoxi;

(17) el compuesto o sal farmacológicamente aceptable del inciso (1) anterior, en donde la fórmula general (I) es la fórmula general (Ia), A es un átomo de oxígeno, R^1 es un grupo metilo o un grupo 2-cloroetilamino, R^2 es un grupo 4-metilsulfonilfenilo, un grupo 2-metilsulfonil-5-piridilo, un grupo 5-

metilsulfonil-2-pirazinilo, o un grupo 5-(1-azetidinil)carbonil-3-cloro-2-piridilo, y R^3 es un grupo hidroxi o un grupo metoxi;

(18) el compuesto o sal farmacológicamente aceptable del inciso (1) anterior, en donde la fórmula general (I) es la fórmula general (Ia), el grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están unidos y que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, es un grupo 2-piridilo, un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo, un grupo 1,3-tiazol-2-ilo, un grupo 1,3-oxazol-2-ilo, un grupo 1,3,4-oxadiazol-2-ilo, un grupo 1,3,4-tiadiazol-2-ilo, un grupo 4,5-dihidro-1,3-tiazol-2-ilo, un grupo 4,5-dihidro-1,3-oxazol-2-ilo, o un grupo 1,3-benzotiazol-2-ilo, que pueden estar sustituidos con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes γ, R^3 es un grupo fenilo que puede estar sustituido con 1 a 5 grupos seleccionados independientemente del conjunto de sustituyentes δ, o un grupo 2-piridilo, un grupo 3-piridilo, o un grupo 2-pirazinilo que pueden estar sustituidos con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes δ, y R^3 es un grupo hidroxi o un grupo metoxi;

(19) el compuesto o sal farmacológicamente aceptable del inciso (1) anterior, en donde la fórmula general (I) es la fórmula general (Ia), el grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están unidos y que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, es un grupo 1,3-tiazol-2-

ilo, un grupo 5-metil-1,3-tiazol-2-ilo, un grupo 5-metil-1,3,4-oxadiazol-2-ilo, un grupo 4,5-dihidro-1,3-tiazol-2-ilo, un grupo 4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo 5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-etil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1R)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1S)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-4-hidroxi-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4-hidroximetil-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5R)-5-hidroximetil-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo 5-carboxil-1,3-tiazol-2-ilo, un grupo 5-dimetilaminocarbonil-1,3-tiazol-2-ilo, un grupo 5-metil-1,3,4-tiadiazol-2-ilo, o un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo, R^2 es un grupo 4-metilsulfonilfenilo, un grupo 4-(1-azetidinil)carbonil-2-fluorofenilo, un grupo 2-fluoro-4-(1-pirrolidinil)carbonilfenilo, un grupo 5-(1-azetidinil)carbonil-3-cloro-2-piridilo, un grupo 2-metilsulfonil-5-piridilo, un grupo 5-(4-metil-1-piperazinil)carbonil-2-pirazinilo, un grupo 2-metilaminocarbonil-5-piridilo, un grupo 2-metilaminosulfonil-5-piridilo, o un grupo 5-metilsulfonil-2-pirazinilo, y R^3 es un grupo hidroxi o un grupo metoxi;

(20) el compuesto o sal farmacológicamente aceptable del inciso (1) anterior, en donde la fórmula general (I) es la fórmula general (Ia), el grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están

unidos y que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, es un grupo 4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-etil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1R)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1S)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4-hidroximetil-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5R)-5-hidroximetil-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo 1,3-tiazol-2-ilo, un grupo 5-carboxil-1,3-tiazol-2-ilo, un grupo 5-dimetilaminocarbonil-1,3-tiazol-2-ilo, un grupo 5-metil-1,3,4-tiadiazol-2-ilo, un grupo 5-metil-1,3,4-oxadiazol-2-ilo, un grupo 4,5-dihidro-1,3-tiazol-2-ilo, o un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo, R^2 es un grupo 4-metilsulfonilfenilo, un grupo 2-metilsulfonil-5-piridilo, un grupo 5-metilsulfonil-2-pirazinilo, o un grupo 5-(1-azetidinil)carbonil-3-cloro-2-piridilo, y R^3 es un grupo hidroxi o un grupo metoxi;

(21) el compuesto o sal farmacológicamente aceptable del inciso (1) anterior, en donde la fórmula general (I) es la fórmula general (Ia), el grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están unidos y que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, es un grupo 4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo

(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1R)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1S)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4-hidroximetil-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, o un grupo (4R,5R)-5-hidroximetil-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, R^2 es un grupo 4-metilsulfonilfenilo, un grupo 2-metilsulfonil-5-piridilo, un grupo 5-metilsulfonil-2-pirazinilo, o un grupo 5-(1-azetidinil)carbonil-3-cloro-2-piridilo, y R^3 es un grupo hidroxi o un grupo metoxi;

(22) el compuesto o sal farmacológicamente aceptable del inciso (1) anterior, en donde el compuesto representado por la fórmula general (I) es:

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-1,3-tiazol,

(2S)-2-{3-[4-(metilsulfonil)fenoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}propan-1-ol,

ácido 2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol-5-carboxílico,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-N,N-dimetil-1,3-tiazol-5-carboxamida,

1-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)etanona,

(2S)-2-{3-[5-(4,5-dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[4-

(metilsulfonil)fenoxi]fenoxi}propan-1-ol,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-5-metil-1,3,4-tiadiazol,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-tiazol,

(2S)-2-{3-[5-(4,5-dihidro-1,3-tiazol-2-il)-1H-pirrol-2-il]-5-[4-(metilsulfonil)fenoxi]fenoxi}propan-1-ol,

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[4-(metilsulfonil)fenoxi]fenoxi)propan-1-ol,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-5,6-dihidro-4H-1,3-oxazina,

(2S)-2-(3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]fenoxi)propan-1-ol,

(2S)-2-(3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

{(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}-metanol,

(2S)-2-(3-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-

il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

{(4R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}metanol,

(2S)-2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

{(4R,5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4-metil-4,5-dihidro-1,3-oxazol-5-il}metanol,

{(4R,5S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol,

(1S)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol,

(1R)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol,

(2S)-2-(3-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

{(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol,

(2S)-2-(3-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

{(4R,5S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol,

(1S)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol, o

(1R)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol;

(23) el compuesto o sal farmacológicamente aceptable del inciso (1) anterior, en donde el compuesto representado por la fórmula general (I) es:

(2S)-2-{3-[5-(4,5-dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[4-(metilsulfonil)fenoxi]fenoxi}propan-1-ol,

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[4-(metilsulfonil)fenoxi]fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

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{(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol,

(2S)-2-(3-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

{(4R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}metanol,

(2S)-2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

{(4R,5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4-metil-4,5-dihidro-1,3-oxazol-5-il}metanol,

{(4R,5S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol,

(1S)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol,

(1R)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol,

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

{(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)-

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pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol,

(2S)-2-(3-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

{(4R,5S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol,

(1S)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol, o

(1R)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol;

(24) el compuesto descrito en el inciso (1) anterior, en donde el compuesto representado por la fórmula general (I) es:

(2S)-2-{3-[5-(4,5-dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[4-(metilsulfonil)fenoxi]fenoxi}propan-1-ol,

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[4-(metilsulfonil)fenoxi]fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-

il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

{(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol,

(2S)-2-(3-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

{(4R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}metanol,

(2S)-2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

{(4R,5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4-metil-4,5-dihidro-1,3-oxazol-5-il}metanol,

{(4R,5S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol,

(1S)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol,

(1R)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol,

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

{(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol,

(2S)-2-(3-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

{(4R,5S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol,

(1S)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol, o

(1R)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol;

(25) el compuesto o sal farmacológicamente aceptable del inciso (1) anterior, en donde el compuesto representado por la fórmula general (I) es:

1-(4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}fenil)etanona,

1-(4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}fenil)etanol,

1-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)etanona,

N-(2-cloroetil)-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida,

ácido 6-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)nicotínico,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-5,6-dihidro-4H-1,3-oxazina,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-1,3-tiazol,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-5-metil-1,3-tiazol,

[2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-1,3-tiazol-5-il]metanol,

ácido 2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]-fenil}-1H-pirrol-2-il)-1,3-tiazol-5-carboxílico,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-N,N-dimetil-1,3-tiazol-5-carboxamida,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-1,3-oxazol,

5-metoxi-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-1,3-oxazol,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-

fenil}-1H-pirrol-2-il)-5-metil-1,3,4-oxadiazol,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-5-metil-1,3,4-tiadiazol,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-tiazol,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol,

(5S)-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol,

(5R)-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5,5-dimetil-4,5-dihidro-1,3-oxazol,

[2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol-5-il]metanol,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-1,3-benzotiazol,

2-(5-{3-[4-(azetidin-1-ilsulfonil)fenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol,

3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzoato de metilo,

3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzamida,

3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-N-metilbenzamida,

3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-N,N-dimetilbenzamida,

2-(5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol,

2-(5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-5-metil-1,3,4-oxadiazol,

2-(5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol,

(5S)-2-(5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol,

2-(5-{3-[2-fluoro-4-(pirrolidin-1-ilcarbonil)fenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol,

4-(3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzoil)morfolina,

3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-N-metilbencenosulfonamida,

2-(5-{3-[4-(azetidin-1-ilsulfonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol,

2-(3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}fenil)-5-metil-1,3,4-oxadiazol,

2-(3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-

1H-pirrol-2-il]fenoxi}fenil)-5-metil-1,3,4-tiadiazol,

2-(5-{3-[4-(azetidin-1-ilcarbonil)-2-metilfenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol,

2-(5-{3-[4-(azetidin-1-ilcarbonil)-2-(trifluorometil)fenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol,

5-(azetidin-1-ilcarbonil)-2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}piridina,

5-(azetidin-1-ilcarbonil)-3-cloro-2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}piridina,

5-(azetidin-1-ilcarbonil)-3-cloro-2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]fenoxi}piridina,

5-(azetidin-1-ilcarbonil)-3-cloro-2-{3-[5-(4,5-dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi}piridina,

5-(azetidin-1-ilcarbonil)-3-cloro-2-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)piridina,

5-(azetidin-1-ilcarbonil)-2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-3-metilpiridina,

5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-2-(metilsulfonil)piridina,

5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-2-(metilsulfonil)piridina,

2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-5-[(4-metilpiperazin-1-il)carbonil]pirazina,

5-(fluorometil)-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol,

(5R)-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5-(trifluorometil)-4,5-dihidro-1,3-oxazol,

[(5R)-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol-5-il]metanol,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-N,N-dimetil-4,5-dihidro-1,3-oxazol-5-carboxamida,

N-(2-cloroetil)-5-{3-[(1S)-2-hidroxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida,

(2S)-2-{3-[4-(metilsulfonil)fenoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}propan-1-ol,

(2S)-2-{3-[5-(4,5-dihidro-1,3-tiazol-2-il)-1H-pirrol-2-il]-5-[4-(metilsulfonil)fenoxi]fenoxi}propan-1-ol,

(2S)-2-{3-[5-(4,5-dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[4-(metilsulfonil)fenoxi]fenoxi}propan-1-ol,

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[4-(metilsulfonil)fenoxi]fenoxi)propan-1-ol,

(2S)-2-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]fenoxi}propan-1-ol,

(2S)-2-(3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)propan-1-ol,

(2S)-2-(3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[5-(5-

metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]fenoxi)propan-1-ol,

(2S)-2-(3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)propan-1-ol, o

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol;

(26) el compuesto o sal farmacológicamente aceptable del inciso (1) anterior, en donde el compuesto representado por la fórmula general (I) es:

1-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)etanona,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-1,3-tiazol,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-5-metil-1,3-tiazol,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-tiazol,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol,

(5S)-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol,

(5R)-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol,

[2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol-5-il]metanol,

2-(5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol,

2-(5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol,

(5S)-2-(5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol,

2-(5-{3-[2-fluoro-4-(pirrolidin-1-ilcarbonil)fenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol,

5-(azetidin-1-ilcarbonil)-3-cloro-2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}piridina,

5-(azetidin-1-ilcarbonil)-3-cloro-2-{3-[5-(4,5-dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi}piridina,

5-(azetidin-1-ilcarbonil)-3-cloro-2-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)piridina,

5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-2-(metilsulfonil)piridina,

5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-2-(metilsulfonil)piridina,

2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-5-[(4-metilpiperazin-1-il)carbonil]pirazina,

[(5R)-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol-5-il]metanol,

(2S)-2-{3-[4—(metilsulfonil)fenoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-

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2-il]fenoxi}propan-1-ol,

(2S)-2-{3-[5-(4,5-dihidro-1,3-tiazol-2-il)-1H-pirrol-2-il]-5-[4-(metilsulfonil)fenoxi]fenoxi}propan-1-ol,

(2S)-2-{3-[5-(4,5-dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[4-(metilsulfonil)fenoxi]fenoxi}propan-1-ol,

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[4-(metilsulfonil)fenoxi]fenoxi)propan-1-ol,

(2S)-2-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]fenoxi}propan-1-ol,

(2S)-2-(3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)propan-1-ol,

(2S)-2-(3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)propan-1-ol, o

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol;

(27) el compuesto descrito en el inciso (1) anterior, en donde el compuesto representado por la fórmula general (I) es:

1-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)etanona,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-1,3-tiazol,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-5-metil-1,3-tiazol,

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2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-tiazol,

2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol,

(5S)-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol,

(5R)-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol,

[2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol-5-il]metanol,

2-(5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol,

2-(5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol,

(5S)-2-(5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol,

2-(5-{3-[2-fluoro-4-(pirrolidin-1-ilcarbonil)fenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol,

5-(azetidin-1-ilcarbonil)-3-cloro-2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}piridina,

5-(azetidin-1-ilcarbonil)-3-cloro-2-{3-[5-(4,5-dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi}piridina,

5-(azetidin-1-ilcarbonil)-3-cloro-2-(3-[(1S)-2-metoxi-1-metiletoxi]-

5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)piridina,

5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-2-(metilsulfonil)piridina,

5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-2-(metilsulfonil)piridina,

2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-5-[(4-metilpiperazin-1-il)carbonil]pirazina,

[(5R)-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol-5-il]metanol,

(2S)-2-{3-[4-(metilsulfonil)fenoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}propan-1-ol,

(2S)-2-{3-[5-(4,5-dihidro-1,3-tiazol-2-il)-1H-pirrol-2-il]-5-[4-(metilsulfonil)fenoxi]fenoxi}propan-1-ol,

(2S)-2-{3-[5-(4,5-dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[4-(metilsulfonil)fenoxi]fenoxi}propan-1-ol,

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[4-(metilsulfonil)fenoxi]fenoxi)propan-1-ol,

(2S)-2-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]fenoxi}propan-1-ol,

(2S)-2-(3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)propan-1-ol,

(2S)-2-(3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)propan-1-ol, o

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol;

(28) el compuesto o sal farmacológicamente aceptable del inciso (1) anterior, en donde el compuesto representado por la fórmula general (I) es:

(2S)-2-(3-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

{(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol,

(2S)-2-(3-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

{(4R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}metanol,

(2S)-2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

{(4R,5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4-metil-4,5-dihidro-1,3-oxazol-5-il}metanol,

{(4R,5S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol,

(1S)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol,

(1R)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol,

(2S)-2-(3-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

{(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol,

(5S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-ol,

(2S)-2-(3-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

{(4R,5S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol,

(1S)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol,

(1R)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol,

5-(3-[(1S)-2-Hidroxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-N-metilpiridin-2-sulfonamida,

5-(3-[(1S)-2-hidroxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-N-metilpiridin-2-carboxamida,

5-(3-{5-[(5R)-5-(hidroximetil)-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)-N-metilpiridin-2-carboxamida, o

5-(3-{5-[(5R)-5-(hidroximetil)-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)-N-metilpiridin-2-sulfonamida;

(29) el compuesto o sal farmacológicamente aceptable del inciso (1) anterior, en donde el compuesto representado por la fórmula general (I) es:

{(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol,

(2S)-2-(3-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

{(4R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}metanol,

(2S)-2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

{(4R,5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4-metil-4,5-dihidro-1,3-oxazol-5-il}metanol,

{(4R,5S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol,

(1S)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol,

(1R)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol,

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

{(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol,

(2S)-2-(3-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

{(4R,5S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol,

(1S)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol, o

(1R)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol;

(30) el compuesto descrito en el inciso (1) anterior, en donde el compuesto representado por la fórmula general (I) es:

{(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol,

(2S)-2-(3-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

{(4R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}metanol,

(2S)-2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol,

{(4R,5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4-metil-4,5-dihidro-1,3-oxazol-5-il}metanol,

{(4R,5S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol,

(1S)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-

(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol,

(1R)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol,

(2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

{(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol,

(2S)-2-(3-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

(2S)-2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol,

{(4R,5S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol,

(1S)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol, o

(1R)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-

il}etanol;

(31) un activador de glucocinasa que contiene como ingrediente activo un compuesto o sal farmacológicamente aceptable que se describen en cualquiera de los incisos (1) a (30) anteriores;

(32) una composición farmacéutica que contiene como ingrediente activo un compuesto o sal farmacológicamente aceptable que se describen en cualquiera de los incisos (1) a (30) anteriores

(33) la composición farmacéutica que se describe en el inciso (32) anterior, que tiene actividad activadora de glucocinasa;

(34) la composición farmacéutica que se describe en el inciso (32) anterior, para el tratamiento o prevención de una enfermedad que se puede tratar o prevenir activando la glucocinasa;

(35) la composición farmacéutica que se describe en el inciso (32) anterior, para el tratamiento o prevención de una enfermedad cuyos síntomas se tratan, mejoran, disminuyen o se previenen por activación de la glucocinasa y mantenimiento de la homeostasis de la glucosa o regulación de la concentración de glucosa en la sangre;

(36) la composición farmacéutica que se describe en el inciso (32) anterior, para el tratamiento o prevención de la diabetes, deterioro de tolerancia a la glucosa, diabetes gestacional, complicaciones crónicas de la diabetes (que incluyen neuropatía periférica diabética, nefropatía diabética, retinopatía diabética y macroangiopatía diabética), o síndrome metabólico;

(37) la composición farmacéutica que se describe en el inciso

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(32) anterior, para el tratamiento o prevención de la diabetes o el deterioro de tolerancia a la glucosa;

(38) el uso de un compuesto o sal farmacológicamente aceptable que se describen en cualquiera de los incisos (1) a (30) anteriores, para producir una composición farmacéutica;

(39) el uso que se describe en el inciso (38) anterior, en donde la composición farmacéutica es una composición para activar la glucocinasa;

(40) el uso que se describe en el inciso (38) anterior, en donde la composición farmacéutica es una composición para el tratamiento o prevención de la diabetes, deterioro de tolerancia a la glucosa, diabetes gestacional, complicaciones crónicas de la diabetes (que incluyen neuropatía periférica diabética, nefropatía diabética, retinopatía diabética y macroangiopatía diabética), o síndrome metabólico;

(41) el uso que se describe en el inciso (38) anterior, en donde la composición farmacéutica es una composición para el tratamiento o prevención de la diabetes o el deterioro de tolerancia a la glucosa;

(42) un método de activación de glucocinasa, que comprende administrar a un animal de sangre caliente una cantidad farmacológicamente efectiva de un compuesto o sal farmacológicamente aceptable que se describen en cualquiera de los incisos (1) a (30) anteriores;

(43) un método de tratamiento o prevención de una enfermedad, que comprende administrar a un animal de sangre caliente una cantidad farmacológicamente efectiva de un compuesto o sal farmacológicamente

aceptable que se describen en cualquiera de los incisos (1) a (30) anteriores;

(44) el método que se describe en el inciso (43) anterior, en donde la enfermedad es la diabetes, deterioro de tolerancia a la glucosa, diabetes gestacional, complicaciones crónicas de la diabetes (que incluyen neuropatía periférica diabética, nefropatía diabética, retinopatía diabética y macroangiopatía diabética), o síndrome metabólico;

(45) el método que se describe en el inciso (43) anterior, en donde la enfermedad es la diabetes o el deterioro de tolerancia a la glucosa; y

(46) el método que se describe en cualquiera de los incisos (42) a (45) anteriores, en donde el animal de sangre caliente es un humano.

En la presente invención, un "átomo de halógeno" se refiere a un átomo de flúor, un átomo de cloro, un átomo de bromo o un átomo yodo. Preferiblemente, el átomo de halógeno es un átomo de flúor o un átomo de cloro, de preferencia un átomo de cloro.

En la presente invención, un "grupo alquilo de C_1-C_6" se refiere a un grupo alquilo lineal o ramificado que tiene de 1 a 6 átomos de carbono. Ejemplos del grupo alquilo incluyen un grupo metilo, un grupo etilo, un grupo propilo, un grupo isopropilo, un grupo butilo, un grupo isobutilo, un grupo s-butilo, un grupo t-butilo, un grupo pentilo, un grupo isopentilo, un grupo 2-metilbutilo, un grupo neopentilo, un grupo 1-etilpropilo, un grupo hexilo, un grupo isohexilo, un grupo 4-metilpentilo, un grupo 3-metilpentilo, un grupo 2-metilpentilo, un grupo 1-metilpentilo, un grupo 3,3-dimetilbutilo, un grupo 2,2-dimetilbutilo, un grupo 1,1-dimetilbutilo, y un grupo 1,2-dimetilbutilo, y

preferiblemente el grupo alquilo de C_1-C_6 es un grupo alquilo lineal o ramificado que tiene de 1 a 4 átomos de carbono (grupo alquilo de C_1-C_4), de preferencia un grupo metilo o un grupo etilo (grupo alquilo de C_1-C_2), y muy de preferencia un grupo metilo.

En la presente invención, un "grupo de alquilo de C_1-C_6 halogenado" se refiere a un grupo en el cual están unidos de 1 a 5 de los "átomos de halógeno" anteriormente mencionados, iguales o diferentes, al "grupo alquilo de C_1-C_6" anteriormente mencionado. Ejemplos de los grupos de alquilo de C_1-C_6 halogenado incluyen un grupo trifluorometilo, un grupo triclorometilo, un grupo difluorometilo, un grupo diclorometilo, un grupo dibromometilo, un grupo fluorometilo, un grupo 2,2,2-trifluoroetilo, un grupo 2,2,2-tricloroetilo, un grupo 2-bromoetilo, un grupo 2-cloroetilo y un grupo 2-fluoroetilo; preferiblemente, el grupo alquilo de C_1-C_6 halogenado es un grupo en el que están unidos de 1 a 5 de los "átomos de halógeno" anteriormente mencionados, iguales o diferentes, al "grupo alquilo de C_1-C_4" anteriormente mencionado (grupo alquilo de C_1-C_4 halogenado), de preferencia un grupo en el que están unidos de 1 a 5 de los "átomos de halógeno" anteriormente mencionados, iguales o diferentes, al "grupo alquilo de C_1-C_2" anteriormente mencionado (grupo alquilo de C_1-C_2 halogenado), muy de preferencia un grupo trifluorometilo o un grupo fluorometilo.

En la presente invención, un "grupo alquenilo de C_2-C_6" se refiere a un "grupo alquilo de C_1-C_6" anteriormente mencionado que tiene un enlace doble y de 2 a 6 átomos de carbono. Ejemplos del grupo alquenilo de C_2-C_6

incluyen un grupo etenilo, un grupo 1-propenilo, un grupo 2-propenilo, un grupo 1-metil-2-propenilo, un grupo 1-metil-1-propenilo, un grupo 2-metil-1-propenilo, un grupo 2-metil-2-propenilo, un grupo 1-butenilo, un grupo 2-butenilo, un grupo 3-butenilo, un grupo 1-pentenilo, un grupo 4-pentenilo, un grupo 1-metil-4-pentenilo y un grupo 5-hexenilo; preferiblemente, el grupo alquenilo de C_2-C_6 es un grupo alquenilo que tiene de 2 a 4 átomos de carbono (grupo alquenilo de C_2-C_4), y muy de preferencia un grupo 2-propenilo.

En la presente invención, un "grupo alquinilo de C_2-C_6" se refiere a un "grupo alquilo de C_1-C_6" anteriormente mencionado que tiene un enlace triple y de 2 a 6 átomos de carbono. Ejemplos del grupo alquinilo de C_2-C_6 incluyen un grupo etinilo, un grupo 1-propinilo, un grupo 2-propinilo, un grupo 1-metil-2-propinilo, un grupo 1-butinilo, un grupo 2-butinilo, un grupo 1-metil-2-butinilo, un grupo 3-butinilo, un grupo 2-pentinilo y un grupo 5-hexinilo; preferiblemente, el grupo alquinilo de C_2-C_6 es un grupo alquinilo que tiene de 2 a 4 átomos de carbono (grupo alquinilo de C_2-C_4), y muy de preferencia un grupo 2-propinilo o un grupo 2-butinilo.

En la presente invención, un "grupo alquilo de C_1-C_6 sustituido con 1 o 2 grupos hidroxi" se refiere a un grupo en el que están unidos 1 o 2 grupos hidroxi al "grupo alquilo de C_1-C_6" anteriormente mencionado. Ejemplos del grupo alquilo de C_1-C_6 sustituido con 1 o 2 grupos hidroxi incluyen un grupo hidroximetilo, un grupo 2-hidroxietilo, un grupo 1-hidroxietilo, un grupo 3-hidroxipropilo, un grupo 1,2-dihidroxietilo y un grupo

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2,3-dihidroxipropilo; preferiblemente, el grupo alquilo de C_1-C_6 sustituido con 1 o 2 grupos hidroxi es un grupo en el que 1 o 2 grupos hidroxi están unidos al "grupo alquilo de C_1-C_4" anteriormente mencionado, de preferencia un grupo en el que están unidos 1 o 2 grupos hidroxi al "grupo alquilo de C_1-C_2" anteriormente mencionado, de preferencia un grupo hidroximetilo o un grupo hidroxietilo.

En la presente invención, un "grupo alcoxi de C_1-C_6" se refiere a un grupo en donde el "grupo alquilo de C_1-C_6" anteriormente mencionado está unido a un átomo de oxígeno, y es un grupo alcoxi lineal o ramificado que tiene de 1 a 6 átomos de carbono. Ejemplos del grupo alcoxi de C_1-C_6 incluyen un grupo metoxi, un grupo etoxi, un grupo propoxi, un grupo isopropoxi, un grupo butoxi, un grupo isobutoxi, un grupo s-butoxi, un grupo t-butoxi, un grupo pentoxi, un grupo 2-metilbutoxi, un grupo 3-etilpropoxi, un grupo neopentoxi, un grupo hexiloxi y un grupo 2,3-dimetilbutoxi; preferiblemente, el grupo alcoxi de C_1-C_6 es un grupo alcoxi lineal o ramificado que tiene de 1 a 4 átomos de carbono (grupo alcoxi de C_1-C_4), de preferencia un grupo metoxi, un grupo etoxi, un grupo propoxi o un grupo isopropoxi (grupo alcoxi de C_1-C_3), de preferencia un grupo metoxi o un grupo etoxi (grupo alcoxi de C_1-C_2), y en particular preferiblemente un grupo metoxi.

En la presente invención, un "grupo alcoxi de C_1-C_6 halogenado" se refiere a un grupo en donde están unidos de 1 a 5 de los "átomos de halógeno" anteriormente mencionados, iguales o diferentes, al "grupo alcoxi de C_1-C_6" anteriormente mencionado. Ejemplos del grupo alcoxi de C_1-C_6

halogenado incluyen un grupo trifluorometoxi, un grupo triclorometoxi, un grupo difluorometoxi, un grupo diclorometoxi, un grupo dibromometoxi, un grupo fluorometoxi, un grupo 2,2,2-trifluoroetoxi, un grupo 2,2,2-tricloroetoxi, un grupo 2-cloroetoxi, un grupo 2-fluoroetoxi y un grupo pentafluoroetoxi; preferiblemente, el grupo alcoxi de C_1-C_6 halogenado es un grupo en el que están unidos de 1 a 5 de los "átomos de halógeno" anteriormente mencionados, iguales o diferentes, al grupo "alcoxi de C_1-C_4" anteriormente mencionado (grupo alcoxi de C_1-C_4 halogenado), de preferencia un grupo en el que están unidos de 1 a 5 de los "átomos de halógeno" anteriormente mencionados, iguales o diferentes, al "grupo alcoxi de C_1-C_2" anteriormente mencionado (grupo alcoxi de C_1-C_2 halogenado), muy de preferencia un grupo trifluorometoxi.

En la presente invención, un "grupo alcoxi(C_1-C_6)-alquilo(C_1-C_6)" se refiere a un grupo en donde un "grupo alcoxi de C_1-C_6" anteriormente mencionado está unido al "grupo alquilo de C_1-C_6" anteriormente mencionado. Ejemplos del grupo alcoxi(C_1-C_6)-alquilo(C_1-C_6) incluyen un grupo metoximetilo, un grupo etoximetilo, un grupo propoximetilo, un grupo isopropoximetilo, un grupo butoximetilo, un grupo s-butoximetilo, un grupo t-butoximetilo, un grupo 2-metoxietilo y un grupo 3-isopropoxipropilo; preferiblemente, el grupo alcoxi(C_1-C_6)-alquilo(C_1-C_6) es un grupo en donde un "grupo alcoxi de C_1-C_4" anteriormente mencionado está unido al "grupo alquilo de C_1-C_4" anteriormente mencionado (grupo alcoxi(C_1-C_4)-alquilo(C_1-C_4)), de preferencia un grupo en donde un "grupo alcoxi de C_1-C_2" anteriormente

mencionado está unido al "grupo alquilo de C_1-C_2" anteriormente mencionado (grupo alcoxi(C_1-C_2)-alquilo(C_1-C_2)), muy de preferencia un grupo metoximetilo.

En la presente invención, un "grupo alcoxi(C_1-C_6)-alcoxi(C_1-C_6) se refiere a un grupo en donde un "grupo alcoxi de C_1-C_6" anteriormente mencionado está unido al "grupo alcoxi de C_1-C_6" anteriormente mencionado. Ejemplos del grupo alcoxi(C_1-C_6)-alcoxi(C_1-C_6) incluyen un grupo etoximetiloxi, un grupo propoximetiloxi, un grupo butoximetiloxi, un grupo 2-metoxietiloxi y un grupo 3-isopropoxipropiloxi; preferiblemente, el grupo alcoxi(C_1-C_6)-alcoxi(C_1-C_6) es un grupo en donde un "grupo alcoxi de C_1-C_4" anteriormente mencionado está unido al "grupo alcoxi de C_1-C_4" anteriormente mencionado (grupo alcoxi(C_1-C_4)-alcoxi(C_1-C_4)), de preferencia un grupo en donde un "grupo alcoxi de C_1-C_2" anteriormente mencionado está unido al "grupo alcoxi de C_1-C_2" anteriormente mencionado (grupo alcoxi(C_1-C_2)-alcoxi(C_1-C_2)), muy de preferencia un grupo metoximetiloxi.

En la presente invención, un "grupo alquilcarbonilo de C_2-C_7" se refiere a un grupo en donde un "grupo alquilo de C_1-C_6" anteriormente mencionado está unido a un grupo carbonilo. Ejemplos del grupo alquilcarbonilo de C_2-C_7 incluyen un grupo acetilo, un grupo propionilo, un grupo butirilo, un grupo isobutirilo, un grupo pentanoilo, un grupo pivaloilo y un grupo valerilo; preferiblemente, el grupo alquilcarbonilo de C_2-C_7 es un grupo en donde un "grupo alquilo de C_1-C_4" anteriormente mencionado está unido a un grupo carbonilo (grupo alquilcarbonilo de C_2-C_5), de preferencia un grupo

acetilo o un grupo propionilo (grupo alquilcarbonilo de C_2-C_3), de preferencia un grupo acetilo.

En la presente invención, un "grupo alcoxicarbonilo de C_2-C_7" se refiere a un grupo en donde un "grupo alcoxi de C_1-C_6" anteriormente mencionado está unido a un grupo carbonilo. Ejemplos del grupo alcoxicarbonilo de C_2-C_7 incluyen un grupo metoxicarbonilo, un grupo etoxicarbonilo, un grupo propoxicarbonilo, un grupo isopropoxicarbonilo, un grupo butoxicarbonilo, un grupo isobutoxicarbonilo, un grupo s-butoxicarbonilo y un grupo t-butoxicarbonilo; preferiblemente, el grupo alcoxicarbonilo de C_2-C_7 es un grupo en donde un "grupo alcoxi de C_1-C_4" anteriormente mencionado está unido a un grupo carbonilo (grupo alcoxicarbonilo de C_2-C_5), de preferencia un grupo metoxicarbonilo o un grupo etoxicarbonilo (grupo alcoxicarbonilo de C_2-C_3), de preferencia un grupo metoxicarbonilo.

En la presente invención, un "grupo alquilcarboniloxi de C_2-C_7" se refiere a un grupo en donde el grupo carbonilo al que está unido un "grupo alquilo de C_1-C_6" anteriormente mencionado, está unido a un átomo de oxígeno. Ejemplos del grupo alquilcarboniloxi de C_2-C_7 incluyen un grupo acetoxi, un grupo propioniloxi, un grupo butiriloxi, un grupo isobutiriloxi, un grupo pentanoiloxi, un grupo pivaloiloxi, un grupo valeriloxi y un grupo isovaleriloxi; preferiblemente, el grupo alquilcarboniloxi de C_2-C_7 es un grupo en donde el grupo carbonilo al que está unido un "grupo alquilo de C_1-C_4" anteriormente mencionado está unido a un átomo de oxígeno (grupo alquilcarboniloxi de C_2-C_5), de preferencia un grupo acetoxi o un grupo

propioniloxi (grupo alquilcarboniloxi de C_2-C_3), muy de preferencia un grupo acetoxi.

En la presente invención, un "grupo alcoxicarboniloxi de C_2-C_7" se refiere a un grupo en donde el grupo carbonilo al que está unido el "grupo alcoxi de C_1-C_6" anteriormente mencionado, está unido a un átomo de oxígeno. Ejemplos del grupo alcoxicarboniloxi de C_2-C_7 incluyen un grupo metoxicarboniloxi, un grupo etoxicarboniloxi, un grupo propoxicarboniloxi, un grupo isopropoxicarboniloxi, un grupo butoxicarboniloxi, un grupo s-butoxicarboniloxi y un grupo t-butoxicarboniloxi; preferiblemente, el grupo alcoxicarboniloxi de C_2-C_7 es un grupo en donde un grupo carbonilo al que está unido un "grupo alcoxi de C_1-C_4" anteriormente mencionado, está unido a un átomo de oxígeno (grupo alcoxicarboniloxi de C_2-C_5), de preferencia un grupo metoxicarboniloxi o un grupo etoxicarboniloxi (grupo alcoxicarboniloxi de C_2-C_3), muy de preferencia un grupo metoxicarboniloxi.

En la presente invención, un "grupo mono-alquil(C_1-C_6)-amino" se refiere a un grupo en donde un "grupo alquilo de C_1-C_6" anteriormente mencionado está unido a un grupo amino. Ejemplos del grupo mono-alquil(C_1-C_6)-amino incluyen un grupo metilamino, un grupo etilamino, un grupo propilamino, un grupo isopropilamino, un grupo butilamino, un grupo isobutilamino, un grupo s-butilamino, un grupo t-butilamino, un grupo pentilamino, un grupo isopentilamino, un grupo 2-metilbutilamino, un grupo neopentilamino, un grupo 1-etilpropilamino, un grupo hexilamino y un grupo isohexilamino; preferiblemente, el grupo mono-alquil(C_1-C_6)-amino es un

grupo en donde el "grupo alquilo de C_1-C_4" anteriormente mencionado está unido a un grupo amino (grupo mono-alquil(C_1-C_4)-amino), de preferencia un grupo metilamino o un grupo etilamino (grupo mono-alquil(C_1-C_2)-amino), muy de preferencia un grupo metilamino.

En la presente invención, un "grupo mono-alquilo halogenado (C_1-C_6)-amino" se refiere a un grupo en donde un "grupo alquilo de C_1-C_6 halogenado" anteriormente mencionado está unido a un grupo amino. Ejemplos del grupo mono-alquilo halogenado (C_1-C_6)-amino incluyen un grupo trifluorometilamino, un grupo triclorometilamino, un grupo difluorometilamino, un grupo diclorometilamino, un grupo dibromometilamino, un grupo fluorometilamino, un grupo 2,2,2-trifluoroetilamino, un grupo 2,2,2-tricloroetilamino, un grupo 2-bromoetilamino, un grupo 2-cloroetilamino y un grupo 2-fluoroetilamino; preferiblemente, el grupo mono-alquilo halogenado (C_1-C_6)-amino es un grupo en donde un "grupo alquilo de C_1-C_4 halogenado" está unido a un grupo amino (grupo mono-alquilo halogenado (C_1-C_4)-amino), de preferencia un grupo en donde un "grupo alquilo de C_1-C_2 halogenado" anteriormente mencionado está unido a un grupo amino (grupo mono-alquilo halogenado (C_1-C_2)-amino), muy de preferencia un grupo 2-cloroetilamino.

En la presente invención, un "grupo di-alquil(C_1-C_6)-amino" se refiere a un grupo en donde dos grupos "alquilo de C_1-C_6" anteriormente mencionados, iguales o diferentes, están unidos a un grupo amino. Ejemplos del grupo di-alquil(C_1-C_6)-amino incluyen un grupo dimetilamino, un grupo dietilamino, un grupo dipropilamino, un grupo diisopropilamino, un grupo

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dibutilamino, un grupo diisobutilamino, un grupo dipentilamino, un grupo diisopentilamino, un grupo dineopentilamino, un grupo dihexilamino, un grupo N-etil-N-metilamino, un grupo N-metil-N-propilamino, un grupo N-isopropil-N-metilamino, un grupo N-butil-N-metilamino, un grupo N-isobutil-N-metilamino, un grupo N-metil-N-pentilamino, un grupo N-isopentil-N-metilamino, un grupo N-etil-N-propilamino, un grupo N-etil-N-isopropilamino, un grupo N-butil-N-etilamino y un grupo N-etil-N-isopentilamino; preferiblemente, el grupo di-alquil(C_1-C_6)-amino es un grupo en donde dos grupos "alquilo de C_1-C_4" anteriormente mencionados están unidos a un grupo amino (grupo di-alquil(C_1-C_4)-amino), de preferencia un grupo dimetilamino, dietilamino o N-etil-N-metilamino (grupo di-alquil(C_1-C_2)-amino), y muy de preferencia un grupo dimetilamino.

En la presente invención, un "grupo di-alquilo halogenado (C_1-C_6)-amino" se refiere a un grupo en donde dos grupos de "alquilo de C_1-C_6 halogenado" anteriormente mencionados, iguales o diferentes, están unidos a un grupo amino. Ejemplos del grupo "di-alquilo halogenado (C_1-C_6)-amino" incluyen un grupo di-(trifluorometil)amino, un grupo di-(fluorometil)amino, un grupo di-(2,2,2-tricloroetil)amino, un grupo di-(2-cloroetil)amino y un grupo N-(2-cloroetil)-N-(2-fluoroetil)amino; preferiblemente, el grupo di-alquilo halogenado (C_1-C_6)-amino es un grupo en donde dos grupos de "alquilo de C_1-C_4 halogenado" anteriormente mencionados, iguales o diferentes, están unidos a un grupo amino (grupo di-alquilo halogenado (C_1-C_4)-amino), de preferencia un grupo di-(2-cloroetil)-amino.

En la presente invención, un "grupo alquiltio de C_1-C_6" se refiere a un grupo en donde un "grupo alquilo de C_1-C_6" anteriormente mencionado está unido a un átomo de azufre, y es un grupo alquiltio lineal o ramificado que tiene de 1 a 6 átomos de carbono. Ejemplos del grupo alquiltio de C_1-C_6 incluyen un grupo metiltio, un grupo etiltio, un grupo propiltio, un grupo isopropiltio, un grupo butiltio, un grupo isobutiltio, un grupo s-butiltio, un grupo pentiltio, un grupo 1-etilpropiltio y un grupo hexiltio; preferiblemente, el grupo alquiltio de C_1-C_6 es un alquiltio lineal o ramificado que tiene de 1 a 4 átomos de carbono (grupo alquiltio de C_1-C_4), de preferencia un grupo metiltio o un grupo etiltio (grupo alquiltio de C_1-C_2), y muy de preferencia un grupo metiltio.

En la presente invención, un "grupo alquilsulfonilo de C_1-C_6" se refiere a un grupo en donde un "grupo alquilo de C_1-C_6" anteriormente mencionado está unido a un grupo sulfonilo, y es un grupo alquilsulfonilo lineal o ramificado que tiene de 1 a 6 átomos de carbono. Ejemplos del grupo alquilsulfonilo de C_1-C_6 incluyen un grupo metilsulfonilo, un grupo etilsulfonilo, un grupo propilsulfonilo, un grupo isopropilsulfonilo, un grupo butilsulfonilo, un grupo isobutilsulfonilo, un grupo s-butilsulfonilo y un grupo pentilsulfonilo; preferiblemente, el grupo alquilsulfonilo de C_1-C_6 es un grupo alquilsulfonilo lineal o ramificado que tiene de 1 a 4 átomos de carbono (grupo alquilsulfonilo de C_1-C_4), de preferencia un grupo metilsulfonilo o un grupo etilsulfonilo (grupo alquilsulfonilo de C_1-C_2), y muy de preferencia un grupo metilsulfonilo.

En la presente invención, un "grupo cicloalquilsulfonilo de C_3-C_6" se refiere a un grupo ciclopropilsulfonilo, un grupo ciclobutilsulfonilo, un grupo

ciclopentilsulfonilo, o un grupo ciclohexilsulfonilo. El grupo cicloalquilsulfonilo de C_3-C_6 es preferiblemente un grupo ciclopropilsulfonilo.

En la presente invención, un "grupo hidroxialquilsulfonilo de C_1-C_6" se refiere a un grupo en donde un "grupo alquilo de C_1-C_6" anteriormente mencionado que está unido a un grupo hidroxi, está unido a un grupo sulfonilo, y es un grupo hidroxialquilsulfonilo lineal o ramificado que tiene de 1 a 6 átomos de carbono. Ejemplos del grupo hidroxialquilsulfonilo de C_1-C_6 incluyen un grupo hidroximetilsulfonilo, un grupo 2-hidroxietilsulfonilo, un grupo 1-hidroxietilsulfonilo y un grupo 3-hidroxipropilsulfonilo; preferiblemente, el grupo hidroxialquilsulfonilo es un grupo hidroxialquilsulfonilo lineal o ramificado que tiene de 1 a 4 átomos de carbono (grupo hidroxialquilsulfonilo de C_1-C_4), de preferencia un grupo hidroximetilsulfonilo o un grupo hidroxietilsulfonilo (grupo hidroxialquilsulfonilo de C_1-C_2), muy de preferencia un grupo hidroximetilsulfonilo.

En la presente invención, un "grupo alcoxi(C_1-C_6)-alquilsulfonilo(C_1-C_6)" se refiere a un grupo en donde un "grupo alcoxi de C_1-C_6" anteriormente mencionado está unido al "grupo alquilsulfonilo de C_1-C_6" anteriormente mencionado. Ejemplos del grupo alcoxi(C_1-C_6)-alquilsulfonilo(C_1-C_6) incluyen un grupo metoximetilsulfonilo, un grupo etoximetilsulfonilo, un grupo propoximetilsulfonilo, un grupo isopropoximetilsulfonilo, un grupo butoximetilsulfonilo y un grupo s-butoximetilsulfonilo; preferiblemente, el grupo alcoxi(C_1-C_6)-alquilsulfonilo(C_1-C_6) es un grupo en donde el "grupo alcoxi de C_1-C_4" anteriormente

mencionado está unido al "grupo alquilsulfonilo de C_1-C_4" anteriormente mencionado (grupo alcoxi(C_1-C_4)-alquilsulfonilo(C_1-C_4)), de preferencia un grupo en donde un "grupo alcoxi de C_1-C_2" anteriormente mencionado está unido al "grupo alquilsulfonilo de C_1-C_2" anteriormente mencionado (grupo alcoxi(C_1-C_2)-alquilsulfonilo(C_1-C_2)), muy de preferencia un grupo metoximetilsulfonilo.

En la presente invención, un "grupo representado por la fórmula –V-NR^5R^6 (en donde V representa un grupo carbonilo o un grupo sulfonilo y R^5 y R^6 pueden ser iguales o diferentes y representan respectivamente un átomo de hidrógeno o un grupo alquilo de C_1-C_6, o R^5 y R^6, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros que puede estar sustituido con 1 o 2 grupos seleccionados independientemente de un grupo alquilo de C_1-C_6 y un grupo hidroxi, y el heterociclo saturado de 4 a 6 miembros puede contener también un átomo de oxígeno o un átomo de nitrógeno)", se refiere a un "grupo representado por la fórmula –C(=O)-NR^5R^6" o un "grupo representado por la fórmula –SO_2-NR^5R^6", el "grupo representado por la fórmula –C(=O)-NR^5R^6" es un grupo carbamoilo, un grupo "mono-alquil(C_1-C_6)aminocarbonilo (grupo en donde un grupo amino al que está unido un "grupo alquilo de C_1-C_6" anteriormente mencionado, está unido a un grupo carbonilo)", un grupo "di-alquil(C_1-C_6)-aminocarbonilo (grupo en donde un grupo amino al que están unidos dos de los "grupos alquilo de C_1-C_6" anteriormente mencionados, iguales o diferentes, está unido a un grupo carbonilo)", o un "grupo en donde un átomo de

nitrógeno de un heterociclo saturado de 4 a 6 miembros, que puede estar sustituido con 1 o 2 grupos seleccionados independientemente de un grupo alquilo de C_1-C_6 y un grupo hidroxi (grupo heterocíclico saturado de 4 a 6 miembros completamente reducido que contiene un átomo de nitrógeno y puede contener también un átomo de oxígeno o un átomo de nitrógeno), está unido a un grupo carbonilo", y el "grupo representado por la fórmula $-SO_2-NR^5R^6$" es un grupo sulfamoilo, un "grupo mono-alquil(C_1-C_6)-aminosulfonilo (grupo en donde un grupo amino al que está unido un "grupo alquilo de C_1-C_6" anteriormente mencionado está unido a un grupo sulfonilo", un "grupo di-alquil(C_1-C_6)-aminosulfonilo (grupo en donde un grupo amino al que están unidos dos de los "grupos alquilo de C_1-C_6" anteriormente mencionados, iguales o diferentes, está unido a un grupo sulfonilo", o un "grupo en donde un átomo de nitrógeno de un heterociclo saturado de 4 a 6 miembros, que puede estar sustituido con 1 o 2 grupos seleccionados independientemente de un grupo alquilo de C_1-C_6 y un grupo hidroxi (grupo heterocíclico saturado de 4 a 6 miembros completamente reducido que contiene un átomo de nitrógeno y puede contener también un átomo de oxígeno o un átomo de nitrógeno), está unido a un grupo sulfonilo". Ejemplos del grupo anteriormente mencionado incluyen un grupo carbamoilo, un grupo metilaminocarbonilo, un grupo etilaminocarbonilo, un grupo propilaminocarbonilo, un grupo dimetilaminocarbonilo, un grupo dietilaminocarbonilo, un grupo dipropilaminocarbonilo, un grupo N-etil-N-metilaminocarbonilo, un grupo N-metil-N-propilaminocarbonilo, un grupo (1-azetidinil)carbonilo, un grupo (3-

hidroxi-1-azetidinil)carbonilo, un grupo (1-pirrolidinil)carbonilo, un grupo (4-morfolinil)carbonilo, un grupo (4-metil-1-piperazinil)carbonilo, un grupo sulfamoilo, un grupo metilaminosulfonilo, un grupo etilaminosulfonilo, un grupo propilaminosulfonilo, un grupo dimetilaminosulfonilo, un grupo dietilaminosulfonilo, un grupo dipropilaminosulfonilo, un grupo N-etil-N-metilaminosulfonilo, un grupo N-metil-N-propilaminosulfonilo y un grupo (1-azetidinil)sulfonilo; preferiblemente, el grupo anteriormente mencionado es un grupo carbamoilo, un grupo metilaminocarbonilo, un grupo dimetilaminocarbonilo, un grupo (1-azetidinil)carbonilo, un grupo (1-pirrolidinil)carbonilo, un grupo (4-morfolinil)carbonilo, un grupo (4-metil-1-piperazinil)carbonilo, un grupo metilaminosulfonilo, o un grupo (1-azetidinil)sulfonilo, de preferencia un grupo dimetilaminocarbonilo, un grupo (1-azetidinil)carbonilo, un grupo (1-pirrolidinil)carbonilo, o un grupo (4-metil-1-piperazinil)carbonilo, muy de preferencia un grupo dimetilaminocarbonilo o un grupo (1-azetidinil)carbonilo.

En la presente invención, un "grupo mono-alquilcarbonilamino de C_2-C_7" se refiere a un grupo en donde un grupo carbonilo al que está unido un "grupo alquilo de C_{1-6}" anteriormente mencionado, está unido a un grupo amino. Ejemplos del grupo mono-alquilcarbonilamino de C_2-C_7 incluyen un grupo acetamido, un grupo etilcarbonilamino, un grupo propilcarbonilamino, un grupo isopropilcarbonilamino, un grupo butilcarbonilamino y un grupo isobutilcarbonilamino; preferiblemente, el grupo mono-alquilcarbonilamino de C_2-C_7 es un grupo en donde un grupo carbonilo al que está unido un "grupo

alquilo de C_1-C_4" está unido a un grupo amino (grupo mono-alquilcarbonilamino de C_2-C_5), de preferencia un grupo acetamido o un grupo etilcarbonilamino (grupo mono-alquilcarbonilamino de C_2-C_3), muy de preferencia un grupo acetamido.

En la presente invención, un "grupo mono-alquil(C_1-C_6)-aminocarboniloxi" se refiere a un grupo en donde un grupo carbonilo al que está unido un grupo amino unido a un "grupo alquilo de C_1-C_6" anteriormente mencionado, está unido a un átomo de oxígeno. Ejemplos del grupo mono-alquil(C_1-C_6)-aminocarboniloxi incluyen un grupo metilaminocarboniloxi, un grupo etilaminocarboniloxi, un grupo propilaminocarboniloxi, un grupo isopropilaminocarboniloxi y un grupo butilaminocarboniloxi; preferiblemente, el grupo mono-alquil(C_1-C_6)-aminocarboniloxi es un grupo metilaminocarboniloxi o un grupo etilaminocarboniloxi (grupo mono-alquil(C_1-C_2)-aminocarboniloxi), de preferencia un grupo metilaminocarboniloxi.

En la presente invención, un "grupo di-alquil(C_1-C_6)-aminocarboniloxi" se refiere a un grupo en donde un grupo carbonilo, que está unido a un grupo amino unido a dos "grupos alquilo de C_1-C_6" anteriormente mencionados, iguales o diferentes, está unido a un átomo de oxígeno. Ejemplos del grupo di-alquil(C_1-C_6)-aminocarboniloxi incluyen un grupo dimetilaminocarboniloxi, un grupo dietilaminocarboniloxi, un grupo dipropilaminocarboniloxi, un grupo N-etil-N-metilaminocarboniloxi y un grupo N-metil-N-propilaminocarboniloxi; preferiblemente, el grupo di-alquil(C_1-C_6)-aminocarboniloxi es un grupo dimetilaminocarboniloxi, un grupo

dietilaminocarboniloxi o un grupo N-etil-N-metilaminocarboniloxi (grupo di-alquil(C_1-C_2)-aminocarboniloxi), de preferencia un grupo dimetilaminocarboniloxi.

En la presente invención, un "grupo mono-alcoxicarbonilamino de C_2-C_7" se refiere a un grupo en donde un grupo carbonilo al que está unido un "grupo alcoxi de C_1-C_6" anteriormente mencionado está unido a un grupo amino. Ejemplos del grupo mono-alcoxicarbonilamino de C_2-C_7 incluyen un grupo metoxicarbonilamino, un grupo etoxicarbonilamino, un grupo propoxicarbonilamino, un grupo isopropoxicarbonilamino y un grupo butoxicarbonilamino; preferiblemente, el grupo mono-alcoxicarbonilamino de C_2-C_7 es un grupo metoxicarbonilamino o un grupo etoxicarbonilamino (grupo alcoxicarbonilamino de C_2-C_3), de preferencia un grupo metoxicarbonilamino.

En la presente invención, un "grupo mono-alquilsulfonilamino de C_1-C_6" se refiere a un grupo en donde un grupo sulfonilo al que está unido un "grupo alquilo de C_1-C_6" anteriormente mencionado, está unido a un grupo amino. Ejemplos del grupo mono-alquilsulfonilamino de C_1-C_6 incluyen un grupo metilsulfonilamino, un grupo etilsulfonilamino, un grupo propilsulfonilamino, un grupo isopropilsulfonilamino, un grupo butilsulfonilamino, un grupo t-butilsulfonilamino y un grupo 2-etilbutilsulfonilamino; preferiblemente, el grupo mono-alquilsulfonilamino de C_1-C_6 es un grupo en donde un grupo sulfonilo al que está unido un "grupo alquilo de C_1-C_4" anteriormente mencionado, está unido a un grupo amino (grupo mono-alquilsulfonilamino de C_1-C_4), de preferencia un grupo

metilsulfonilamino o un grupo etilsulfonilamino (grupo mono-alquilsulfonilamino de C_1-C_2), muy de preferencia un grupo metilsulfonilamino.

En la presente invención, un "grupo 1,3,4-oxadiazol-2-ilo" sustituido opcionalmente con un grupo alquilo de C_1-C_6 en la posición 5" se refiere a un grupo en donde un grupo alquilo de C_1-C_6 está como sustituyente en la posición 5 de un grupo 1,3,4-oxadiazol-2-ilo. Ejemplos del grupo anteriormente mencionado incluyen un grupo 5-metil-1,3,4-oxadiazol-2-ilo y un grupo 5-etil-1,3,4-oxadiazol-2-ilo; preferiblemente, el grupo anteriormente mencionado es un grupo 5-metil-1,3,4-oxadiazol-2-ilo.

En la presente invención, un "grupo 1,3,4-tiadiazol-2-ilo sustituido opcionalmente con un grupo alquilo de C_1-C_6 en la posición 5" se refiere a un grupo en donde un grupo alquilo de C_1-C_6 está como sustituyente en la posición 5 de un grupo 1,3,4-tiadiazol-2-ilo. Ejemplos del grupo anteriormente mencionado incluyen un grupo 5-metil-1,3,4-tiadiazol-2-ilo y un grupo 5-etil-1,3,4-tiadiazol-2-ilo; preferiblemente, el grupo anteriormente mencionado es un grupo 5-metil-1,3,4-tiadiazol-2-ilo.

En la presente invención, un "grupo heterocíclico" se refiere a un grupo heterocíclico de 4 a 7 miembros que contiene de 1 a 3 átomos de azufre, oxígeno o nitrógeno, y puede contener además 1 o 2 átomos de nitrógeno, y en donde el átomo de azufre puede estar unido a 2 átomos de oxígeno. Ejemplos del grupo heterocíclico incluyen un "grupo heterocíclico aromático", tal como un grupo furilo, un grupo tienilo, un grupo pirrolilo, un grupo azepinilo, un grupo pirazolilo, un grupo imidazolilo, un grupo oxazolilo,

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un grupo isoxazolilo, un grupo tiazolilo, un grupo isotiazolilo, un grupo 1,3,4-oxadiazolilo, un grupo 1,3,4-tiadiazolilo, un grupo triazolilo, un grupo tetrazolilo, un grupo tiadiazolilo, un grupo piranilo, un grupo piridilo, un grupo piridazinilo, un grupo pirimidinilo y un grupo pirazinilo; y un "grupo heterocíclico saturado, parcial o totalmente reducido", tal como un grupo tetrahidropiranilo, un grupo tetrahidrotienilo, un grupo morfolinilo, un grupo tiomorfolinilo, un grupo pirrolidinilo, un grupo pirrolinilo, un grupo imidazolidinilo, un grupo pirazolidinilo, un grupo piperidinilo, un grupo piperazinilo, un grupo oxazolinilo, un grupo oxazolidinilo, un grupo isoxazolidinilo, un grupo tiazolinilo, un grupo tiazolidinilo, un grupo pirazolidinilo, un grupo dioxolanilo, un grupo dioxanilo y un grupo 5,6-dihidro-4H-1,3-oxazina; y el grupo heterocíclico anterior puede estar fusionado con otro grupo cíclico tal como un anillo de benceno ("grupo heteroarilo bicíclico fusionado"), por ejemplo un grupo benzotienilo, un grupo benzotiazolilo, un grupo benzoxazolilo, un grupo isobenzofuranilo, un grupo 1,3-dihidroisobenzofuranilo, un grupo quinolilo, un grupo 1,3-benzodioxolanilo, un grupo 1,4-benzodioxanilo, un grupo indolilo, un grupo isoindolilo y un grupo indolinilo. Los grupos heterocíclicos formados por A y R^1 junto con el átomo de carbono al que están unidos, que pueden estar sustituidos con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, son preferiblemente un grupo 2-piridilo, un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo, un grupo 1,3-tiazol-2-ilo, un grupo 1,3-oxazol-2-ilo, un grupo 1,3,4-oxadiazol-2-ilo, un grupo 1,3,4-tiadiazol-2-ilo, un grupo 4,5-dihidro-1,3-tiazol-2-

ilo, un grupo 4,5-dihidro-1,3-oxazol-2-ilo, o un grupo 1,3-benzotiazol-2-ilo, preferiblemente un grupo 1,3-tiazol-2-ilo, un grupo 1,3,4-oxadiazol-2-ilo, un grupo 4,5-dihidro-1,3-tiazol-2-ilo, un grupo 4,5-dihidro-1,3-oxazol-2-ilo, un grupo 1,3,4-tiadiazol-2-ilo, o un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo, de preferencia un grupo 4,5-dihidro-1,3-oxazol-2-ilo. En R^2, el grupo heterocíclico es preferiblemente un grupo heterocíclico de 6 miembros que contiene 1 o 2 átomos de nitrógeno, de preferencia un grupo piridilo o un grupo pirazinilo, muy de preferencia un grupo 2-piridilo, un grupo 3-piridilo, o un grupo 2-pirazinilo.

En la presente invención, un "grupo representado por la fórmula $=NOR^4$" se refiere a un grupo en donde un grupo hidroxi o un "grupo alcoxi de C_1-C_6" anteriormente mencionado está unido a un grupo imino. Preferiblemente, el grupo representado por la fórmula $=NOR^4$ es un grupo representado por la fórmula =NOH.

En la presente invención, un "grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están unidos, y que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α", se refiere al "grupo heterocíclico" anteriormente mencionado o al "grupo heterocíclico" anteriormente mencionado que está sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α. El grupo anteriormente mencionado es, preferiblemente, un grupo 2-piridilo, un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo, un grupo 1,3-tiazol-2-ilo, un grupo 1,3-oxazol-2-ilo, un grupo 1,3,4-oxadiazol-2-ilo, un grupo

1,3,4-tiadiazol-2-ilo, un grupo 4,5-dihidro-1,3-tiazol-2-ilo, un grupo 4,5-dihidro-1,3-oxazol-2-ilo, o un grupo 1,3-benzotiazol-2-ilo, que pueden estar sustituidos con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes γ, de preferencia un grupo 1,3-tiazol-2-ilo, un grupo 5-metil-1,3-tiazol-2-ilo, un grupo 5-metil-1,3,4-oxadiazol-2-ilo, un grupo 4,5-dihidro-1,3-tiazol-2-ilo, un grupo 4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo 5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-etil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1R)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1S)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-4-hidroxi-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4-hidroximetil-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5R)-5-hidroximetil-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo 5-carboxil-1,3-tiazol-2-ilo, un grupo 5-dimetilaminocarbonil-1,3-tiazol-2-ilo, un grupo 5-metil-1,3,4-tiadiazol-2-ilo, o un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo, muy de preferencia un grupo 4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-etil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1R)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1S)-1-hidroxietil]-4,5-

dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4-hidroximetil-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5R)-5-hidroximetil-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo 1,3-tiazol-2-ilo, un grupo 5-carboxil-1,3-tiazol-2-ilo, un grupo 5-dimetilaminocarbonil-1,3-tiazol-2-ilo, un grupo 5-metil-1,3,4-tiadiazol-2-ilo, un grupo 5-metil-1,3,4-oxadiazol-2-ilo, un grupo 4,5-dihidro-1,3-tiazol-2-ilo, o un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo, y en particular muy preferiblemente un grupo 4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-etil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1R)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1S)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4-hidroximetil-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, o un grupo (4R,5R)-5-hidroximetil-4-metil-4,5-dihidro-1,3-oxazol-2-ilo.

En la presente invención, un “grupo fenilo que puede estar sustituido con 1 a 5 grupos seleccionados independientemente del conjunto de sustituyentes α” se refiere a un grupo fenilo o un grupo fenilo sustituido con 1 a 5 grupos seleccionados independientemente del conjunto de sustituyentes α. El grupo anteriormente mencionado es, preferiblemente, un grupo fenilo que puede estar sustituido con 1 a 5 grupos seleccionados independientemente del conjunto de sustituyentes δ, de preferencia un grupo

4-acetilfenilo, un grupo 4-(1-hidroxietil)fenilo, un grupo 4-metilsulfonilfenilo, un grupo 4-(1-azetidinil)sulfonilfenilo, un grupo 2-fluoro-4-metoxicarbonilfenilo, un grupo 4-carbamoil-2-fluorofenilo, un grupo 2-fluoro-4-metilaminocarbonilfenilo, un grupo 4-dimetilaminocarbonil-2-fluorofenilo, un grupo 4-(1-azetidinil)carbonil-2-fluorofenilo, un grupo 2-fluoro-4-(1-pirrolidinil)carbonilfenilo, un grupo 2-fluoro-4-(4-morfolinil)carbonilfenilo, un grupo 2-fluoro-4-metilaminosulfonilfenilo, un grupo 4-(1-azetidinil)sulfonil-2-fluorofenilo, un grupo 2-fluoro-4-(5-metil-1,3,4-oxadiazol-2-il)fenilo, un grupo 2-fluoro-4-(5-metil-1,3,4-tiadiazol-2-il)fenilo, un grupo 4-(1-azetidinil)carbonil-2-metilfenilo, o un grupo 4-(1-azetidinil)carbonil-2-trifluorometilfenilo, preferiblemente un grupo 4-metilsulfonilfenilo, un grupo 4-(1-azetidinil)carbonil-2-fluorofenilo, o un grupo 2-fluoro-4-(1-pirrolidinil)carbonilfenilo, de preferencia un grupo 4-metilsulfonilfenilo.

En la presente invención, un "grupo heterocíclico que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α" en R^2 se refiere al "grupo heterocíclico" anteriormente mencionado o al "grupo heterocíclico" anteriormente mencionado que está sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α. Preferiblemente, el grupo anteriormente mencionado es un grupo 2-piridilo, un grupo 3-piridilo, o un grupo 2-pirazinilo, que pueden estar sustituidos con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes δ, de preferencia un grupo 5-(1-azetidinil)carbonil-3-cloro-2-piridilo, un grupo 2-

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metilsulfonil-5-piridilo, un grupo 5-(4-metil-1-piperazinil)carbonil-2-pirazinilo, un grupo 2-metilaminocarbonil-5-piridilo, un grupo 2-metilaminosulfonil-5-piridilo, o un grupo 5-metilsulfonil-2-pirazinilo, muy de preferencia un grupo 2-metilsulfonil-5-piridilo, un grupo 5-metilsulfonil-2-pirazinilo, o un grupo 5-(1-azetidinil)carbonil-3-cloro-2-piridilo.

En la presente invención, la fórmula general (I) es preferiblemente la fórmula general (Ia).

En la presente invención, A es preferiblemente un grupo representado por la fórmula =NOH o un átomo de oxígeno, de preferencia un átomo de oxígeno.

En la presente invención, R^1 es preferiblemente un grupo alquilo de C_1-C_6, un grupo alcoxi de C_1-C_6 o un grupo monoalquilamino de C_1-C_6 halogenado, de preferencia un grupo metilo o un grupo 2-cloroetilamino.

En la presente invención, el grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están unidos, que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, es preferiblemente un grupo 2-piridilo, un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo, un grupo 1,3-tiazol-2-ilo, un grupo 1,3-oxazol-2-ilo, un grupo 1,3,4-oxadiazol-2-ilo, un grupo 1,3,4-tiadiazol-2-ilo, un grupo 4,5-dihidro-1,3-tiazol-2-ilo, un grupo 4,5-dihidro-1,3-oxazol-2-ilo, o un grupo 1,3-benzotiazol-2-ilo, que pueden estar sustituidos con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes γ, de preferencia un grupo 1,3-tiazol-2-ilo, un grupo 5-metil-1,3-tiazol-2-ilo, un grupo

5-metil-1,3,4-oxadiazol-2-ilo, un grupo 4,5-dihidro-1,3-tiazol-2-ilo, un grupo 4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo 5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-etil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1R)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1S)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-4-hidroxi-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4-hidroximetil-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5R)-5-hidroximetil-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo 5-carboxil-1,3-tiazol-2-ilo, un grupo 5-dimetilaminocarbonil-1,3-tiazol-2-ilo, un grupo 5-metil-1,3,4-tiadiazol-2-ilo, o un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo, de preferencia un grupo 4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-etil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1R)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1S)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4-hidroximetil-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5R)-5-hidroximetil-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo 1,3-tiazol-2-ilo, un grupo 5-carboxil-1,3-tiazol-2-ilo, un grupo 5-dimetilaminocarbonil-1,3-tiazol-2-

ilo, un grupo 5-metil-1,3,4-tiadiazol-2-ilo, un grupo 5-metil-1,3,4-oxadiazol-2-ilo, un grupo 4,5-dihidro-1,3-tiazol-2-ilo, o un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo, y en particular muy preferiblemente un grupo 4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-etil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1R)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1S)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4-hidroximetil-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, o un grupo (4R,5R)-5-hidroximetil-4-metil-4,5-dihidro-1,3-oxazol-2-ilo.

En la presente invención, R^2 es preferiblemente un grupo fenilo que puede estar sustituido con 1 a 5 grupos seleccionados independientemente del conjunto de sustituyentes δ, o un grupo 2-piridilo, un grupo 3-piridilo o un grupo 2-pirazinilo, que pueden estar sustituidos con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes δ, de preferencia un grupo 4-metilsulfonilfenilo, un grupo 4-(1-azetidinil)carbonil-2-fluorofenilo, un grupo 2-fluoro-4-(1-pirrolidinil)carbonilfenilo, un grupo 5-(1-azetidinil)carbonil-3-cloro-2-piridilo, un grupo 2-metilsulfonil-5-piridilo, un grupo 5-(4-metil-1-piperazinil)carbonil-2-pirazinilo, un grupo 2-metilaminocarbonil-5-piridilo, un grupo 2-metilaminosulfonil-5-piridilo, o un grupo 5-metilsulfonil-2-pirazinilo, y muy de preferencia un grupo 4-metilsulfonilfenilo, un grupo 2-metilsulfonil-5-piridilo, un grupo 5-metilsulfonil-2-pirazinilo, o un grupo 5-(1-

azetidinil)carbonil-3-cloro-2-piridilo.

En la presente invención, R^3 es preferiblemente un grupo hidroxi o un grupo metoxi.

En la presente invención, R^4 es preferiblemente un átomo de hidrógeno.

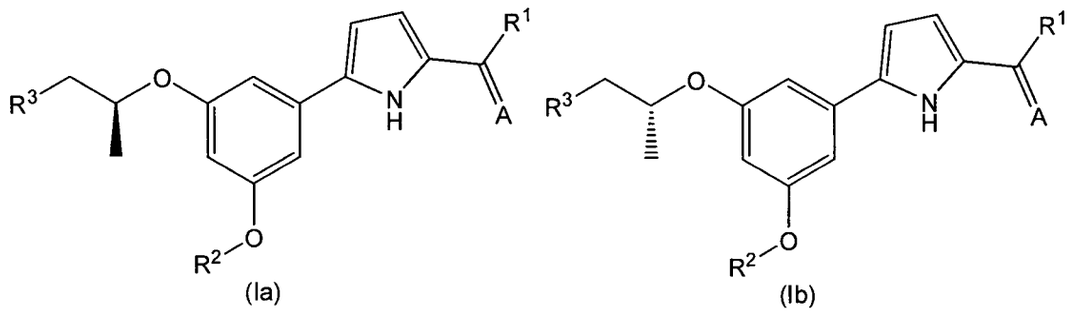
El compuesto representado por la fórmula general (I) o la sal farmacológicamente aceptable del mismo de la presente invención comprende todos sus isómeros (tales como isómeros ceto-enol, diasterómeros, isómeros ópticos, rotámeros, etc.).

El compuesto representado por la fórmula general (I) o la sal farmacológicamente aceptable del mismo de la presente invención tienen varios isómeros porque existen átomos de carbono asimétricos en la molécula. Todos estos isómeros y sus mezclas de la presente invención son representados por una sola fórmula, específicamente la fórmula general (I). Por consiguiente, la presente invención incluye todos estos isómeros y las mezclas de estos isómeros en relaciones arbitrarias.

Los estereoisómeros anteriormente mencionados se pueden obtener sintetizando el compuesto de la presente invención usando como materia prima un compuesto ópticamente activo, o usando una síntesis asimétrica o técnica de inducción asimétrica, o si se desea aislando el compuesto sintetizado de la presente invención por medio de un método común de resolución o separación óptica.

El compuesto representado por la fórmula general (Ia) o su sal

farmacológicamente aceptable de la presente invención se prefieren más que un compuesto representado por la fórmula general (Ib) o su sal farmacológicamente aceptable de la presente invención.



Una "sal farmacológicamente aceptable" se refiere a una sal libre de toxicidad prominente y que se puede usar como agente farmacéutico. El compuesto representado por la fórmula general (I) de la presente invención se pueden convertir en una sal haciéndolo reaccionar con un ácido cuando el compuesto tiene un grupo básico como un grupo amino, o haciéndolo reaccionar con una base cuando tiene un grupo ácido como un grupo carboxilo.

Ejemplos de las sales basadas en un grupo básico incluyen las sales de los ácidos halogenhídricos tales como fluorhidratos, clorhidratos, bromhidratos o yodhidratos, sales de ácidos inorgánicos, tales como nitratos, percloratos, sulfatos o fosfatos; alquilsulfonatos de C_1-C_6 como metanosulfonatos, trifluorometanosulfonatos o etanosulfonatos, arilsulfonatos como bencenosulfonatos o p-toluenosulfonatos; sales de ácidos orgánicos tales como acetatos, malatos, fumaratos, succinatos, citratos, ascorbatos, tartratos, oxalatos o maleatos; y sales de aminoácidos tales como las sales de

glicina, lisina, arginina, ornitina, ácido glutámico y ácido aspártico.

Por otra parte, ejemplos de sales basadas en grupos ácidos incluyen sales de metal, tales como las sales de sodio, potasio o litio, las sales de metal alcalino, tales como las sales de calcio o magnesio, las sales de metal, tales como las sales de aluminio o hierro; las sales de amina, inorgánicas tales como las sales de amonio, u orgánicas tales como las sales de t-octilamina, dibencilamina, morfolina, glucosamina, ésteres alquílicos de fenilglicina, etilendiamina, N-metilglucamina, guanidina, dietilamina, trietilamina, diciclohexilamina, N,N'-dibenciletilendiamina, cloroprocaína, procaína, dietanolamina, N-bencilfenetilamina, piperazina, tetrametilamonio o tris(hidroximetil)aminometano; y las sales de aminoácidos, tales como las sales de glicina, lisina, arginina, ornitina, ácido glutámico y ácido aspártico.

El compuesto representado por la fórmula general (I) o una sal farmacológicamente aceptable del mismo de la presente invención se pueden convertir en hidratos incorporando moléculas de agua al dejarse en la atmósfera o por recristalización, y tales hidratos también están incluidos en las sales de la presente invención.

El compuesto representado por la fórmula general (I) o una sal farmacológicamente aceptable del mismo de la presente invención se pueden convertir en solvatos absorbiendo otro tipo de disolvente, y tales solvatos también están incluidos en las sales de la presente invención.

En la presente invención, el "síndrome metabólico" se refiere a un estado patológico basado en la resistencia a la insulina, por el cual el

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riesgo de enfermedad de la arteria coronaria aumenta considerablemente debido a la acumulación de múltiples factores de riesgo para los vasos coronarios (que incluyen enfermedades del estilo de vida como hiperlipemia, diabetes, obesidad e hipertensión) (*Diabetes, Obesity and Metabolism*, 9, 2007, 246-258; *Journal of the American Medical Association*, 285, 2486-2497 (2001); *Diabet. Med.*, 15, 539-553 (1998)).

Efecto de la invención

El compuesto representado por la fórmula general (I) de la presente invención, o una sal farmacológicamente aceptable del mismo, tiene una actividad activadora de GK superior y es útil como agente farmacéutico para la prevención o tratamiento de una enfermedad seleccionada del conjunto que consiste en diabetes, deterioro de tolerancia a la glucosa, diabetes gestacional, complicaciones crónicas de la diabetes (que incluyen neuropatía periférica diabética, nefropatía diabética, retinopatía diabética y macroangiopatía diabética), y síndrome metabólico, en animales de sangre caliente (preferiblemente en mamíferos, incluyendo humanos). Además, el compuesto novedoso representado por la fórmula general (I) provisto por la presente invención, o una sal farmacológicamente aceptable del mismo, tiene una actividad activadora de GK superior y es útil como ingrediente activo de una composición farmacéutica para la prevención o tratamiento de las enfermedades anteriormente mencionadas en animales de sangre caliente. Los ejemplos preferidos de enfermedades incluyen diabetes y deterioro de

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tolerancia a la glucosa. El compuesto representado por la fórmula general (I) de la presente invención, o una sal farmacológicamente aceptable del mismo, se puede usar preferiblemente como una composición farmacéutica para el tratamiento de las enfermedades anteriormente mencionadas.

DESCRIPCION DETALLADA DE LA INVENCION

El compuesto representado por la fórmula general (I) de la presente invención se puede producir de acuerdo con los métodos A-L que se describen más abajo.

No hay limitaciones particulares sobre el disolvente utilizado en las reacciones de cada paso de los siguientes métodos A-L, siempre que disuelva hasta cierto grado la materia prima inicial sin perjudicar la reacción; el disolvente se selecciona, por ejemplo, del conjunto de disolventes indicado más abajo. El conjunto de disolventes está compuesto de hidrocarburos tales como pentano, hexano, octano, éter de petróleo, ligroína o ciclohexano; amidas como formamida, N,N-dimetilformamida, N,N-dimetilacetamida, N-metil-2-pirrolidona, N-metil-2-pirrolidinona o hexametilfosfato triamida; éteres como éter dietílico, éter diisopropílico, tetrahidrofurano, dioxano, dimetoxietano o éter dimetílico de dietilenglicol; alcoholes como metanol, etanol, n-propanol, i-propanol, n-butanol, 2-butanol, 2-metil-1-propanol, t-butanol, alcohol isoamílico, dietilenglicol, glicerina, octanol, ciclohexanol o metil celosolve; sulfóxidos como sulfóxido de dimetilo; sulfonas como

sulfolano; nitrilos como acetonitrilo, propionitrilo, butironitrilo o isobutironitrilo; ésteres como formiato de etilo, acetato de etilo, acetato de propilo, acetato de butilo o carbonato de dietilo; cetonas como acetona, metil-etil-cetona, 4-metil-2-pentanona, metil-isobutil-cetona, isoforona o ciclohexanona; compuestos nitro como nitroetano o nitrobenceno; hidrocarburos halogenados como diclorometano, 1,2-dicloroetano, clorobenceno, diclorobenceno, cloroformo o tetracloruro de carbono; hidrocarburos aromáticos como benceno, tolueno o xileno; ácidos carboxílicos como ácido acético, pacido fórmico, ácido propiónico, ácido butírico o ácido trifluoroacético; aminas como N-metilmorfolina, trietilamina, tripropilamina, tributilamina, diisopropiletilamina, diciclohexilamina, N-metilpiperidina, piridina, 2,6-lutidina, 4-pirrolidinopiridina, picolina, 4-dimetilaminopiridina, 2,6-di(t-butil)-4-metilpiridina, quinolina, N,N-dimetilanilina, N,N-dietilanilina, 1,5-diazabiciclo[4.3.0]-5-noneno (DBN), 1,4-diazabiciclo[2.2.2]octano (DABCO), 1,8-diazabiciclo[5.4.0]-7-undeceno (DBU) o piperidina; agua; y disolventes combinados de los mismos.

Ejemplos de bases usadas en las reacciones de cada paso de los métodos A-L siguientes incluyen bases inorgánicas tales como carbonatos de metal alcalino como carbonato de sodio, carbonato de potasio, carbonato de litio o carbonato de cesio; carbonatos ácidos de metal alcalino tales como carbonato ácido de sodio, carbonato ácido de potasio o carbonato ácido de litio; acetatos de metal alcalino como acetato de sodio, acetato de potasio, acetato de litio o acetato de cesio; hidruros de metal alcalino como hidruro de litio, hidruro de sodio o hidruro de potasio; hidróxidos de metal alcalino como

hidróxido de sodio, hidróxido de potasio, hidróxido de bario o hidróxido de litio; y fluoruros de metal alcalino como fluoruro de sodio o fluoruro de potasio; alcóxidos de metal alcalino como metóxido de sodio, etóxido de sodio, t-butóxido de sodio, metóxido de potasio, etóxido de potasio, t-butóxido de potasio o metóxido de litio; trialquil-silóxidos de metal alcalino como trimetilsilóxido de sodio, trimetilsilóxido de potasio o trimetilsilóxido de litio; mercaptanos de metal alcalino como tiometóxido de sodio o tioetóxido de sodio; bases orgánicas tales como N-metilmorfolina, trietilamina, tripropilamina, tributilamina, N,N-diisopropiletilamina, diciclohexilamina, N-metilpiperidina, piridina, 2,6-lutidina, 4-pirrolidinopiridina, picolina, 4-dimetilaminopiridina, 2,6-di(t-butil)-4-metilpiridina, quinolina, N,N-dimetilanilina, N,N-dietilanilina, 1,5-diazabiciclo[4.3.0]-5-noneno (DBN), 1,4-diazabiciclo[2.2.2]octano (DABCO) o 1,8-diazabiciclo[5.4.0]-7-undeceno (DBU); bases organometálicas como n-butil-litio, diisopropilamida de litio o bis(trimetilsilil)amida de litio; y aminoácidos como prolina.

Ejemplos de los agentes de condensación usados en las reacciones de cada paso de los métodos A-L siguientes incluyen hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (HATU), anhídrido cíclico del ácido 1-propanofosfónico (T3P), diciclohexilcarbodiimida (DCCD), clorhidrato de 1-etil-3-(dimetilaminopropil)carbodiimida (WSCI·HCl), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (EDCI), 1-etil-3-(3-dimetilaminopropil)-carbodiimida (EDAC), cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-

metilmorfolinio n-hidratado (DMT-MM), cloroformiato de isobutilo (IBCF), 1,1'-carbonilbis-1H-imidazol (CDI), cianofosfonato de dietilo (DEPC), fosforazidato de difenilo (DPPA), N-hidroxisuccinimida, N-hidroxi-5-norborneno-2,3-dicarboxiimida y disulfuro de dipiridilo, y estos se pueden usar en presencia de 1-hidroxibenzotriazol (HOBt) o 1-hidroxibenzotriazol monohidratado conforme sea necesario.

Ejemplos de los agentes de desmetilación usados en las reacciones de cada paso de los métodos A-L siguientes incluyen tiometóxido de sodio, tioetóxido de sodio, tiofenóxido de sodio, yodotrimetilsilano, cloruro de aluminio, bromuro de aluminio, tribromuro de boro, triyoduro de boro, yoduro de metilmagnesio y bromuro de hidrógeno.

Ejemplos de los catalizadores de paladio usados en las reacciones de cada paso de los métodos A-L siguientes incluyen catalizadores de paladio de valencia cero o catalizadores de paladio divalentes, tales como tetrakis(trifenilfosfina) paladio (0), paladio-carbón activado, acetato de paladio (II), trifluoroacetato de paladio (II), negro de paladio, bromuro de paladio (II), cloruro de paladio (II), yoduro de paladio (II), cianuro de paladio (II), nitrato de paladio (II), óxido de paladio (II), sulfato de paladio (II), diclorobis(acetonitrilo)paladio (II), diclorobis(benzonitrilo)paladio (II), dicloro(1,5-ciclooctadieno)paladio (II), acetilacetona de paladio (II), sulfuro de paladio (II), dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II), tris(dibencilidenacetona) dipaladio (0), tetrafluoroborato de tetrakis(acetonitrilo)paladio (II), y dímeros de cloruro de arilo-paladio.

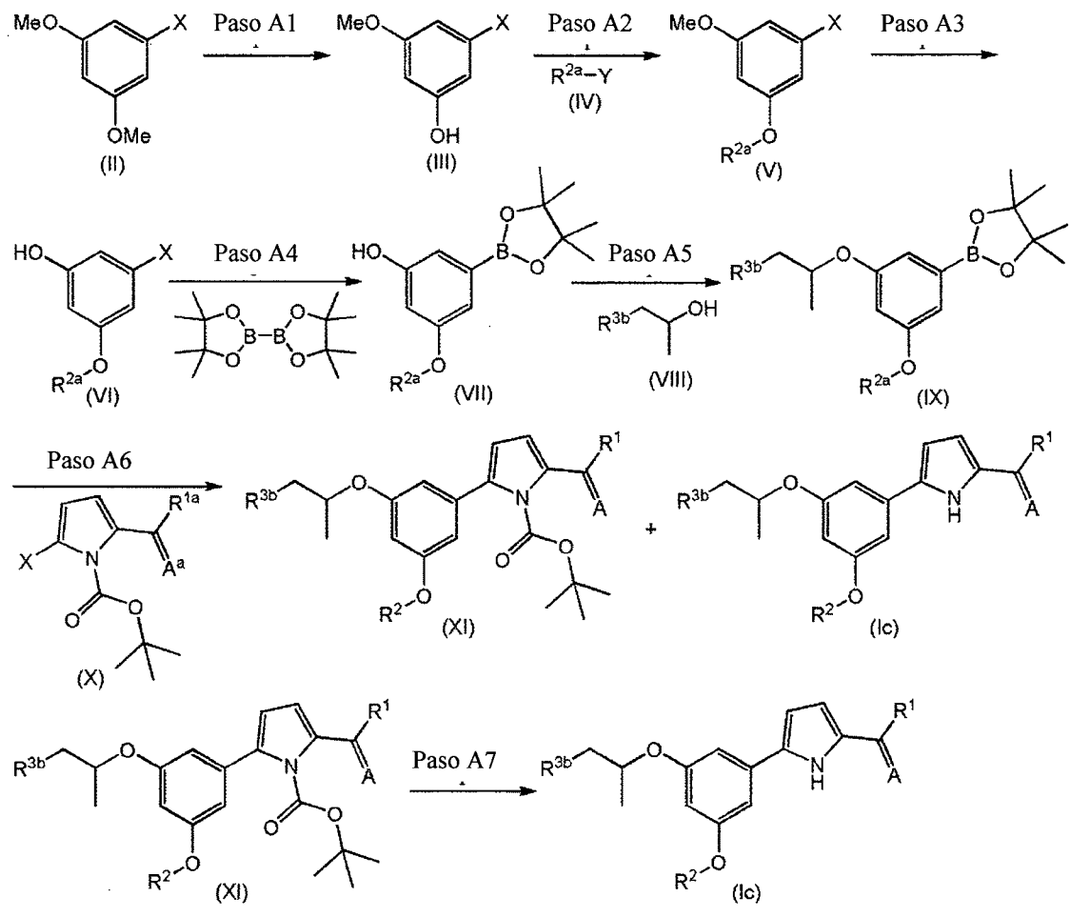
Las temperaturas de reacción de las reacciones de cada paso de los métodos A-L siguientes varían dependiendo del disolvente, la materia prima inicial, los reactivos, etcétera, mientras que los tiempos de reacción varían dependiendo del disolvente, la materia prima inicial, los reactivos, la temperatura de reacción, etcétera.

En las reacciones de cada paso de los métodos A-L siguientes, cada compuesto deseado se recoge de la mezcla de reacción de acuerdo con los métodos convencionales después de que termina la reacción. El compuesto deseado se obtiene, por ejemplo, de la siguiente manera. La mezcla de reacción se neutraliza adecuadamente, y si hay materia insoluble se quita por filtración. Después se le agrega agua y un disolvente orgánico inmiscible, tal como acetato de etilo, y la capa orgánica que contiene el compuesto deseado se separa. La capa orgánica se lava con agua o similar y después se seca sobre sulfato de magnesio anhidro, sulfato de sodio anhidro, bicarbonato de sodio anhidro o similares, y se filtra. Después se evapora el disolvente. El compuesto resultante deseado se puede aislar y purificar, si es necesario, combinando adecuadamente los métodos usuales, por ejemplo, métodos usados convenientemente para el aislamiento y purificación de compuestos orgánicos, tales como recristalización y reprecipitación, y eluyendo con un eluente adecuado por aplicación de cromatografía. El compuesto deseado insoluble en un disolvente se puede purificar lavando el producto crudo sólido resultante con un disolvente. El compuesto deseado en cada paso también se puede usar como tal para la siguiente reacción sin

purificar.

El método A es un método para producir un compuesto representado por la fórmula general (Ic) en donde R^3 es un grupo alcoxi de C_1-C_6, entre los compuestos representados por la fórmula general (I).

METODO A



En la presente invención, A, R^1 y R^2 son como se define arriba, R^{3b} representa un grupo alcoxi de C_1-C_6, X representa un átomo de halógeno

(preferiblemente un átomo de cloro, un átomo de bromo o un átomo de yodo, de preferencia un átomo de bromo), Y representa un átomo de halógeno, un grupo alquilsulfoniloxi de C_1-C_6, un grupo alcoxisulfoniloxi de C_1-C_6 o un grupo arilsulfoniloxi de C_6-C_{10} (preferiblemente un átomo de halógeno, de preferencia un átomo de flúor o un átomo de cloro, muy de preferencia un átomo de flúor), y A^a, R^{1a} y R^{2a} son grupos en donde un grupo amino, un grupo hidroxi o un grupo carboxilo contenidos como sustituyentes en los grupos A, R^1 y R^2, son un grupo amino, un grupo hidroxi o un grupo carboxilo opcionalmente protegidos, o representan los mismos grupos definidos para los grupos A, R^1 y R^2.

Paso A1

Este paso es para producir un compuesto representado por la fórmula general (III).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (II) con un agente de desmetilación en un disolvente.

El compuesto representado por la fórmula general (II) usado en este paso es un compuesto conocido, o se produce fácilmente de acuerdo con un método conocido o un método similar al mismo usando como materia prima inicial un compuesto conocido.

El disolvente usado en este paso es preferiblemente una amida, de preferencia N-metil-2-pirrolidona.

El agente de desmetilación usado en este paso es

preferiblemente tiometóxido de sodio.

La temperatura de reacción en este paso normalmente es de 50 °C a 140°C, de preferencia de 80 °C a 120°C.

El tiempo de reacción en este paso normalmente es de 0.5 horas a 12 horas, de preferencia de 1 hora a 5 horas.

Paso A2

Este paso es para producir un compuesto representado por la fórmula general (V).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (III) con un compuesto representado por la fórmula general (IV) en un disolvente y en presencia de una base.

El compuesto representado por la fórmula (IV) usado en este paso es un compuesto conocido, o se produce fácilmente de acuerdo con un método conocido o un método similar al mismo usando como materia prima inicial un compuesto conocido.

El disolvente usado en este paso es preferiblemente una amida, de preferencia N,N-dimetilformamida.

La base usada en este paso es preferiblemente un carbonato de metal alcalino, de preferencia carbonato de potasio.

La temperatura de reacción en este paso normalmente es de 50 °C a 140°C, de preferencia de 80 °C a 120°C.

El tiempo de reacción en este paso normalmente es de 12 horas a 72 horas, de preferencia de 24 horas a 48 horas.

1077

Paso A3

Este paso es para producir un compuesto representado por la fórmula general (VI).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (V) con un agente de desmetilación en un disolvente.

El disolvente usado en este paso es preferiblemente un hidrocarburo halogenado, de preferencia diclorometano.

El agente de desmetilación usado en este paso es preferiblemente tribromuro de boro.

La temperatura de reacción en este paso normalmente es de -100 °C a 40°C, de preferencia de -78 °C a 25°C.

El tiempo de reacción en este paso normalmente es de 1 hora a 72 horas, de preferencia de 12 horas a 36 horas.

Paso A4

Este paso es para producir un compuesto representado por la fórmula general (VII).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (VI) con bis(pinacolato)diboro en un disolvente, en presencia de un catalizador de paladio y una base inorgánica.

El disolvente usado en este paso es preferiblemente una amida, de preferencia N,N-dimetilformamida.

El catalizador de paladio usado en este paso es preferiblemente

1018

un catalizador de paladio divalente, de preferencia complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]-paladio (II)-diclorometano.

La base inorgánica usada en este paso es preferiblemente un acetato de metal alcalino, de preferencia acetato de potasio.

La temperatura de reacción en este paso normalmente es de 50 °C a 130 °C, de preferencia de 70 °C a 110 °C.

El tiempo de reacción en este paso normalmente es de 1 hora a 24 horas, de preferencia de 2 horas a 10 horas.

Paso A5

Este paso es para producir un compuesto representado por la fórmula general (IX).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (VII) con un compuesto representado por la fórmula general (VIII) en un disolvente, en presencia de trifenilfosfina y azodicarboxilato de dietilo.

El compuesto representado por la fórmula (VIII) usado en este paso y sus isómeros ópticos son compuestos conocidos, o se producen fácilmente de acuerdo con los métodos conocidos o similares usando como materia prima inicial un compuesto conocido.

El disolvente usado en este paso es preferiblemente un éter, de preferencia tetrahidrofurano.

La temperatura de reacción en este paso normalmente es de -20 °C a 40 °C, de preferencia de 0 °C a 25 °C.

1019

El tiempo de reacción en este paso normalmente es de 0.5 horas a 72 horas, de preferencia de 1 hora a 36 horas.

Paso A6

Este paso es para producir un compuesto representado por la fórmula general (XI) y un compuesto representado por la fórmula general (Ic).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (IX) con un compuesto representado por la fórmula general (X) en un disolvente, en presencia de un catalizador de paladio y una base inorgánica, seguido por la eliminación del grupo protector del grupo amino, hidroxi o carboxilo en A^a, R^{1a} y R^{2a} según se requiera.

El disolvente usado en este paso es preferiblemente un éter, un hidrocarburo aromático, un alcohol, agua, o un disolvente combinado de los mismos, de preferencia dioxano, tolueno, etanol, agua o un disolvente combinado de los mismos, muy de preferencia un disolvente combinado de dioxano y agua o un disolvente combinado de tolueno, etanol y agua.

El catalizador de paladio usado en este paso es preferiblemente un catalizador de paladio divalente, de preferencia complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano.

La base inorgánica usada en este paso es preferiblemente un carbonato de metal alcalino, de preferencia carbonato de potasio.

La temperatura de reacción en este paso normalmente es de 25 °C a 100 °C, de preferencia de 40 °C a 70 °C.

El tiempo de reacción en este paso normalmente es de 0.5 horas

1020

a 12 horas, de preferencia de 1 hora a 5 horas.

Paso A7

Este paso es para producir un compuesto representado por la fórmula general (Ic).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (XI) con un ácido en un disolvente.

El disolvente usado en este paso es preferiblemente un hidrocarburo halogenado, de preferencia diclorometano.

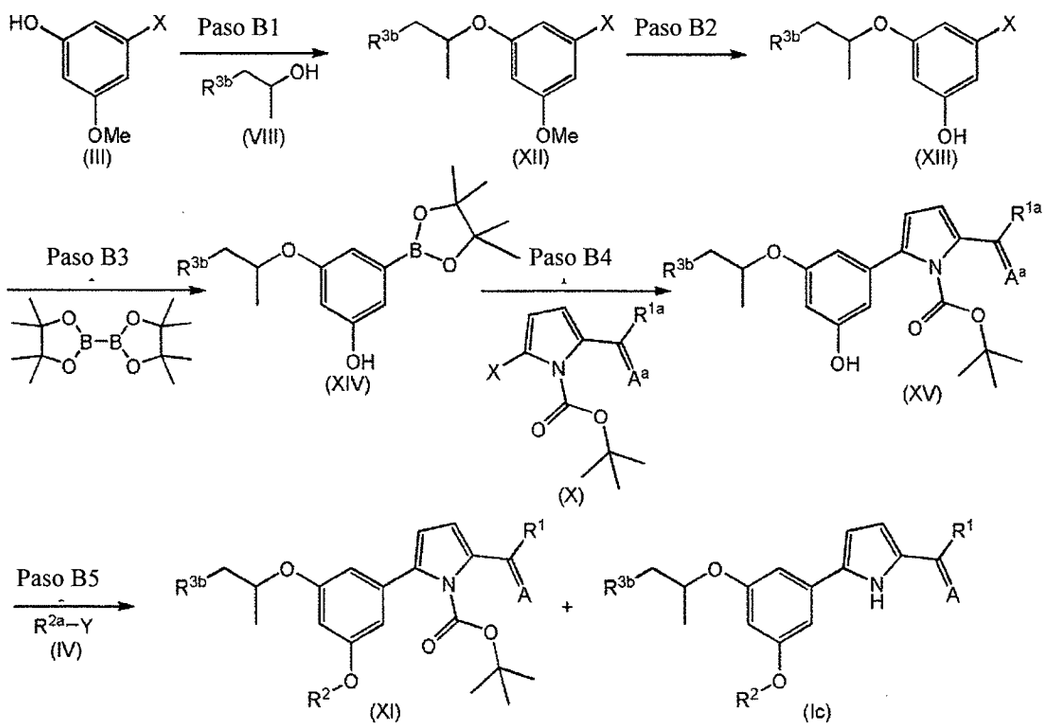
El ácido usado en este paso es, por ejemplo, un halogenuro de hidrógeno como cloruro de hidrógeno gaseoso o bromuro de hidrógeno gaseoso; un ácido mineral como ácido sulfúrico, ácido bromhídrico o ácido clorhídrico; un ácido sulfónico orgánico como ácido metanosulfónico, ácido p-toluenosulfónico, p-toluenosulfonato de piridinio (PPTS), ácido alcanforsulfónico o ácido trifluorometanosulfónico; un ácido carboxílico como ácido acético, ácido fórmico o ácido trifluoroacético; un ácido de Lewis como cloruro de aluminio, cloruro de zinc, yoduro de zinc, tetracloruro de estaño, tricloruro de titanio, trifluoruro de boro, tribromuro de boro o sulfato de metilo; o una resina ácido de intercambio iónico; preferiblemente un ácido carboxílico, de preferencia ácido trifluoroacético.

La temperatura de reacción en este paso normalmente es de -20 °C a 60 °C, de preferencia de 0 °C a 40 °C.

El tiempo de reacción en este paso normalmente es de 0.1 horas a 5 horas, de preferencia de 0.5 horas a 3 horas.

El método B es para producir un compuesto representado por la fórmula general (Ic) en donde R^3 es un grupo alcoxi de C_1-C_6, entre los compuestos representados por la fórmula general (I).

METODO B



En la presente invención, A, R^1, R^2, R^{3b}, A^a, R^{1a}, R^{2a}, X y Y son como se define arriba.

Paso B1

Este paso es para producir un compuesto representado por la fórmula general (XII).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (III) obtenido en el paso A1 del método A

1022

anteriormente mencionado con un compuesto representado por la fórmula general (VIII), en un disolvente y en presencia de trifenilfosfina y azodicarboxilato de dietilo.

El disolvente usado en este paso es preferiblemente un hidrocarburo aromático, de preferencia tolueno.

La temperatura de reacción en este paso normalmente es de -20 °C a 40 °C, de preferencia de 0 °C a 25 °C.

El tiempo de reacción en este paso normalmente es de 0.1 horas a 72 horas, de preferencia de 0.5 horas a 36 horas.

Paso B2

Este paso es para producir un compuesto representado por la fórmula general (XIII).

Este paso se efectúa igual que el paso A1 del método A anteriormente mencionado haciendo reaccionar un compuesto representado por la fórmula general (XII) con un agente de desmetilación.

Paso B3

Este paso es para producir un compuesto representado por la fórmula general (XIV).

Este paso se efectúa igual que el paso A4 del método A anteriormente mencionado haciendo reaccionar un compuesto representado por la fórmula general (XIII) con bis(pinacolato)diboro en un disolvente, en presencia de un catalizador de paladio y una base inorgánica.

Paso B4

Este paso es para producir un compuesto representado por la fórmula general (XV).

Este se efectúa igual que el paso A6 del método A anteriormente mencionado haciendo reaccionar un compuesto representado por la fórmula general (XIV) con un compuesto representado por la fórmula general (X) en un disolvente, en presencia de un catalizador de paladio y una base inorgánica.

Paso B5

Este paso es para producir un compuesto representado por la fórmula general (XI) y un compuesto representado por la fórmula general (Ic).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (XV) con un compuesto representado por la fórmula general (IV) en un disolvente, en presencia de una base, seguido por eliminación del grupo protector del grupo amino, hidroxi o carboxilo en A^a, R^{1a} y R^{2a} según sea necesario.

El disolvente usado en este paso es preferiblemente un sulfóxido o una amida, de preferencia sulfóxido de dimetilo o N,N-dimetilformamida.

La base usada en este paso es preferiblemente un hidruro de metal alcalino o un carbonato de metal alcalino, de preferencia hidruro de sodio o carbonato de potasio.

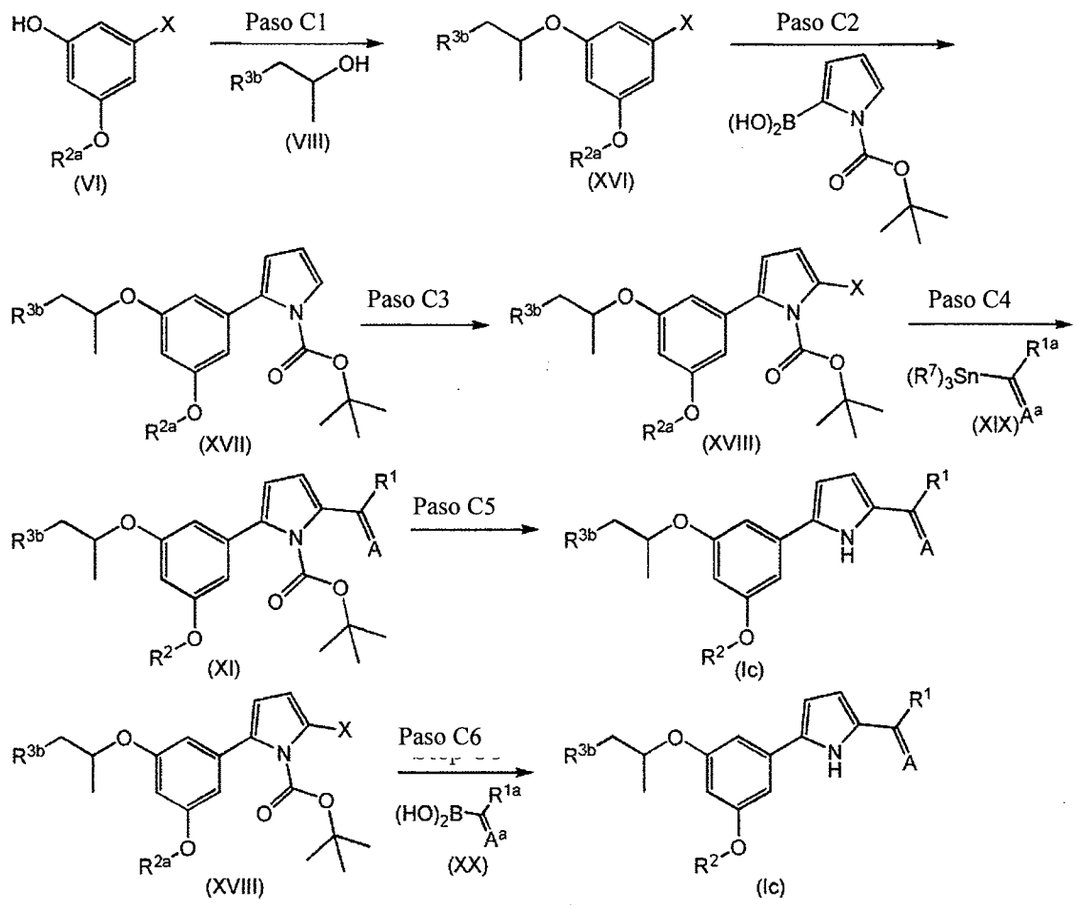
La temperatura de reacción en este paso normalmente es de 50 °C a 140°C, de preferencia de 80 °C a 120°C.

El tiempo de reacción en este paso normalmente es de 1 hora a

72 horas, de preferencia de 3 horas a 36 horas.

El método C es para producir un compuesto representado por la fórmula general (Ic) en donde R^3 es un grupo alcoxi de C_1-C_6, entre los compuestos representados por la fórmula general (I).

METODO C



En la presente invención, A, R^1, R^2, R^{3b}, A^a, R^{1a}, R^{2a} y X son como se define arriba, y R^7 representa un grupo alquilo de C_1-C_6 (preferiblemente un grupo n-butilo).

Paso C1

Este paso es para producir un compuesto representado por la fórmula general (XVI).

Este paso se efectúa igual que el paso B1 del método B anteriormente mencionado haciendo reaccionar un compuesto representado por la fórmula general (VI), obtenido en el paso A3 del método A anteriormente mencionado, con un compuesto representado por la fórmula general (VIII), en un disolvente y en presencia de trifenilfosfina y azodicarboxilato de dietilo.

Paso C2

Este paso es para producir un compuesto representado por la fórmula general (XVII).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (XVI) con ácido 1-(t-butoxicarbonil)pirrol-2-borónico en un disolvente, en presencia de un catalizador de paladio, trifenilfosfina y una base inorgánica.

El disolvente usado en este paso es preferiblemente un éter, agua o un disolvente combinado de los mismos, de preferencia dimetoxietano, agua o un disolvente combinado de los mismos, muy de preferencia un disolvente combinado de dimetoxietano y agua.

El catalizador de paladio usado en este paso es preferiblemente un catalizador de paladio divalente, de preferencia acetato de paladio (II).

La base usada en este paso es preferiblemente un carbonato de

metal alcalino, de preferencia carbonato de potasio.

La temperatura de reacción en este paso normalmente es de 40 °C a 100°C, de preferencia de 60 °C a 90°C.

El tiempo de reacción en este paso normalmente es de 1 hora a 72 horas, de preferencia de 3 horas a 24 horas.

Paso C3

Este paso es para producir un compuesto representado por la fórmula general (XVIII).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (XVII) con un agente de halogenación en un disolvente.

El disolvente usado en este paso es preferiblemente un éter o un disolvente combinado de un éter y un alcohol, de preferencia tetrahidrofurano o un disolvente combinado de tetrahidrofurano y metanol.

El agente de halogenación usado en este paso es, por ejemplo, un ácido inorgánico como ácido clorhídrico, bromuro de hidrógeno o yoduro de hidrógeno; una molécula de halógeno como cloro, bromo o yodo; o una succinimida como N-clorosuccinimida, N-bromosuccinimida o N-yodosuccinimida; preferiblemente una succinimida, de preferencia N-bromosuccinimida.

La temperatura de reacción en este paso normalmente es de -20 °C a 40°C, de preferencia de 0 °C a 25°C.

El tiempo de reacción en este paso normalmente es de 0.5 horas

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a 24 horas, de preferencia de 1 hora a 12 horas.

Paso C4

Este paso es para producir un compuesto representado por la fórmula general (XI).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (XVIII) con un compuesto representado por la fórmula general (XIX) en un disolvente, en presencia de un catalizador de paladio, seguido por la eliminación del grupo protector del grupo amino, hidroxi o carboxilo en A^a, R^{1a} y R^{2a}, conforme sea necesario.

El compuesto representado por la fórmula general (XIX) usado en este paso es un compuesto conocido, o se produce fácilmente de acuerdo con un método conocido o un método similar al mismo usando como materia prima inicial un compuesto conocido.

El disolvente usado en este paso es preferiblemente un hidrocarburo aromático, de preferencia tolueno.

El catalizador de paladio usado en este paso es preferiblemente un catalizador de paladio de valencia cero, de preferencia tetrakis(trifenilfosfina)paladio (0).

La temperatura de reacción en este paso normalmente es de 90 °C a 130°C, de preferencia de 100 °C a 120°C.

El tiempo de reacción en este paso normalmente es de 1 hora a 72 horas, de preferencia de 3 horas a 24 horas.

Paso C5

Este paso es para producir un compuesto representado por la fórmula general (Ic).

Este paso se efectúa igual que el paso A7 del método A anteriormente mencionado haciendo reaccionar un compuesto representado por la fórmula general (XI) con un ácido.

Paso C6

Este paso es para producir un compuesto representado por la fórmula general (Ic).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (XVIII) con un compuesto representado por la fórmula general (XX) en un disolvente, en presencia de un catalizador de paladio y una base inorgánica, seguido por la eliminación del grupo protector del grupo amino, hidroxi o carboxilo en A^a, R^{1a} y R^{2a}, conforme sea necesario.

El compuesto representado por la fórmula general (XX) usado en este paso es un compuesto conocido, o se produce fácilmente de acuerdo con un método conocido o un método similar al mismo usando como materia prima inicial un compuesto conocido.

El disolvente usado en este paso es preferiblemente un éter, agua, o un disolvente combinado de los mismos, de preferencia dimetoxietano, agua o un disolvente combinado de los mismos, muy de preferencia un disolvente combinado de dimetoxietano y agua.

El catalizador de paladio usado en este paso es preferiblemente un catalizador de paladio divalente, de preferencia complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano.

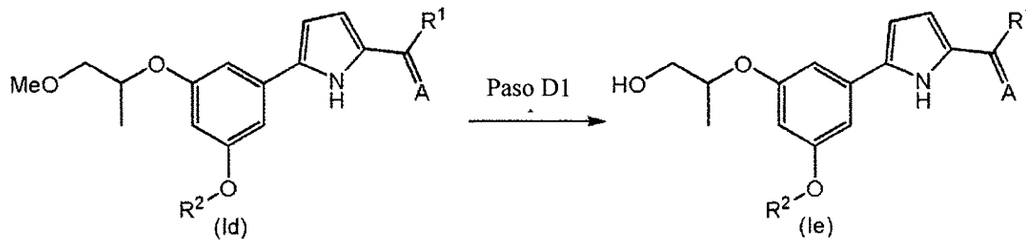
La base inorgánica usada en este paso es preferiblemente un carbonato de metal alcalino, de preferencia carbonato de potasio.

La temperatura de reacción en este paso normalmente es de 60 °C a 120°C, de preferencia de 80 °C a 100°C.

El tiempo de reacción en este paso normalmente es de 1 hora a 480 horas, de preferencia de 12 horas a 240 horas.

El método D es para producir un compuesto representado por la fórmula general (Ie) en donde R^3 es un grupo hidroxi, entre los compuestos representados por la fórmula general (I).

METODO D



En la presente invención, A, R^1 y R^2 son como se define arriba.

Paso D1

Este paso es para producir un compuesto representado por la fórmula general (Ie).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (Id) en donde R^{3b} es un grupo metoxi entre los compuestos representados por la fórmula general (Ic), obtenido en el paso A6 del método A anteriormente mencionado, el paso A7 del método A anteriormente mencionado, el paso B5 del método B anteriormente mencionado, el paso C5 del método C anteriormente mencionado, y el paso C6 del método C anteriormente mencionado, con un agente de desmetilación, en un disolvente.

El disolvente usado en este paso es preferiblemente un hidrocarburo halogenado, de preferencia diclorometano.

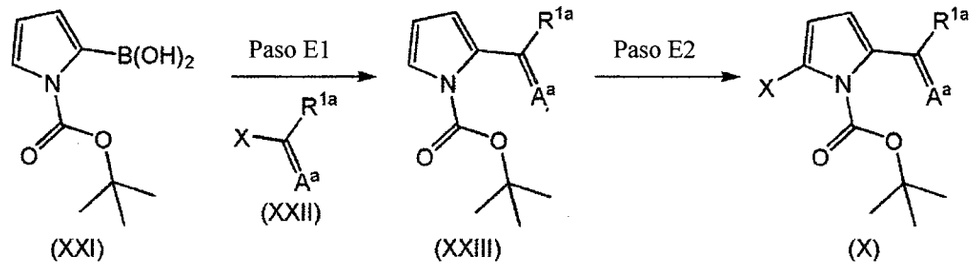
El agente de desmetilación usado en este paso es preferiblemente yodotrimetilsilano o tribromuro de boro, de preferencia tribromuro de boro.

La temperatura de reacción en este paso normalmente es de -100 °C a 40°C, de preferencia de -78 °C a 25°C.

El tiempo de reacción en este paso normalmente es de 0.05 horas a 12 horas, de preferencia de 0.1 horas a 3 horas.

El método E es para producir un compuesto representado por la fórmula general (X), usado en el paso A6 del método A anteriormente mencionado y en el paso B4 del método B anteriormente mencionado.

METODO E



En la presente invención, A^a, R^{1a} y X son como se define arriba.

Paso E1

Este paso es para producir un compuesto representado por la fórmula general (XXIII).

Este paso se efectúa igual que el paso C2 del método C anteriormente mencionado haciendo reaccionar ácido 1-(t-butoxicarbonil)pirrol-2-borónico (XXI) con un compuesto representado por la fórmula general (XXII) en un disolvente, en presencia de un catalizador de paladio, trifenilfosfina y una base inorgánica.

El ácido 1-(t-butoxicarbonil)pirrol-2-borónico (XXI) usado en este paso se produce fácilmente de acuerdo con un método conocido o similar al mismo usando como materia prima inicial un compuesto conocido.

El compuesto representado por la fórmula general (XXII) usado en este paso es un compuesto conocido, o se produce fácilmente de acuerdo con un método conocido o un método similar al mismo usando como materia prima inicial un compuesto conocido.

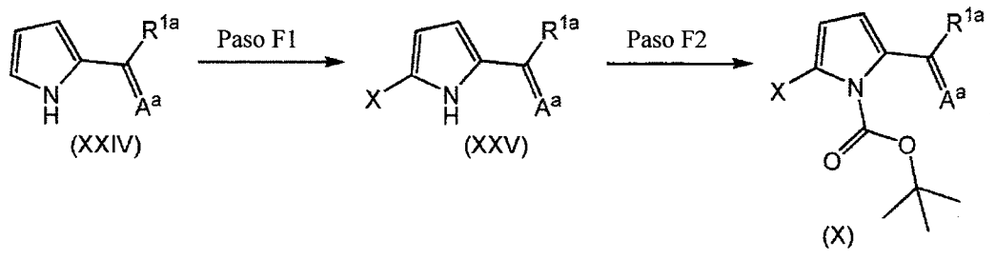
Paso E2

Este paso es para producir un compuesto representado por la fórmula general (X).

Este paso se efectúa igual que el paso C3 del método C anteriormente mencionado haciendo reaccionar un compuesto representado por la fórmula general (XXIII) con un agente de halogenación en un disolvente.

El método F es para producir un compuesto representado por la fórmula general (X), usado en el paso A6 del método A anteriormente mencionado y en el paso B4 del método B anteriormente mencionado.

METODO F



En la presente invención, A^a, R^{1a} y X son como se define arriba.

Paso F1

Este paso es para producir un compuesto representado por la fórmula general (XXV).

Este paso se efectúa igual que el paso C3 del método C haciendo reaccionar un compuesto representado por la fórmula general (XXIV) con un agente de halogenación en un disolvente.

El compuesto representado por la fórmula general (XXIV) usado

en este paso es un compuesto conocido, o se produce fácilmente de acuerdo con un método conocido o un método similar al mismo usando como materia prima inicial un compuesto conocido.

Paso F2

Este paso es para producir un compuesto representado por la fórmula general (X).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (XXV) con dicarbonato de di-t-butilo, en un disolvente y en presencia de una base.

El disolvente usado en este paso es preferiblemente un hidrocarburo halogenado, de preferencia diclorometano.

La base usada en este paso es preferiblemente una base orgánica, de preferencia trietilamina, 4-dimetilaminopiridina, o una base combinada de las mismas, de preferencia una base combinada de trietilamina y 4-dimetilaminopiridina.

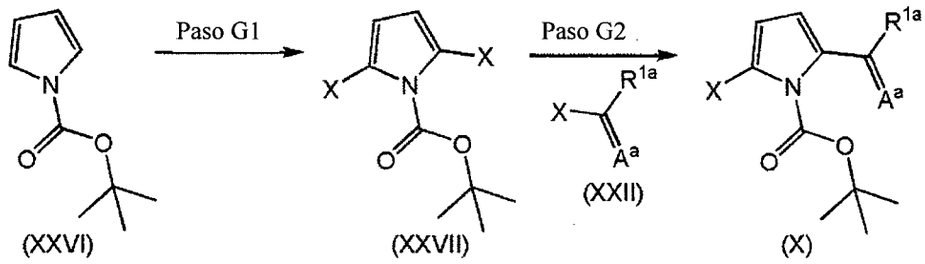
La temperatura de reacción en este paso normalmente es de -20 °C a 40°C, de preferencia de 0 °C a 25°C.

El tiempo de reacción en este paso normalmente es de 0.1 horas a 12 horas, de preferencia de 0.5 horas a 3 horas.

El método G es para producir un compuesto representado por la fórmula general (X), usado en el paso A6 del método A anteriormente mencionado y en el paso B4 del método B anteriormente mencionado.

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METODO G



En la presente invención, A^a, R^{1a} y X son como se define arriba.

Paso G1

Este paso es para producir un compuesto representado por la fórmula general (XXVII).

Este paso se efectúa igual que el paso C3 del método C haciendo reaccionar pirrol-1-carbonato de t-butilo (XXVI) con un agente de halogenación en un disolvente.

El pirrol-1-carbonato de t-butilo (XXVI) usado en este paso se produce fácilmente de acuerdo con un método conocido o similar al mismo usando como materia prima inicial un compuesto conocido.

Paso G2

Este paso es para producir un compuesto representado por la fórmula general (X).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (XXVII) con un compuesto representado por la fórmula general (XXII) en un disolvente y en presencia de una base.

El disolvente usado en este paso es preferiblemente un éter, de

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preferencia éter dietílico.

La base usada en este paso es preferiblemente una base organometálica, de preferencia n-butil-litio.

La temperatura de reacción en este paso normalmente es de -100 °C a 40°C, de preferencia de -78 °C a 25°C.

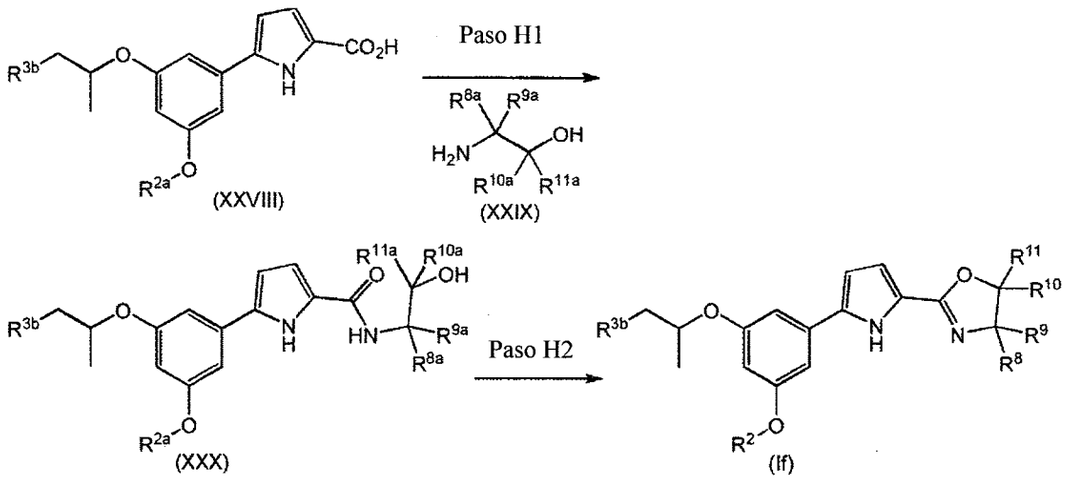
El tiempo de reacción en este paso normalmente es de 0.5 horas a 24 horas, de preferencia de 1 hora a 12 horas.

Un compuesto representado por la fórmula general (I), en donde A y R^1, junto con el átomo de carbono al que están unidos, forman un grupo heterocíclico que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, también se puede producir de acuerdo con un método que construye al último un anillo heterocíclico. Por ejemplo, los métodos H e I indican métodos en donde el grupo heterocíclico es un grupo 4,5-dihidro-1,3-oxazol-2-ilo, o un grupo 1,3,4-oxadiazol-2-ilo. Otros grupos heterocíclicos también se producen fácilmente de acuerdo con métodos similares.

El método H es para producir un compuesto representado por la fórmula general (If), en donde el grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están unidos, que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, es el grupo 4,5-dihidro-1,3-oxazol-2-ilo que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, y

R^3 es un grupo alcoxi de C_1-C_6, entre los compuestos representados por la fórmula general (I).

METODO H



En la presente invención, R^2, R^{3b} y R^{2a} son como se define arriba, R^8, R^9, R^{10} y R^{11} representan un átomo de hidrógeno o un grupo que pertenece al conjunto de sustituyentes α, y R^{8a}, R^{9a}, R^{10a} y R^{11a} son grupos en donde un grupo amino, hidroxi o carboxilo, contenidos como sustituyentes en los grupos R^8, R^9, R^{10} y R^{11}, son un grupo amino, un grupo hidroxi o un grupo carboxilo opcionalmente protegidos, o representan los mismos grupos definidos para R^8, R^9, R^{10} y R^{11}.

Paso H1

Este paso es para producir un compuesto representado por la fórmula general (XXX).

Este paso se efectúa haciendo reaccionar un compuesto

representado por la fórmula general (XXVIII) con un compuesto representado por la fórmula general (XXIX), en un disolvente y en presencia de un agente de condensación y en presencia o ausencia de una base.

El compuesto representado por la fórmula general (XXIX) usado en este paso es un compuesto conocido, o se produce fácilmente de acuerdo con un método conocido o un método similar al mismo usando como materia prima inicial un compuesto conocido.

El disolvente usado en este paso es preferiblemente un alcohol, un hidrocarburo halogenado o una amida, de preferencia metanol, diclorometano o N,N-dimetilformamida.

El agente de condensación usado en este paso es preferiblemente DMT-MM, WSCI·HCl o HATU.

La base usada en este paso es preferiblemente una base orgánica, de preferencia N-metilmorfolina, 4-dimetilaminopiridina o N,N-diisopropiletilamina.

La temperatura de reacción en este paso normalmente es de -20 °C a 60°C, de preferencia de 0 °C a 30°C.

El tiempo de reacción en este paso normalmente es de 0.5 horas a 72 horas, de preferencia de 1 hora a 24 horas.

Paso H2

Este paso es para producir un compuesto representado por la fórmula general (If).

Este paso se efectúa haciendo reaccionar un compuesto

representado por la fórmula general (XXX) con una base y anhídrido del ácido metanosulfónico o trifluoruro de bis(2-metoxietil)aminoazufre en un disolvente, seguido por la eliminación del grupo protector del grupo amino, hidroxi o carboxilo en R^{2a}, R^{8a}, R^{9a}, R^{10a} y R^{11a}.

El disolvente usado en este paso es preferiblemente un éter, de preferencia tetrahidrofurano o dimetoxietano.

En caso de usar anhídrido del ácido metanosulfónico en este paso, la base usada es preferiblemente una base orgánica, de preferencia trietilamina. En caso de usar trifluoruro de bis(2-metoxietil)aminoazufre, la base es preferiblemente un carbonato de metal alcalino, de preferencia carbonato de potasio.

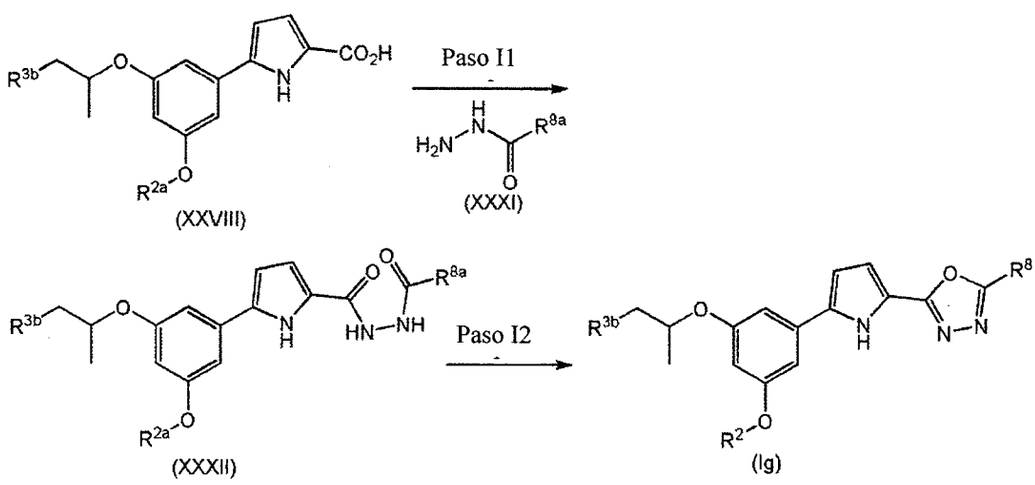
La temperatura de reacción en este paso normalmente es de -100 °C a 85°C, y en caso de usar anhídrido del ácido metanosulfónico, es preferiblemente de 10 °C a 60 °C. En caso de usar trifluoruro de bis(2-metoxietil)aminoazufre, la temperatura de reacción es preferiblemente de -78 °C a 30 °C.

El tiempo de reacción en este paso normalmente es de 0.5 horas a 72 horas, de preferencia de 1 hora a 24 horas.

El método I es para producir un compuesto representado por la fórmula general (Ig), en donde el grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están unidos, que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, es un grupo 1,3,4-oxadiazol-2-ilo que puede estar sustituido con 1 grupo

seleccionado del conjunto de sustituyentes α, y R^3 es un grupo alcoxi de C_1-C_6, entre los compuestos representados por la fórmula general (I).

METODO I



En la presente invención, R^2, R^{3b}, R^8, R^{2a} y R^{8a} son como se define arriba.

Paso I1

Este paso es para producir un compuesto representado por la fórmula general (XXXII).

Este paso se efectúa igual que el paso H1 del método H anteriormente mencionado, haciendo reaccionar un compuesto representado por la fórmula general (XXVIII) con un compuesto representado por la fórmula general (XXXI) en un disolvente, en presencia de un agente de condensación y en presencia o ausencia de una base.

El compuesto representado por la fórmula general (XXXI) usado

en este paso es un compuesto conocido, o se produce fácilmente de acuerdo con un método conocido o un método similar al mismo usando como materia prima inicial un compuesto conocido.

Paso I2

Este paso es para producir un compuesto representado por la fórmula general (Ig).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (XXXII) con cloruro de p-toluenosulfonilo y una base en un disolvente, seguido por la eliminación del grupo protector del grupo amino, hidroxi o carboxilo en R^{2a} y R^{8a} conforme sea necesario.

El disolvente usado en este paso es preferiblemente un hidrocarburo halogenado, de preferencia diclorometano.

La base usada en este paso es preferiblemente una base orgánica, de preferencia trietilamina.

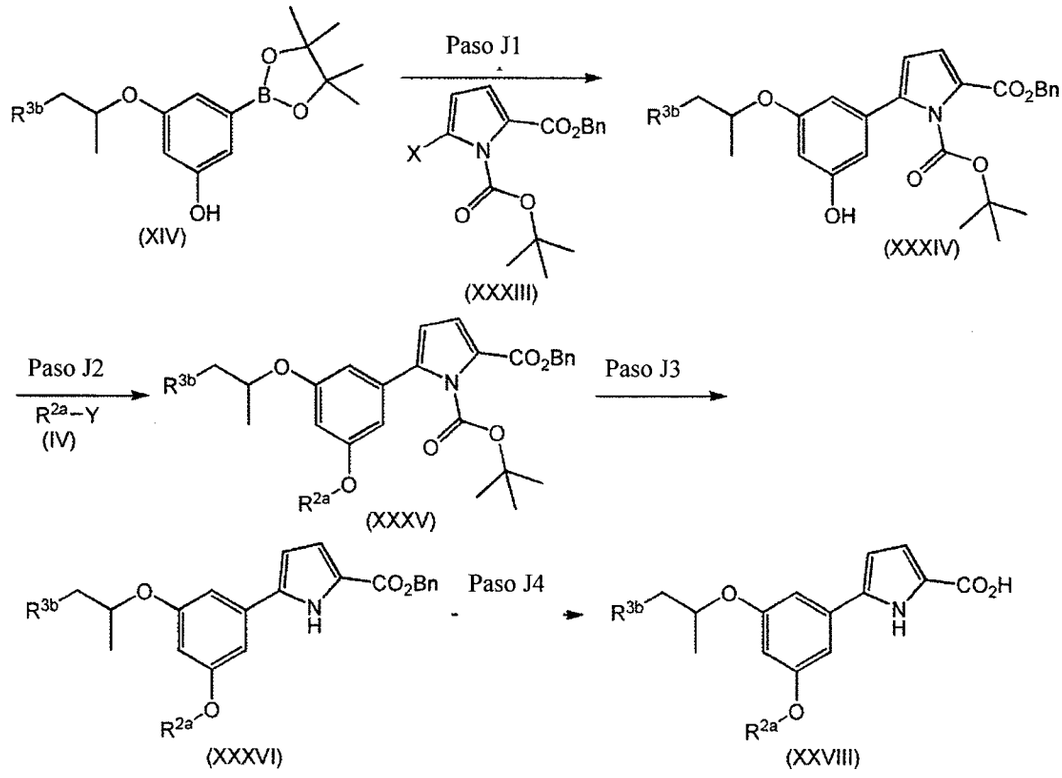
La temperatura de reacción en este paso normalmente es de -20 °C a 40°C, de preferencia de 0 °C a 30°C.

El tiempo de reacción en este paso normalmente es de 0.5 horas a 24 horas, de preferencia de 1 hora a 12 horas.

El método J es para producir un compuesto representado por la fórmula general (XXVIII), usado en el paso H1 del método H anteriormente mencionado, el paso I1 del método I anteriormente mencionado, y el paso L1 del método L anteriormente mencionado.

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METODO J



En la presente invención, R^{2a}, R^{3b}, X y Y son como se define arriba.

Paso J1

Este paso es para producir un compuesto representado por la fórmula general (XXXIV).

Este paso se efectúa igual que el paso A6 del método A anteriormente mencionado, haciendo reaccionar un compuesto representado por la fórmula general (XIV), obtenido en el paso B3 del método B anteriormente mencionado, con un compuesto representado por la fórmula general (XXXIII), en un disolvente y en presencia de un catalizador de paladio

y una base inorgánica.

Paso J2

Este paso es para producir un compuesto representado por la fórmula general (XXXV).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (XXXIV) con un compuesto representado por la fórmula general (IV), en un disolvente y en presencia de una base.

El disolvente usado en este paso es preferiblemente una amida o un nitrilo, de preferencia N,N-dimetilformamida o acetonitrilo.

La base usada en este paso es preferiblemente un carbonato de metal alcalino, de preferencia carbonato de potasio.

La temperatura de reacción en este paso normalmente es de 50 °C a 140°C, de preferencia de 60 °C a 100°C.

El tiempo de reacción en este paso normalmente es de 1 hora a 72 horas, de preferencia de 2 horas a 24 horas.

Paso J3

Este paso es para producir un compuesto representado por la fórmula general (XXXVI).

Este paso se efectúa igual que el paso A7 del método A anteriormente mencionado, haciendo reaccionar un compuesto representado por la fórmula general (XXXV) con un ácido.

Paso J4

Este paso es para producir un compuesto representado por la

fórmula general (XXVIII).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (XXXVI) en un disolvente y bajo una atmósfera de hidrógeno, en presencia de un catalizador de paladio.

El disolvente usado en este paso es preferiblemente un éter, un alcohol o un éster, de preferencia tetrahidrofurano, metanol, etanol o acetato de etilo.

El catalizador de paladio usado en este paso es preferiblemente un catalizador de paladio de valencia cero, de preferencia paladio-carbón activado.

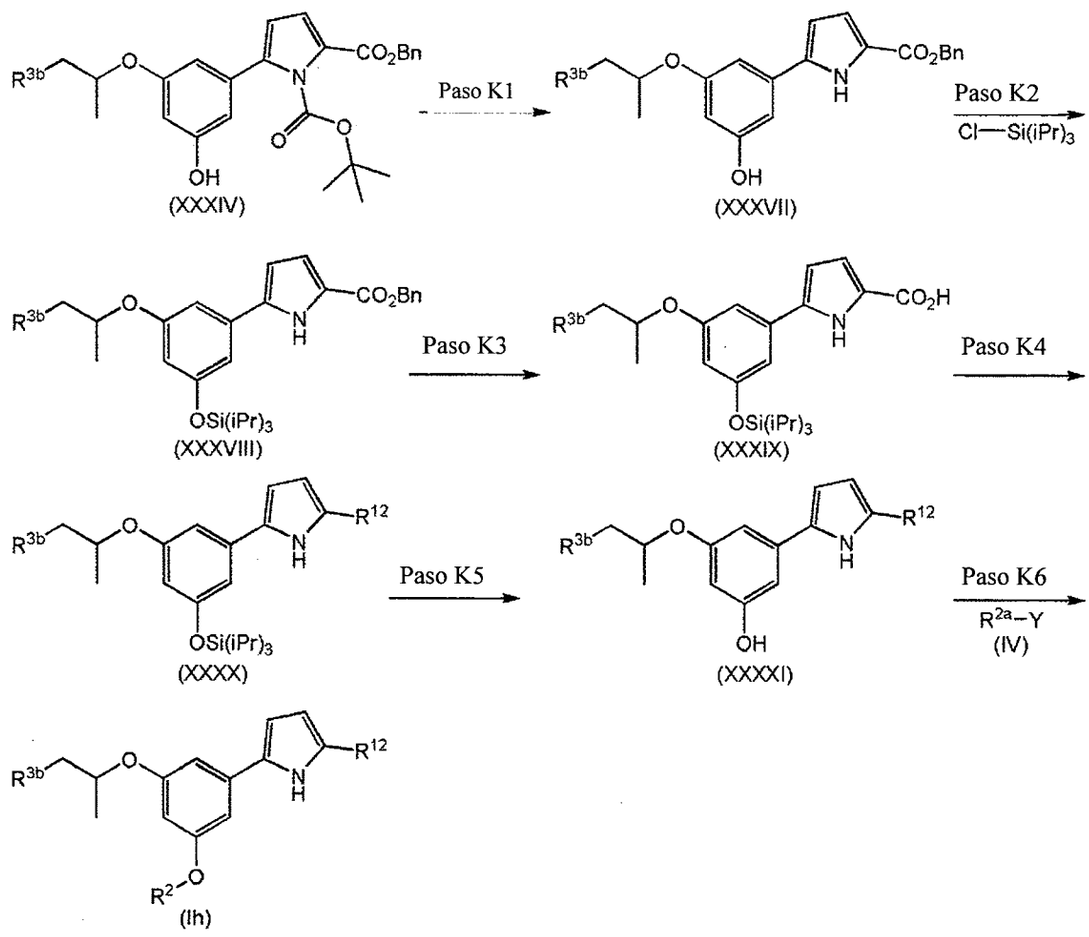
La temperatura de reacción en este paso normalmente es de -10 °C a 40°C, de preferencia de 0 °C a 30°C.

El tiempo de reacción en este paso normalmente es de 0.1 horas a 72 horas, de preferencia de 0.5 horas a 24 horas.

El método K es para producir un compuesto representado por la fórmula general (Ih), en donde el grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están unidos, que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, es un grupo 4,5-dihidro-1,3-oxazol-2-ilo que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, o un grupo 1,3,4-oxadiazol-2-ilo que puede estar sustituido con 1 grupo seleccionado del conjunto de sustituyentes α, y R^3 es un grupo alcoxi de C_1-

C_6, entre los compuestos representados por la fórmula general (I).

METODO K



En la presente invención, R^2, R^{3b}, Y y R^{2a} son como se define arriba, y R^{12} representa un grupo 4,5-dihidro-1,3-oxazol-2-ilo que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, o un grupo 1,3,4-oxadiazol-2-ilo que puede estar sustituido con 1 grupo seleccionado del conjunto de sustituyentes α.

Paso K1

Este paso es para producir un compuesto representado por la fórmula general (XXXVII).

Este paso se efectúa igual que el paso A7 del método A anteriormente mencionado, haciendo reaccionar un compuesto representado por la fórmula general (XXXIV), obtenido en el paso J1 del método J anteriormente mencionado, con un ácido en un disolvente.

Paso K2

Este paso es para producir un compuesto representado por la fórmula general (XXXVIII).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (XXXVII) con cloruro de triisopropilsililo en un disolvente y en presencia de una base.

El disolvente usado en este paso es preferiblemente un hidrocarburo halogenado, de preferencia diclorometano.

La base usada en este paso es preferiblemente una base orgánica, de preferencia trietilamina o una base mixta de trietilamina y 4-dimetilaminopiridina.

La temperatura de reacción en este paso normalmente es de -10 °C a 40°C, de preferencia de 0 °C a 30°C.

El tiempo de reacción en este paso normalmente es de 0.1 horas a 72 horas, de preferencia de 0.5 horas a 24 horas.

Paso K3

Este paso es para producir un compuesto representado por la fórmula general (XXXIX).

Este paso se efectúa igual que el paso J4 del método J haciendo reaccionar un compuesto representado por la fórmula general (XXXVIII) en un disolvente y bajo una atmósfera de hidrógeno, en presencia de un catalizador de paladio.

Paso K4

Este paso es para producir un compuesto representado por la fórmula general (XXXX).

Este paso se efectúa de acuerdo con el método H (pasos H1 y H2), o el método I (pasos I1 e I2).

Paso K5

Este paso es para producir un compuesto representado por la fórmula general (XXXXI).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (XXXX) con fluoruro de tetrabutilamonio en un disolvente.

El disolvente usado en este paso es preferiblemente un éter, de preferencia tetrahidrofurano.

La temperatura de reacción en este paso normalmente es de -10 °C a 40°C, de preferencia de 0 °C a 30°C.

El tiempo de reacción en este paso normalmente es de 0.1 horas

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a 12 horas, de preferencia de 0.5 horas a 3 horas.

Paso K6

Este paso es para producir un compuesto representado por la fórmula general (Ih).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (XXXXI) con un compuesto representado por la fórmula general (IV), en un disolvente y en presencia de una base, seguido por la eliminación del grupo protector del grupo amino, hidroxi o carboxilo en R^{2a} conforme sea necesario.

El disolvente usado en este paso es preferiblemente una amida o un nitrilo, de preferencia N,N-dimetilformamida o acetonitrilo.

La base usada en este paso es preferiblemente un carbonato de metal alcalino, de preferencia carbonato de potasio o carbonato de cesio.

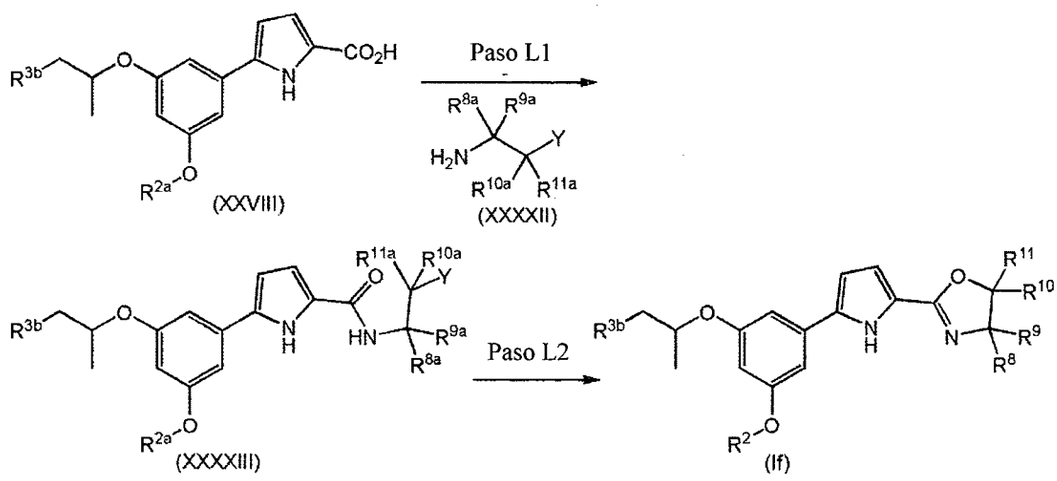
La temperatura de reacción en este paso normalmente es de 10 °C a 140°C, de preferencia de 20 °C a 120°C.

El tiempo de reacción en este paso normalmente es de 1 hora a 72 horas, de preferencia de 2 horas a 24 horas.

El método L es para producir un compuesto representado por la fórmula general (If), en donde el grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están unidos, que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, es un grupo 4,5-dihidro-1,3-oxazol-2-ilo que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α,

y R^3 es un grupo alcoxi de C_1-C_6, entre los compuestos representados por la fórmula general (I).

METODO L



En la presente invención, R^2, R^8, R^9, R^{10}, R^{11}, R^{2a}, R^{3b}, R^{8a}, R^{9a}, R^{10a}, R^{11a} y Y son como se define arriba.

Paso L1

Este paso es para producir un compuesto representado por la fórmula general (XXXXIII).

Este paso se efectúa igual que el paso H1 del método H anteriormente mencionado, haciendo reaccionar un compuesto representado por la fórmula general (XXVIII) con un compuesto representado por la fórmula general (XXXXII) en un disolvente, en presencia de un agente de condensación y una base.

El compuesto representado por la fórmula general (XXXXII)

usado en este paso es un compuesto conocido, o se produce fácilmente de acuerdo con un método conocido o un método similar al mismo usando como materia prima inicial un compuesto conocido.

Paso L2

Este paso es para producir un compuesto representado por la fórmula general (If).

Este paso se efectúa haciendo reaccionar un compuesto representado por la fórmula general (XXXXIII) con una base en un disolvente, seguido por la eliminación del grupo protector del grupo amino, hidroxi o carboxilo en R^{2a}, R^{8a}, R^{9a}, R^{10a} y R^{11a}, conforme sea necesario.

El disolvente usado en este paso es preferiblemente un éter, de preferencia tetrahidrofurano.

La base usada en este paso es preferiblemente un hidruro de metal alcalino, de preferencia hidruro de sodio.

La temperatura de reacción en este paso normalmente es de -20 °C a 40 °C, de preferencia de 0 °C a 25 °C.

El tiempo de reacción en este paso normalmente es de 0.5 horas a 48 horas, de preferencia de 1 hora a 24 horas.

En las descripciones anteriores, el grupo protector de un "grupo amino opcionalmente protegido", un "grupo hidroxi opcionalmente protegido" y un "grupo carboxilo opcionalmente protegido" en las definiciones de A^a, R^{1a}, R^{2a}, R^{8a}, R^{9a}, R^{10a} y R^{11a}, se refiere a un grupo protector susceptible de ser separado mediante un método químico como hidrogenólisis, hidrólisis,

electrólisis o fotólisis, usados comúnmente en la química orgánica sintética (véase por ejemplo T.W. Greene, *et al.*, "Protective Groups in Organic Sinthesis", 3ª edición, John Wiley & Sons, Inc. (1999)).

En las descripciones anteriores no hay limitaciones particulares sobre el "grupo protector" del "grupo hidroxi opcionalmente protegido" en las definiciones de A^a, R^{1a}, R^{2a}, R^{8a}, R^{9a}, R^{10a} y R^{11a}, siempre que sea un grupo protector de hidroxi usado en el campo de la química orgánica sintética, y los ejemplos incluyen "grupos alquilcarbonilo" tales como un grupo formilo, el "grupo alquilcarbonilo de C_2-C_7" anteriormente mencionado, grupos alquilcarbonilo halogenados como cloroacetilo, dicloroacetilo, tricloroacetilo y trifluoroacetilo, grupos alcoxialquilcarbonilo como metoxiacetilo, y grupos alquilcarbonilo insaturados como acriloilo, propioloilo, metacriloilo, crotonoilo, isocrotonoilo y (E)-2-metil-2-butenoilo; "grupos arilcarbonilo" tales como arilcarbonilo, como benzoilo, α-naftoilo y β-naftoilo, grupos arilcarbonilo halogenados como 2-bromobenzoilo y 4-clorobenzoilo, grupos aril(C_1-C_6)-carbonilo alquilados como 2,4,6-trimetilbenzoilo y 4-toluoilo, grupos aril(C_1-C_6)carbonilo alcoxilados como 4-anisoilo, grupos nitroarilcarbonilo como 4-nitrobenzoilo y 2-nitrobenzoilo, grupos arilcarbonilo de C_2-C_7 alcoxicarbonilados como 2-(metoxicarbonil)benzoilo, y grupos arilcarbonilo arilados como 4-fenilbenzoilo; "grupos alcoxicarbonilo" como el "grupo alcoxicarbonilo de C_2-C_7" anteriormente mencionado, y grupos alcoxicarbonilo de C_2-C_7 sustituidos con un halógeno o tri-alquil(C_1-C_6)sililo como 2,2,2-tricloroetoxicarbonilo y 2-trimetilsililetoxicarbonilo; "grupos tetrahidropiranilo o

tetrahidrotiopiranilo" como tetrahidropiran-2-ilo, 3-bromotetrahidropiran-2-ilo, 4-metoxitetrahidropiran-4-ilo, tetrahidrotiopiran-2-ilo y 4-metoxitetrahidrotiopiran-4-ilo; "grupos tetrahidrofuranilo o tetrahidrotiofuranilo" como tetrahidrofuran-2-ilo y tetrahidrotiofuran-2-ilo; "grupos sililo" tales como grupos como tri-alquil(C_1-C_6)sililo como trimetilsililo, trietilsililo, isopropildimetilsililo, t-butildimetilsililo, metildiisopropilsililo, metil-di-t-butilsililo y triisopropilsililo, y grupos alquil(C_1-C_6)diarilsililo y di-alquil(C_1-C_6)arilsililo como difenilmetilsililo, difenilbutilsililo, difenilisopropilsililo y fenildiisopropilsililo; "grupos alcoximetilo" tales como los grupos alcoxi(C_1-C_6)metilo como metoximetilo, 1,1-dimetil-1-metoximetilo, etoximetilo, propoximetilo, isopropoximetilo, butoximetilo y t-butoximetilo, grupos alcoxi(C_1-C_6)-alcoxi(C_1-C_6)-metilo como 2-metoxietoximetilo, y grupos alcoxi(C_1-C_6)metilo halogenados como 2,2,2-tricloroetoximetilo y bis(2-cloroetoxi)metilo; "grupos etilo sustituidos" tales como los grupos alcoxi(C_1-C_6)etilo como 1-etoxietilo y 1-(isopropoxi)etilo, y grupos etilo halogenados como 2,2,2-tricloroetilo; "grupos aralquilo" tales como los grupos alquilo de C_1-C_6 sustituidos con 1 a 3 grupos arilo como bencilo, α-naftilmetilo, β-naftilmetilo, difenilmetilo, trifenilmetilo, α-naftildifenilmetilo y 9-antrilmetilo, y grupos alquilo de C_1-C_6 sustituidos con 1 a 3 grupos arilo, en donde un anillo de arilo está sustituido con un alquilo de C_1-C_6, alcoxi de C_1-C_6, nitro, halógeno o ciano, como 4-metilbencilo, 2,4,6-trimetilbencilo, 3,4,5-trimetilbencilo, 4-metoxibencilo, 4-metoxifenildifenilmetilo, 2-nitrobencilo, 4-nitrobencilo, 4-clorobencilo, 4-bromobencilo y 4-cianobencilo; "grupos alqueniloxicarbonilo" como viniloxicarbonilo y aliloxicarbonilo; y

"grupos aralquiloxicarbonilo" en donde un anillo de arilo está sustituido opcionalmente con 1 o 2 grupos alcoxi de C_1-C_6 o nitro, como benciloxicarbonilo, 4-metoxibenciloxicarbonilo, 3,4-dimetoxibenciloxicarbonilo, 2-nitrobenciloxicarbonilo y 4-nitrobenciloxicarbonilo; de preferencia grupos alquilcarbonilo, grupos sililo o grupos aralquilo.

En las descripciones anteriores no hay limitaciones particulares sobre el "grupo protector" de un "grupo carboxilo opcionalmente protegido" en las definiciones de A^a, R^{1a}, R^{2a}, R^{8a}, R^{9a}, R^{10a} y R^{11a}, siempre que sea un grupo protector de carboxilo usado en el campo de la química orgánica sintética, y los ejemplos incluyen el "grupo alquilo de C_1-C_6" anteriormente mencionado; el "grupo alquenilo de C_2-C_6" anteriormente mencionado; el "grupo alquinilo de C_2-C_6" anteriormente mencionado; el "grupo alquilo de C_1-C_6 halogenado" anteriormente mencionado; grupos hidroxialquilo de C_1-C_6 como hidroximetilo y 2-hidroxietilo; grupos alquilcarbonil(C_2-C_7)-alquilo(C_1-C_6) como acetilmetilo; los "grupos aralquilo" anteriormente mencionados, y los "grupos sililo" anteriormente mencionados; de preferencia grupos alquilo o aralquilo de C_1-C_6.

En las descripciones anteriores, no hay limitaciones particulares sobre el "grupo protector" del "grupo amino opcionalmente protegido" en las definiciones de A^a, R^{1a}, R^{2a}, R^{8a}, R^{9a}, R^{10a} y R^{11a}, siempre que sea un grupo protector de amino usado en el campo de la química orgánica sintética, y ejemplos de los mismos incluyen grupos similares a los "grupos alquilcarbonilo", "grupos arilcarbonilo", "grupos alcoxicarbonilo", "grupos sililo",

"grupos aralquilo", "grupos alqueniloxicarbonilo" y "grupos aralquiloxicarbonilo" mencionados anteriormente como "grupos protectores de hidroxi", y "grupos metileno sustituidos que forman una base de Schiff", tales como N,N-dimetilaminometileno, bencilideno, 4-metoxibencilideno, 4-nitrobencilideno, salicilideno, 5-clorosalicilideno, difenilmetileno y (5-cloro-2-hidroxifenil)fenilmetileno; preferiblemente grupos alquilcarbonilo, grupos arilcarbonilo o grupos alcoxicarbonilo, de preferencia grupos alcoxicarbonilo.

Los pasos que requieren protección/desprotección se realizan de acuerdo con los métodos conocidos (por ejemplo, los métodos descritos en Theodora W. Greene, Peter G. M. Wuts, "Protective Groups in Organic Sinthesis", 1999, A Wiley-Interscience Publication, etc.).

El compuesto de la presente invención o su sal farmacológicamente aceptable se pueden administrar de varias maneras. Ejemplos de las vías de administración incluyen administración oral usando tabletas, cápsulas, gránulos, emulsiones, píldoras, polvos, jarabes (soluciones), etcétera; y administración parenteral usando inyecciones (administración intravenosa, intramuscular, subcutánea o intraperitoneal), infusiones de goteo, supositorios (administración rectal), etcétera. Estas composiciones farmacéuticas se preparan de acuerdo con los métodos usuales, usando los auxiliares comunes en el campo de la farmacia, tales como excipientes, aglutinantes, desintegradores, lubricantes, agentes saborizantes, auxiliares de disolución, agentes de suspensión y agentes de recubrimiento, además del principio activo.

Para usarse como tableta, los ejemplos de los vehículos que se pueden usar incluyen excipientes como lactosa, sacarosa, cloruro de sodio, glucosa, urea, almidón, carbonato de calcio, caolin, celulosa cristalina y ácido silícico; aglutinantes como agua, etanol, propanol, jarabe simple, solución de glucosa, solución de almidón, solución de gelatina, carboximetilcelulosa, goma laca, metilcelulosa, fosfato de potasio y polivinilpirrolidona; desintegradores como almidón seco, alginato de sodio, polvo de agar, polvo de laminaran, carbonato ácido de sodio, carbonato de calcio, ésteres de ácido graso de polioxietilensorbitán, laurilsulfato de sodio, monoglicérido esteárico, almidón y lactosa; inhibidores de desintegración como sacarosa, estearina, manteca de cacao y aceite hidrogenado; incrementadores de absorción como sales de amonio cuaternario y laurilsulfato de sodio; humectantes como glicerina y almidón; adsorbentes como almidón, lactosa, caolín, bentonita y ácido silícico coloidal; lubricantes como talco purificado, estearato, polvo de ácido fluobórico y polietilenglicol, etcétera. Además, si se requiere, se pueden preparar tabletas recubiertas comunes, tales como por ejemplo tabletas grageadas, tabletas con recubrimiento de gelatina, tabletas con recubrimiento entérico, tabletas con recubrimiento de película, tabletas de doble capa y tabletas de multicapa.

Para usarse como píldora, los ejemplos de los vehículos que se pueden usar incluyen excipientes tales como glucosa, lactosa, manteca de cacao, aceite vegetal hidrogenado, caolin y talco; aglutinantes como goma arábiga pulverizada, tragacanto pulverizado, gelatina y etanol;

desintegradores como laminaran y agar, etcétera.

Para usarse como supositorio se puede usar una amplia gama de vehículos conocidos en este campo, por ejemplo polietilenglicol, manteca de cacao, alcoholes superiores, ésteres de alcoholes superiores, gelatina, glicéridos semisintéticos, etcétera.

Para usarse como inyección se pueden preparar soluciones, emulsiones o suspensiones. Preferiblemente, estas soluciones, emulsiones y suspensiones se esterilizan y se hacen isotónicas con la sangre. Los disolventes para producir estas soluciones, emulsiones y suspensiones no están limitados particularmente, en tanto se puedan usar como diluentes para uso medicinal, por ejemplo agua, etanol, propilenglicol, alcohol isoestearílico etoxilado, alcohol isoestearílico polioxilado, ésteres de ácido graso de polioxietilensorbitán, etcétera. En este caso se puede agregar una cantidad suficiente de cloruro de sodio, glucosa o glicerina para hacer una solución isotónica, y también se pueden agregar los auxiliares de disolución usuales, amortiguadores, agentes balsámicos, etcétera.

Además, si es necesario se pueden agregar a las composiciones farmacéuticas anteriormente mencionadas agentes colorantes, conservadores, perfumes, agentes saborizantes, edulcorantes, etcétera. Además también se pueden agregar otros fármacos.

La cantidad de compuesto contenido como principio activo en las composiciones farmacéuticas anteriormente mencionadas no está limitada particularmente, pero usualmente es de 0.5% a 70% en peso del total de la

composición farmacéutica, de preferencia de 1% a 30% en peso.

La dosis varía dependiendo de los síntomas, la edad, etcétera del paciente (un animal de sangre caliente, en particular un humano). En caso de administración oral, la dosis diaria recomendada para un adulto es de 0.1 mg como límite inferior (preferiblemente 1 mg, de preferencia 10 mg), a 2000 mg como límite superior (preferiblemente 100 mg), que se dividen en 1 a 6 dosis dependiendo de los síntomas.

EJEMPLOS

Aunque lo siguiente provee una explicación más detallada de la presente invención por medio de ejemplos y ejemplos de prueba, el alcance de la presente invención no se limita a los mismos.

La elución de cromatografía en columna indicada en los ejemplos se hizo bajo observación por medio de cromatografía en capa delgada (TLC). Para las observaciones de TLC se usó una placa de TLC de gel de sílice $60F_{254}$ de Merck; el disolvente de elución usado en la cromatografía en columna se usó como disolvente de desarrollo, y para la detección se usó un detector de UV. Para la cromatografía en columna se usó gel de sílice SK-85 (malla 230 a 400) de Merck, o gel de sílice FL100B de Fuji Silysia Chemical. Además de la cromatografía en columna común se usó un sistema de cromatografía automático (Purif-α2) y una columna desechable (Purif-pack) de Moritex. Para purificación por TLC preparativa se usó una

placa de gel de sílice $60F_{254}$ de Merck que tiene un grosor de 0.5 mm y mide 20 cm x 20 cm. Además, las abreviaturas usadas en los ejemplos tienen los significados que se indican: mg: miligramos, g: gramos, mL: mililitros, MHz: megaHertz, HATU: hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio, WSCI·HCl: clorhidrato de 1-etil-3-(dimetilaminopropil)carbodiimida, HOBT·H_2O: 1-hidroxibenzotriazol monohidratado.

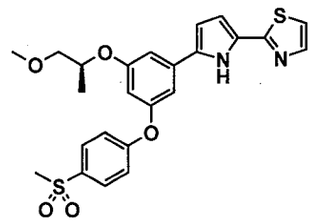
En los siguientes ejemplos se obtuvieron espectros de resonancia magnética nuclear (llamados ^{1}H-RMN) usando como estándar tetrametilsilano, y los valores de desplazamiento químico se indican con valores δ (ppm). En los patrones de división, un singulete se indica con una "s", un doblete con una "d", un triplete con una "t", un cuarteto con una "q", un patrón amplio con "br" y un multiplete con una "m".

Se efectuó espectrometría de masa, referida como (MS), con el método de bombardeo atómico rápido (FAB), el método de ionización electrónica (EI), o el método de ionización de electroaspersión (ESI).

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EJEMPLO 1

2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol



(1a) 3-Bromo-5-metoxifenol

Se disolvió 1-bromo-3,5-dimetoxibenceno (18.74 g, 86.3 mmol), disponible comercialmente, en 1-metil-2-pirrolidona (100 mL), y se le agregó tiometóxido sodio (6.74 g, 96.2 mmol), seguido por agitación a 100°C durante 3 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó ácido clorhídrico 1N (200 mL) y se extrajo con éter dietílico (500 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-25%), para producir el compuesto deseado como un sólido blanco (15.03 g, rendimiento de 86%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 3.77 (3H, s), 4.82 (1H, s), 6.33 (1H, t, J = 2.4 Hz), 6.61 (1H, t, J = 2.0 Hz), 6.66 (1H, t, J = 2.0 Hz).

(1b) 1-Bromo-3-metoxi-5-[4-(metilsulfonil)fenoxi]benceno

El 3-bromo-5-metoxifenol (13.10 g, 64.5 mmol) sintetizado en el

ejemplo (1a) y 4-fluorofenilmetilsulfona (10.45 g, 60.0 mmol), disponible comercialmente, se disolvieron en N,N-dimetilformamida (100 mL), y a esto se le agregó carbonato de potasio (25.00 g, 181 mmol), seguido por agitación a 100°C durante 36 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, el carbonato de potasio se removió por filtración en Celite; subsiguientemente se agregó a la solución ácido clorhídrico 0.1N (500 mL) y se extrajo dos veces con éter dietílico (400 mL) y acetato de etilo (100 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el sólido resultante se lavó con éter dietílico para producir el compuesto deseado como un sólido pardo pálido (18.30 g, rendimiento de 79%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 3.07 (3H, s), 3.80 (3H, s), 6.56 (1H, t, J = 2.4 Hz), 6.81 (1H, t, J = 2.0 Hz), 6.92 (1H, t, J = 2.0 Hz), 7.12 (2H, d, J = 9.0 Hz), 7.92 (2H, d, J = 9.0 Hz).

(1c) 3-Bromo-5-[4-(metilsulfonil)fenoxi]fenol

El 1-bromo-3-metoxi-5-[4-(metilsulfonil)fenoxi]benceno (18.29 g, 51.2 mmol) sintetizado en el ejemplo (1b) se disolvió en diclorometano (400 mL) y se enfrió a -78°C; se le agregó tribromuro de boro (solución 1.0M en diclorometano, 100 mL, 100 mmol) usando un embudo de goteo durante 30 minutos bajo una atmósfera de nitrógeno. La mezcla se agitó a -78°C durante 2 horas, seguido por aumento de la temperatura de forma natural y agitación a temperatura ambiente durante la noche. Se le agregó una solución acuosa

saturada de carbonato ácido de sodio bajo enfriamiento en un baño de hielo para neutralizar la solución de reacción, y se extrajo dos veces con diclorometano (500 mL) y metanol (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida para producir el compuesto deseado como un sólido amarillo pálido (16.89 g, rendimiento de 96%).

^{1}H-RMN (DMSO-D_6, 400 MHz): δ 3.19 (3H, s), 6.49 (1H, t, J = 2.1 Hz), 6.77 (1H, t, J = 2.0 Hz), 6.84 (1H, t, J = 2.0 Hz), 7.23 (2H, d, J = 8.6 Hz), 7.94 (2H, d, 9.0 Hz), 10.27 (1H, s).

(1d) 3-[4-(Metilsulfonil)fenoxi]-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenol

El 3-bromo-5-[4-(metilsulfonil)fenoxi]fenol (10.10 g, 29.4 mmol) sintetizado en el ejemplo (1c) se disolvió en N,N-dimetilformamida (100 mL) y se le agregó bis(pinacolato)diboro (11.09 g, 43.7 mmol), complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano (722 mg, 0.884 mmol) y acetato de potasio (14.92 g, 152 mmol), seguido por agitación a 90°C durante 5 horas bajo una atmósfera de nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente, se diluyó con acetato de etilo (400 mL) y el material insoluble se removió por filtración en Celite. Se agregó agua (400 mL) al filtrado para separarlo y la capa orgánica se lavó con salmuera saturada, seguido por secado sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se

purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-50%), para producir el compuesto deseado como un sólido blanco (11.88 g, rendimiento de ~100%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (12H, s), 3.06 (3H, s), 5.16 (1H, s), 6.69 (1H, t, J = 2.4 Hz), 7.06-7.12 (4H, m), 7.87 (2H, t, J = 9.0 Hz).

(1e) 2-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-4,4,5,5-tetrametil-1,3,2-dioxaborolano

El 3-[4-(metilsulfonil)fenoxi]-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenol (13.20 g, 33.8 mmol) sintetizado en el ejemplo (1d) se disolvió en tetrahidrofurano (300 mL) y se le agregó (R)-(-)-1-metoxi-2-propanol (3.70 mL, 37.8 mmol) y trifenilfosfina (9.78 g, 37.3 mmol); subsiguientemente se enfrió a 0°C. Se le agregó a gotas azodicarboxilato de dietilo (solución en tolueno al 40%, 16.2 mL, 37.2 mmol) durante 10 minutos, bajo una atmósfera de nitrógeno, y se agitó a 0°C durante 30 minutos, seguido por aumento natural de la temperatura y agitación a temperatura ambiente durante la noche. Se le agregó agua (300 mL) y acetato de etilo (300 mL) y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-40%), para producir el compuesto deseado como un aceite incoloro (11.94 g, rendimiento de 76%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J = 6.7 Hz), 1.33 (12H,

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s), 3.05 (3H, s), 3.40 (3H, s), 3.48 (1H, dd, J = 4.3, 10.2 Hz), 3.57 (1H, dd, J = 5.9, 10.2 Hz), 4.58-4.62 (1H, m), 6.76 (1H, t, J = 2.4 Hz), 7.05-7.09 (3H, m), 7.24 (1H, d, J = 2.4 Hz), 7.87 (2H, d, J = 9.0 Hz).

(1f) 2-(1,3-Tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo

Se disolvió ácido 1-(t-butoxicarbonil)pirrol-2-borónico (10.06 g, 47.7 mmol), disponible comercialmente, en un disolvente mixto de 1,2-dimetoxietano (150 mL) y agua (25 mL), y se le agregó 2-bromotiazol (4.40 mL, 48.8 mmol), acetato de paladio (II) (535 mg, 2.38 mmol), trifenilfosfina (2.50 g, 9.53 mmol) y carbonato de potasio (19.50 g, 141 mmol), seguido por agitación a 90°C durante 16 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (300 mL) y acetato de etilo (400 mL), y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-20%), para producir el compuesto deseado como un aceite amarillo pálido (6.71 g, rendimiento de 56%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.42 (9H, s), 6.26 (1H, t, J = 3.4 Hz), 6.58 (1H, dd, J = 1.6, 3.5 Hz), 7.37 (1H, d, J = 3.1 Hz), 7.41 (1H, dd, J = 1.6, 3.1 Hz), 7.85 (1H, d, J = 3.1 Hz).

(1g) 2-Bromo-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo

El 2-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (6.70 g,

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26.8 mmol) sintetizado en el ejemplo (1f) se disolvió en tetrahidrofurano (100 mL) y se enfrió a 0°C. Con agitación y bajo una atmósfera de nitrógeno se dividió en 5 partes N-bromosuccinimida (4.79 g, 26.9 mmol) para agregarse cada 10 minutos, seguido por más agitación a 0°C durante 2 horas. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (200 mL) y se extrajo con acetato de etilo (300 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-16%), para producir el compuesto deseado como un sólido blanco (7.55 g, rendimiento de 86%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.47 (9H, s), 6.30 (1H, d, J = 3.9 Hz), 6.52 (1H, d, J = 3.9 Hz), 7.29 (1H, d, J = 3.1 Hz), 7.79 (1H, d, J = 3.1 Hz).

(1h) 2-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo

El 2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-4,4,5,5-tetrametil-1,3,2-dioxaborolano (6.44 g, 13.9 mmol) sintetizado en el ejemplo (1e), y el 2-bromo-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (5.21 g, 15.8 mmol) sintetizado en el ejemplo (1g), se disolvieron en un disolvente mixto de 1,4-dioxano (200 mL) y agua (50 mL) y se les agregó complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano (564 mg, 0.691 mmol) y carbonato de potasio (9.67 g, 70.0 mmol), seguido por agitación a 50°C durante 3 horas bajo una atmósfera de

nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente se le agregó agua (200 mL) y se extrajo con acetato de etilo (400 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-50%), para producir el compuesto deseado como un aceite amarillo pálido (7.12 g, rendimiento de 88%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.31 (9H, s), 1.32 (3H, d, J = 6.4 Hz), 3.05 (3H, s), 3.40 (3H, s), 3.49 (1H, dd, J = 3.9, 10.3 Hz), 3.58 (1H, dd, J = 5.9, 10.3 Hz), 4.53-4.57 (1H, m), 6.27 (1H, d, J = 3.9 Hz), 6.58 (1H, d, J = 3.9 Hz), 6.65 (1H, s), 6.72 (1H, s), 6.89 (1H, s), 7.15 (2H, d, J = 8.8 Hz), 7.31 (1H, d, J = 3.4 Hz), 7.81 (1H, d, J = 3.4 Hz), 7.89 (2H, d, J = 8.8 Hz).

(1i) 2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-1,3-tiazol

El 2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (7.16 g, 12.2 mmol) sintetizado en el ejemplo (1h) se disolvió en diclorometano (15 mL) y se enfrió a 0°C. Se le agregó a gotas ácido trifluoroacético (30 mL) con agitación y bajo una atmósfera de nitrógeno. Se agitó a temperatura ambiente durante 30 minutos, seguido por más agitación a 40°C durante 30 minutos. El disolvente se removió por destilación bajo presión reducida, seguido por dilución con acetato de etilo (300 mL); se le agregó una solución acuosa saturada de

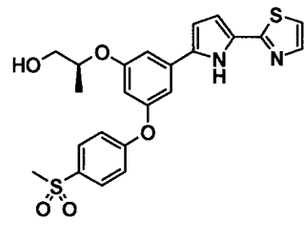
carbonato ácido de sodio (200 mL) y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-50%), para producir el compuesto deseado como un sólido amarillo pálido (5.21 g, rendimiento de 88%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 3.9, 10.2 Hz), 3.59 (1H, dd, J = 5.9, 10.2 Hz), 4.55-4.60 (1H, m), 6.53-6.56 (2H, m), 6.73 (1H, dd, J = 2.4, 3.5 Hz), 6.85 (1H, t, J = 2.0 Hz), 7.02 (1H, t, J = 2.0 Hz), 7.14 (2H, d, J = 8.6 Hz), 7.17 (1H, d, J = 3.5 Hz), 7.67 (1H, d, J = 3.5 Hz), 7.91 (2H, d, J = 8.6 Hz), 9.60 (1H, brs).

MS (ESI) m/z: 485.12291 $(M+H)^+$.

EJEMPLO 2

(2S)-2-{3-[4-(Metilsulfonil)fenoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}propan-1-ol



Bajo una atmósfera de nitrógeno, el 2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol (88.8 mg,

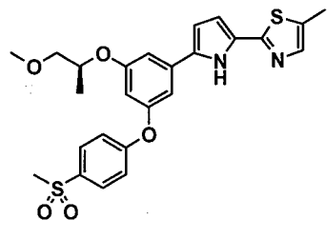
0.183 mmol) sintetizado en el ejemplo (1i) se disolvió en diclorometano (5 mL), y se le agregó una solución de tribromuro de boro/diclorometano (1.0M, 220 μL, 0.22 mmol) a -78°C. Subsiguientemente, la temperatura se regresó a la temperatura ambiente, seguido por agitación durante 30 minutos. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio, y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-50%), para producir el compuesto deseado como un sólido amarillo pálido (52.2 mg, rendimiento de 61%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.76-3.79 (2H, m), 4.56 (1H, dd, J = 10.6, 6.3 Hz), 6.52-6.55 (2H, m), 6.74 (1H, dd, J = 3.7, 2.5 Hz), 6.87 (1H, t, J = 1.8 Hz), 7.01 (1H, t, J = 1.8 Hz), 7.14 (2H, d, J = 9.0 Hz), 7.68 (1H, d, J = 3.5 Hz), 7.91 (2H, dt, J = 9.5, 2.3 Hz), 9.73 (1H, s).

MS (FAB) m/z: 471 $(M+H)^+$.

EJEMPLO 3

2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-5-metil-1,3-tiazol



(3a) 2-[1-(Triisopropilsilil)-1H-pirrol-2-il]-1,3-tiazol

El 2-(1H-pirrol-2-il)-1,3-tiazol (1.42 g, 9.45 mmol), conocido en la literatura (*European Journal of Organic Chemistry*, vol. 2000, No. 13, 2449-2458 (2000)), se disolvió en N,N-dimetilformamida (100 mL) y se enfrió a 0°C. Se le agregó hidruro de sodio (aceite al 60%, 570 mg, 14.3 mmol) y cloruro de triisopropilsililo (4.0 mL, 18.7 mmol), y se agitó a temperatura ambiente durante 30 minutos bajo una atmósfera de nitrógeno. Se le agregó agua (100 mL) y éter dietílico (100 mL) y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: hexano), para producir el compuesto deseado como un aceite amarillo pálido (2.33 g, rendimiento de 80%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.09 (18H, d, J = 7.4 Hz), 1.74 (3H, m), 6.30 (1H, t, J = 3.1 Hz), 6.78 (1H, dd, J = 1.5, 3.1 Hz), 7.04 (1H, m), 7.13 (1H, d, J = 3.1 Hz), 7.64 (1H, d, J = 3.1 Hz).

(3b) 5-Metil-2-[1-(triisopropilsilil)-1H-pirrol-2-il]-1,3-tiazol

El 2-[1-(triisopropilsilil)-1H-pirrol-2-il]-1,3-tiazol (317 mg, 1.03 mmol) sintetizado en el ejemplo (3a) se disolvió en tetrahidrofurano (10 mL) y se enfrió a -78°C. Se le agregó a gotas n-butil-litio (solución en hexano 2.64M, 0.51 mL, 1.35 mmol), seguido por agitación durante 40 minutos; subsiguientemente se le agregó yodometano (0.13 mL, 2.09 mmol) y se agitó durante 3 horas aumentando gradualmente la temperatura de -78°C a temperatura ambiente. Se le agregó agua (10 mL) y se extrajo con éter dietílico (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: hexano), para producir el compuesto deseado como un aceite incoloro (215 mg, rendimiento de 65%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.09 (18H, d, J = 7.8 Hz), 1.73 (3H, m), 2.44 (3H, s), 6.28 (1H, m), 6.68 (1H, m), 7.04 (1H, m), 7.01 (1H, m), 7.27 (1H, brs).

(3c) 5-Metil-2-(1H-pirrol-2-il)-1,3-tiazol

El 5-metil-2-[1-(triisopropilsilil)-1H-pirrol-2-il]-1,3-tiazol (215 mg, 0.67 mmol) sintetizado en el ejemplo (3b) se disolvió en tetrahidrofurano (8 mL), y se le agregó fluoruro de tetrabutilamonio (solución en tetrahidrofurano 1M, 0.87 mL, 0.87 mmol), seguido por agitación a temperatura ambiente durante 30 minutos bajo una atmósfera de nitrógeno. Se le agregó agua (10

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mL) y se extrajo con éter dietílico (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 5%-30%), para producir el compuesto deseado como un sólido blanco (100 mg, rendimiento de 91%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.46 (3H, s), 6.25 (1H, m), 6.61 (1H, m), 6.87 (1H, m), 7.30 (1H, brs), 9.68 (1H, brs).

(3d) 2-(5-Bromo-1H-pirrol-2-il)-5-metil-1,3-tiazol

El 5-metil-2-(1H-pirrol-2-il)-1,3-tiazol (100 mg, 0.61 mmol) sintetizado en el ejemplo (3c) se disolvió en tetrahidrofurano (7 mL) y se enfrió a 0°C. Se le agregó N-bromosuccinimida (108 mg, 0.61 mmol) y se agitó a temperatura ambiente durante 18 horas bajo una atmósfera de nitrógeno. Se le agregó agua (10 mL) y la solución se separó con éter dietílico (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se usó como tal en la siguiente reacción.

(3e) 2-Bromo-5-(5-metil-1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo

Un producto crudo purificado del 2-(5-bromo-1H-pirrol-2-il)-5-metil-1,3-tiazol sintetizado en el ejemplo (3d), se disolvió en diclorometano (8 mL), y se le agregó dicarbonato de di-t-butilo (165 mg, 1.35 mmol), trietilamina

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(0.18 mL, 1.29 mmol) y 4-dimetilaminopiridina (8.0 mg, 0.065 mmol), seguido por agitación a temperatura ambiente durante 1.5 horas bajo una atmósfera de nitrógeno. Se le agregó agua (10 mL) y se extrajo con diclorometano (10 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-20%), para producir el compuesto deseado como un aceite incoloro (172 mg, rendimiento de 84%, 2 pasos).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.48 (9H, s), 2.47 (3H, s), 6.28 (1H, d, J = 3.5 Hz), 6.45 (1H, d, J = 3.5 Hz), 7.42 (1H, m).

(3f) 2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-5-metil-1,3-tiazol

El 2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-4,4,5,5-tetrametil-1,3,2-dioxaborolano (220 mg, 0.492 mmol) sintetizado en el ejemplo (1e), y el 2-bromo-5-(5-metil-1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (598 mg, 1.49 mmol) sintetizado en el ejemplo (3e), se disolvieron en 1,4-dioxano (10 mL) y se les agregó complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano (20.0 mg, 0.024 mmol) y una solución acuosa de carbonato de sodio (3M, 0.33 mL, 0.990 mmol), seguido por agitación a 50°C durante 20 horas bajo una atmósfera de nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente, se le agregó agua (10 mL) y se extrajo con acetato de etilo (20 mL).

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La capa orgánica se lavó con salmuera saturada; subsiguientemente se secó sobre sulfato de magnesio anhidro y el disolvente se removió por destilación bajo presión reducida.

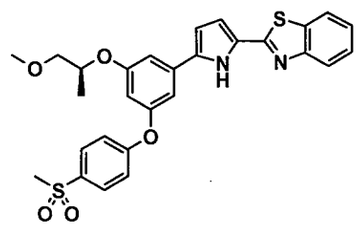
El residuo resultante se disolvió en diclorometano (10 mL) y se enfrió a 0°C. Se le agregó a gotas ácido trifluoroacético (10 mL) con agitación y bajo una atmósfera de nitrógeno. Después de agitar a temperatura ambiente durante 30 minutos, el disolvente se removió por destilación bajo presión reducida, seguido por dilución con acetato de etilo (30 mL); se le agregó una solución acuosa saturada de carbonato ácido de sodio (20 mL) y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-40%), para producir el compuesto deseado como un sólido amarillo pálido (49.6 mg, rendimiento de 20%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 2.46 (3H, brs), 3.07 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 3.9, 10.2 Hz), 3.61 (1H, dd, J = 5.9, 10.2 Hz), 4.56 (1H, m), 6.50-6.54 (2H, m), 6.63 (1H, dd, J = 2.4, 3.9 Hz), 6.85 (1H, t, J = 2.0 Hz), 7.02 (1H, t, J = 2.0 Hz), 7.13 (1H, d, J = 8.6 Hz), 7.29 (1H, t, J = 2.0 Hz), 7.90 (2H, d, J = 8.6 Hz), 9.89 (1H, brs).

MS (ESI) m/z: 521.11551 $(M+Na)^+$.

EJEMPLO 4

2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-1,3-benzotiazol



(4a) 2-(1,3-Benzotiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo

Se disolvió ácido 1-(t-butoxicarbonil)pirrol-2-borónico (417 mg, 1.98 mmol), disponible comercialmente, en 1,2-dimetoxietano (20 mL), y se le agregó 2-cloro-1,3-benzotiazol (0.25 mL, 2.02 mmol), acetato de paladio (II) (23.0 mg, 0.102 mmol), trifenilfosfina (105 mg, 0.400 mmol) y una solución acuosa de carbonato de potasio (3M, 1.3 mL, 0.433 mmol), seguido por agitación a 100°C durante 22 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) y acetato de etilo (20 mL) y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-20%), para producir el compuesto deseado como un aceite amarillo pálido (490 mg, rendimiento de 82%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.38 (9H, s), 6.30 (1H, t, J = 3.1

1073

Hz), 6.72 (1H, dd, J = 2.0, 3.1 Hz), 7.39 (1H, ddd, J = 1.2, 7.0, 8.0 Hz), 7.46 (1H, dd, J = 2.0, 3.1 Hz), 7.49 (1H, ddd, J = 1.2, 7.0, 8.0 Hz), 7.89 (1H, brd, J = 8.0 Hz), 8.05 (1H, dt, J = 1.2, 8.0 Hz).

(4b) 2-Bromo-5-(1,3-benzotiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo

El 2-(1,3-benzotiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (490 mg, 1.63 mmol) sintetizado en el ejemplo (4a) se disolvió en tetrahidrofurano (20 mL), y se enfrió a 0°C. Se le agregó N-bromosuccinimida (290 mg, 1.63 mmol) y se agitó a temperatura ambiente durante 14 horas bajo una atmósfera de nitrógeno. Se le agregó agua (20 mL) y se extrajo con éter dietílico (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-16%), para producir el compuesto deseado como un sólido amarillo pálido (548 mg, rendimiento de 89%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.52 (9H, s), 6.34 (1H, d, J = 3.9 Hz), 6.69 (1H, d, J = 3.9 Hz), 7.37 (1H, dt, J = 1.2, 8.0 Hz), 7.46 (1H, dt, J = 1.2, 8.0 Hz), 7.86 (1H, brd, J = 8.0 Hz), 7.93 (1H, brd, J = 8.0 Hz).

(4c) 2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-1,3-benzotiazol

El 2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-4,4,5,5-tetrametil-1,3,2-dioxaborolano (305 mg, 0.682 mmol) sintetizado

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en el ejemplo (1e), y el 2-bromo-5-(1,3-benzotiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (260 mg, 0.686 mmol) sintetizado en el ejemplo (4b), se disolvieron en 1,2-dimetoxietano (20 mL) y se les agregó complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano (28 mg, 0.034 mmol) y una solución acuosa de carbonato de potasio (3M, 0.44 mL, 1.32 mmol), seguido por agitación a 50°C durante 17 horas bajo una atmósfera de nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) y se extrajo con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada; subsiguientemente se secó sobre sulfato de magnesio anhidro y el disolvente se removió por destilación bajo presión reducida.

El residuo resultante se disolvió en diclorometano (10 mL) y se enfrió a 0°C. Se le agregó a gotas ácido trifluoroacético (10 mL) con agitación y bajo una atmósfera de nitrógeno. Después de agitar a temperatura ambiente durante 30 minutos, el disolvente se removió por destilación bajo presión reducida, seguido por dilución con acetato de etilo (30 mL); se le agregó una solución acuosa saturada de carbonato ácido de sodio (20 mL) y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-40%), para producir el compuesto deseado como un sólido amarillo (174 mg, rendimiento de 48%).

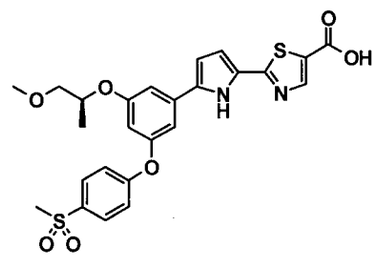
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^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 3.9, 10.2 Hz), 3.61 (1H, dd, J = 6.3, 10.2 Hz), 4.58 (1H, m), 6.57 (1H, t, J = 2.0 Hz), 6.60 (1H, dd, J = 2.7, 3.9 Hz), 6.88 (1H, dd, J = 2.4, 3.9 Hz), 6.92 (1H, t, J = 2.0 Hz), 7.08 (1H, t, J = 2.0 Hz), 7.13 (2H, d, J = 8.6 Hz), 7.32 (1H, dt, J = 1.2, 7.4 Hz), 7.44 (1H, brt, J = 7.4 Hz), 7.83 (1H, brd, J = 7.4 Hz), 7.91 (2H, d, J = 8.6 Hz), 10.10 (1H, brs).

MS (ESI) m/z: 535.13653 $(M+H)^+$.

EJEMPLO 5

Acido 2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol-5-carboxílico



(5a) 2-[1-(t-Butoxicarbonil)-1H-pirrol-2-il]-1,3-tiazol-5-carboxilato de etilo

Se disolvió ácido 1-(t-butoxicarbonil)pirrol-2-borónico (850 mg, 4.3 mmol) en 1,2-dimetoxietano (30 mL), y se le agregó 2-bromo-1,3-tiazol-5-carboxilato de etilo (0.50 mL, 3.35 mmol), disponible comercialmente, acetato de paladio (II) (38.0 mg, 0.169 mmol), trifenilfosfina (176 mg, 0.671 mmol) y una solución acuosa de carbonato de potasio (3M, 2.20 mL, 6.60 mmol),

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seguido por agitación a 100°C durante 14 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (30 mL) y acetato de etilo (40 mL) y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-30%), para producir el compuesto deseado como un sólido amarillo (800 mg, rendimiento de 74%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.39 (3H, t, J = 7.0 Hz), 1.50 (9H, s), 4.38 (2H, q, J = 7.0 Hz), 6.28 (1H, dd, J = 3.1,3.5 Hz), 6.79 (1H, dd, J = 2.0, 3.5 Hz), 7.43 (1H, dd, J = 2.0, 3.1 Hz), 8.39 (1H, s).

(5b) 2-[5-Bromo-1-(t-butoxicarbonil)-1H-pirrol-2-il]-1,3-tiazol-5-carboxilato de etilo

El 2-[1-(t-butoxicarbonil)-1H-pirrol-2-il]-1,3-tiazol-5-carboxilato de etilo (800 mg, 2.48 mmol) sintetizado en el ejemplo (5a) se disolvió en tetrahidrofurano (30 mL) y se enfrió a 0°C. Se le agregó N-bromosuccinimida (442 mg, 2.48 mmol) con agitación y bajo una atmósfera de nitrógeno, y subsiguientemente se agitó a temperatura ambiente durante 19 horas. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (30 mL) y se extrajo con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el

residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-30%), para producir el compuesto deseado como un sólido amarillo pálido (598 mg, rendimiento de 60%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.39 (3H, t, J = 7.0 Hz), 1.50 (9H, s), 4.38 (2H, q, J = 7.0 Hz), 6.32 (1H, d, J = 3.8 Hz), 6.64 (1H, d, J = 3.8 Hz), 8.31 (1H, s).

(5c) 2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-1,3-tiazol-5-carboxilato de etilo

El 2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-4,4,5,5-tetrametil-1,3,2-dioxaborolano (666 mg, 1.49 mmol) sintetizado en el ejemplo (1e), y el 2-[5-bromo-1-(t-butoxicarbonil)-1H-pirrol-2-il]-1,3-tiazol-5-carboxilato de etilo (598 mg, 1.49 mmol) sintetizado en el ejemplo (5b), se disolvieron en un disolvente mixto de tolueno (14 mL) y etanol (6 mL) y se les agregó complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano (61.0 mg, 0.075 mmol) y una solución acuosa de carbonato de sodio (2M, 1.50 mL, 3.00 mmol), seguido por agitación a 100°C durante 19 horas bajo una atmósfera de nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente, se le agregó agua (10 mL) y se extrajo con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada; subsiguientemente se secó sobre sulfato de magnesio anhidro y el disolvente se removió por destilación bajo presión reducida.

El residuo resultante se disolvió en diclorometano (10 mL) y se

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enfrió a 0°C. Se le agregó a gotas ácido trifluoroacético (10 mL) con agitación y bajo una atmósfera de nitrógeno. Después de agitar a temperatura ambiente durante 30 minutos, el disolvente se removió por destilación bajo presión reducida, seguido por dilución con acetato de etilo (30 mL); se le agregó una solución acuosa saturada de carbonato ácido de sodio (20 mL) y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-50%), para producir el compuesto deseado como un sólido amarillo pálido (505 mg, rendimiento de 61%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 1.39 (3H, t, J = 7.0 Hz), 3.07 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 4.3, 10.2 Hz), 3.61 (1H, dd, J = 6.3, 10.2 Hz), 4.37 (2H, q, J = 7.0 Hz), 4.59 (1H, m), 6.56 (1H, dd, J = 2.7, 3.9 Hz), 6.58 (1H, t, J = 2.0 Hz), 6.83 (1H, dd, J = 2.7, 3.9 Hz), 6.87 (1H, t, J = 2.0 Hz), 7.03 (1H, t, J = 2.0 Hz), 7.14 (2H, d, J = 9.0 Hz), 7.91 (2H, d, J = 9.0 Hz), 8.25 (1H, s), 9.64 (1H, brs).

MS (ESI) m/z: 557.14052 $(M+H)^+$.

(5d) Acido 2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol-5-carboxílico

El 2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-1,3-tiazol-5-carboxilato de etilo (53.5 mg, 0.096 mmol) sintetizado en el ejemplo (5c) se disolvió en etanol (4 mL). Se le agregó una

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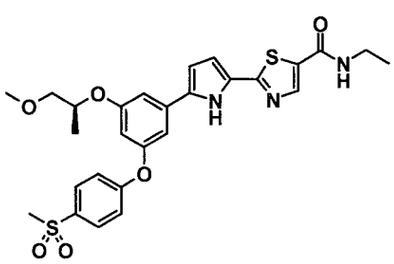
solución acuosa de hidróxido de sodio (5M, 2 mL) y se agitó a 70°C durante 30 minutos. Después de enfriar a temperatura ambiente, se le agregó ácido clorhídrico (2M, 5 mL) y acetato de etilo (10 mL), y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida para producir el compuesto deseado como un sólido amarillo pálido (52.5 mg, rendimiento de ~100%).

^{1}H-RMN (DMSO, 400 MHz): δ 1.25 (3H, d, J = 6.3 Hz), 3.19 (3H, s), 3.30 (3H, s), 3.44-3.52 (2H, m), 4.78 (1H, m), 6.56 (1H, brt, J = 2.0 Hz), 6.73 (1H, brd, J = 10.2 Hz), 7.21 (2H, d, J = 8.6 Hz), 7.27 (1H, brt, J = 2.0 Hz), 7.41 (1H, brt, J = 2.0 Hz), 7.93 (2H, d, J = 8.6 Hz), 12.0 (1H, brs).

MS (ESI) m/z: 529.11053 $(M+H)^+$.

EJEMPLO 6

N-Etil-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol-5-carboxamida



El ácido 2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol-5-carboxílico (62.8 mg, 0.119 mmol)

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sintetizado en el ejemplo (5d) se disolvió en N,N-dimetilformamida (5 mL), y se le agregó clorhidrato de etilamina (23.3 mg, 0.286 mmol), HATU (63.8 mg, 0.168 mmol) y N,N-diisopropiletilamina (80 μL, 0.46 mmol), seguido por agitación a temperatura ambiente durante 20 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó agua (20 mL) y se extrajo con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-80%), para producir el compuesto deseado como un sólido amarillo (57.7 mg, rendimiento de 87%).

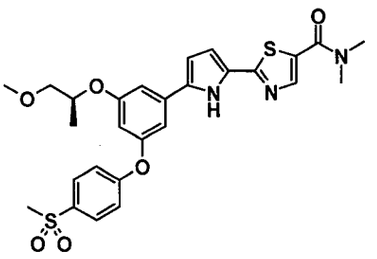
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.27 (3H, t, J = 7.4 Hz), 1.34 (3H, d, J = 6.3 Hz), 3.08 (3H, s), 3.43 (3H, s), 3.47-3.53 (3H, m), 3.60 (1H, dd, J = 6.3, 10.2 Hz), 4.56-4.60 (1H, m), 5.88 (1H, brs), 6.55-6.59 (2H, m), 6.80 (1H, dd, J = 2.3, 3.9 Hz), 6.86 (1H, t, J = 1.6 Hz), 7.02 (1H, t, J = 1.8 Hz), 7.14 (2H, d, J = 6.6 Hz), 7.92 (2H, d, J = 6.6 Hz), 7.98 (1H, s), 9.56 (1H, brs).

MS (ESI) m/z: 556.15812 $(M+H)^+$.

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EJEMPLO 7

2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-N,N-dimetil-1,3-tiazol-5-carboxamida



El ácido 2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol-5-carboxílico (62.8 mg, 0.119 mmol) sintetizado en el ejemplo (5d) se disolvió en N,N-dimetilformamida (5 mL), y se le agregó clorhidrato de dimetilamina (27.0 mg, 0.331 mmol), HATU (68.2 mg, 0.179 mmol) y N,N-diisopropiletilamina (80 μL, 0.46 mmol), seguido por agitación a temperatura ambiente durante 20 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó agua (20 mL), y se extrajo con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 60%-90%), para producir el compuesto deseado como un sólido amarillo (59.8 mg, rendimiento de 90%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.32 (6H, brs), 3.42 (3H, s), 3.51 (1H, dd, J = 4.3, 10.2 Hz), 3.59 (1H, dd, J

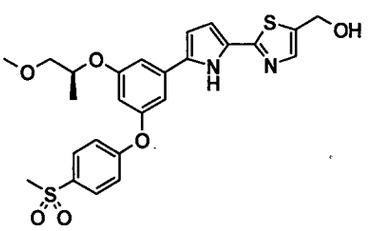
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= 6.3, 10.2 Hz), 4.55-4.60 (1H, m), 6.55-6.58 (2H, m), 6.79 (1H, dd, J = 2.4, 3.9 Hz), 6.86 (1H, t, J = 1.8 Hz), 7.02 (1H, t, J = 1.8 Hz), 7.14 (2H, d, J = 9.0 Hz), 7.89 (1H, s), 7.91 (2H, d, J = 9.0 Hz), 9.52 (1H, brs).

MS (ESI) m/z: 556.15717 $(M+H)^+$.

EJEMPLO 8

[2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol-5-il]metanol



Se suspendió hidruro de litio y aluminio (22 mg, 0.580 mmol) en tetrahidrofurano (2 mL). El 2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol-5-carboxilato de etilo (106 mg, 0.190 mmol) sintetizado en el ejemplo (5c) se disolvió en tetrahidrofurano (2 mL), seguido por su adición gota a gota a 0°C bajo una atmósfera de nitrógeno. Después de agitar a 0°C durante 30 minutos, se le agregó lenta y secuencialmente, gota a gota, agua (22 μL) y una solución acuosa de hidróxido de sodio (5M, 88 μL). después de filtración a través de Celite, el disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-100%), para producir el compuesto

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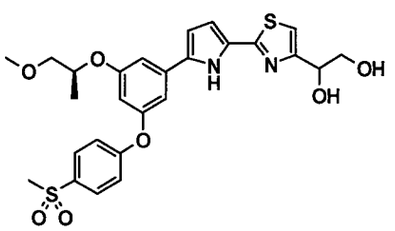
deseado como un sólido amarillo pálido (48 mg, rendimiento de 49%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.30 (3H, d, J = 6.3 Hz), 3.06 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 3.9, 10.5 Hz), 3.58 (1H, dd, J = 6.3, 10.5 Hz), 4.48 (1H, m), 4.82 (2H, brs), 6.51-6.54 (2H, m), 6.70 (1H, dd, J = 2.4, 3.9 Hz), 6.86 (1H, brt, J = 2.0 Hz), 7.00 (1H, brt, J = 2.0 Hz), 7.12 (2H, d, J = 9.0 Hz), 7.47 (1H, brs), 7.89 (2H, d, J = 9.0 Hz), 10.20 (1H, brs).

MS (ESI) m/z: 515.12920 $(M+H)^+$.

EJEMPLO 9

1-[2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol-4-il]etano-1,2-diol



(9a) (2-Bromo-1,3-tiazol-4-il)(oxo)acetato de etilo

Se disolvió (2-formamido-1,3-tiazol-4-il)(oxo)acetato de etilo (5.09 g, 22.3 mmol), disponible comercialmente, en un disolvente mixto de etanol (50 mL) y 1,4-dioxano, y se le agregó ácido sulfúrico al 30% (12 mL), seguido por agitación a 60°C durante 1 hora. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) y acetato de etilo (20 mL), y la solución se separó. El disolvente se removió por destilación bajo presión reducida y se le agregó ácido sulfúrico al 30% (40 mL) y bromuro de

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potasio (9.3 g, 78.2 mmol), seguido por enfriamiento a 0°C. Se disolvió en agua (40 mL) nitrito de sodio (20.0 g, 290 mmol), seguido por su adición gota a gota durante 1 hora y agitación a 0°C durante 1 hora. La solución se separó con acetato de etilo (200 mL), la capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-20%), para producir el compuesto deseado como un aceite amarillo (3.07 g, rendimiento de 52%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.43 (3H, t, J = 7.0 Hz), 4.45 (2H, q, J = 7.0 Hz) 8.55 (1H, s).

(9b) 1-(2-Bromo-1,3-tiazol-4-il)etano-1,2-diol

El (2-bromo-1,3-tiazol-4-il)(oxo)acetato de etilo (3.07 g, 11.6 mmol) sintetizado en el ejemplo (9a) se disolvió en metanol (100 mL), y se enfrió a 0°C. Se le agregó borohidruro de sodio (1.32 g, 34.9 mmol) en pequeñas porciones y se agitó a 0°C durante 1.5 horas, seguido por agitación a temperatura ambiente durante 2 horas más. Se le agregó ácido clorhídrico diluido (1M, 100 mL) y la solución se separó con acetato de etilo (200 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-80%), para producir el compuesto deseado como un aceite amarillo (1.10

g, rendimiento de 42%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 3.87 (1H, dd, J = 5.9, 11.3 Hz), 3.97 (1H, dd, J = 3.5, 11.3 Hz), 4.89 (1H, dd, J = 3.5,5.3 Hz) 7.27 (1H, s).

(9c) 2-[4-(1,2-Dihidroxietil)-1,3-tiazol-2-il]-1H-pirrol-1-carboxilato de t-butilo

El 1-(2-bromo-1,3-tiazol-4-il)etano-1,2-diol (1.10 g, 4.91 mmol) sintetizado en el ejemplo (9b) y ácido 1-(t-butoxicarbonil)pirrol-2-borónico (1.55 g, 7.35 mmol), disponible comercialmente, se disolvieron en 1,2-dimetoxietano (40 mL) y se les agregó acetato de paladio (II) (55.0 mg, 0.245 mmol), trifenilfosfina (260 mg, 0.991 mmol) y una solución acuosa de carbonato de potasio (3M, 4.9 mL, 14.7 mmol), seguido por agitación a 100°C durante 14 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (30 mL) y acetato de etilo (40 mL), y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-100%), para producir el compuesto deseado como un aceite pardo (868 mg, rendimiento de 59%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.46 (9H, s), 3.95 (2H, m), 4.89 (1H, m), 6.25 (1H, t, J = 3.5 Hz), 6.60 (1H, dd, J = 2.0, 3.5 Hz), 7.31 (1H, brs), 7.40 (1H, dd, J = 2.0, 3.5 Hz).

(9d) 2-Bromo-5-[4-(1,2-dihidroxietil)-1,3-tiazol-2-il]-1H-pirrol-1-carboxilato de t-butilo

El 2-[4-(1,2-dihidroxietil)-1,3-tiazol-2-il]-1H-pirrol-1-carboxilato de t-butilo (868 mg, 2.80 mmol) sintetizado en el ejemplo (9c) se disolvió en tetrahidrofurano (30 mL) y se enfrió a 0°C. Se le agregó N-bromosuccinimida (498 mg, 2.80 mmol) y se agitó a temperatura ambiente durante 14 horas bajo una atmósfera de nitrógeno. Se le agregó agua (20 mL) y se extrajo con éter dietílico (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-30%), para producir el compuesto deseado como un aceite amarillo pálido (527 mg, rendimiento de 48%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.53 (9H, s), 3.92 (2H, m), 4.87 (1H, m), 6.31 (1H, d, J = 3.5 Hz), 6.54 (1H, d, J = 3.5 Hz), 7.23 (1H, brs).

(9e) 1-[2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol-4-il]etano-1,2-diol

El 2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-4,4,5,5-tetrametil-1,3,2-dioxaborolano (600 mg, 1.35 mmol) sintetizado en el ejemplo (1e), y el 2-bromo-5-[4-(1,2-dihidroxietil)-1,3-tiazol-2-il]-1H-pirrol-1-carboxilato de t-butilo (525 mg, 1.35 mmol) sintetizado en el ejemplo (9d), se disolvieron en un disolvente mixto de tolueno (30 mL) y etanol (10 mL) y se les agregó complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-

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diclorometano (55 mg, 0.067 mmol) y una solución acuosa de carbonato de potasio (3M, 0.90 mL, 2.70 mmol), seguido por agitación a 100°C durante 16 horas bajo una atmósfera de nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) y se extrajo con acetato de etilo (40 mL). La capa orgánica se lavó con salmuera saturada; subsiguientemente se secó sobre sulfato de magnesio anhidro y el disolvente se removió por destilación bajo presión reducida.

El residuo resultante se disolvió en diclorometano (10 mL) y se enfrió a 0°C. Se le agregó a gotas ácido trifluoroacético (10 mL) con agitación y bajo una atmósfera de nitrógeno. Después de agitar a temperatura ambiente durante 30 minutos, el disolvente se removió por destilación bajo presión reducida, seguido por dilución con acetato de etilo (30 mL); se le agregó una solución acuosa saturada de carbonato ácido de sodio (20 mL) y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-100%), para producir el compuesto deseado como un sólido amarillo pálido (331 mg, rendimiento de 45%).

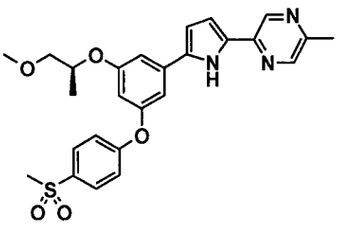
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 3.05 (3H, s), 3.40 (3H, s), 3.50 (1H, dd, J = 3.9, 10.2 Hz), 3.59 (1H, dd, J = 6.3, 10.2 Hz), 3.85-3.98 (2H, m), 4.58 (1H, m), 4.90 (1H, brs), 6.48-6.54 (2H, m), 6.67 (1H, brs), 6.89 (1H, brs), 7.07 (1H, brs), 7.12 (2H, d, J = 8.6 Hz), 7.88 (2H, d, J

= 8.6 Hz), 10.39 (1H, brs).

MS (ESI) m/z: 545.14151 $(M+H)^+$.

EJEMPLO 10

2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-5-metilpirazina



(10a) 2-(5-Metilpirazin-2-il)-1H-pirrol-1-carboxilato de t-butilo

Se disolvió 2-bromo-5-metilpirazina (260 mg, 1.50 mmol), disponible comercialmente, y ácido 1-(t-butoxicarbonil)pirrol-2-borónico (380 mg, 1.80 mmol), disponible comercialmente, en 1,2-dimetoxietano (20 mL), y se le agregó acetato de paladio (II) (17.0 mg, 0.076 mmol), trifenilfosfina (79.0 mg, 0.301 mmol) y una solución acuosa de carbonato de potasio (1.5M, 2.0 mL, 3.00 mmol), seguido por agitación a 100°C durante 19 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) y acetato de etilo (20 mL), y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución:

acetato de etilo/hexano = 5%-30%), para producir el compuesto deseado como un aceite amarillo (373 mg, rendimiento de 96%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.41 (9H, s), 2.59 (3H, s), 6.28 (1H, m), 6.48 (1H, m), 7.41 (1H, m), 8.45 (1H, brs), 8.56 (1H, brs).

(10b) 2-Bromo-5-(5-metilpirazin-2-il)-1H-pirrol-1-carboxilato de t-butilo

El 2-(5-metilpirazin-2-il)-1H-pirrol-1-carboxilato de t-butilo (373 mg, 1.44 mmol) sintetizado en el ejemplo (10a) se disolvió en tetrahidrofurano (20 mL) y se enfrió a 0°C. Se le agregó N-bromosuccinimida (256 mg, 1.44 mmol), y se agitó a temperatura ambiente durante 14 horas bajo una atmósfera de nitrógeno. Se le agregó agua (20 mL) y se extrajo con éter dietílico (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-30%), para producir el compuesto deseado como un aceite amarillo pálido (425 mg, rendimiento de 87%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.50 (9H, s), 2.57 (3H, s), 6.33 (1H, d, J = 3.5 Hz), 6.54 (1H, d, J = 3.5 Hz), 8.35 (1H, brs), 8.62 (1H, brd, J = 1.6 Hz).

(10c) 2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5-metilpirazina

El 2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-

fenil}-4,4,5,5-tetrametil-1,3,2-dioxaborolano (250 mg, 0.559 mmol) sintetizado en el ejemplo (1e), y el 2-bromo-5-(5-metilpirazin-2-il)-1H-pirrol-1-carboxilato de t-butilo (200 mg, 0.591 mmol) sintetizado en el ejemplo (10b), se disolvieron en un disolvente mixto de tolueno (20 mL) y etanol (8 mL) y se les agregó complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano (23 mg, 0.028 mmol) y una solución acuosa de carbonato de potasio (3M, 0.40 mL, 1.20 mmol), seguido por agitación a 100°C durante 7 horas bajo una atmósfera de nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) y se extrajo con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada; subsiguientemente se secó sobre sulfato de magnesio anhidro y el disolvente se removió por destilación bajo presión reducida.

El residuo resultante se disolvió en diclorometano (10 mL) y se enfrió a 0°C. Se le agregó a gotas ácido trifluoroacético (10 mL) con agitación y bajo una atmósfera de nitrógeno. Después de agitar a temperatura ambiente durante 30 minutos, el disolvente se removió por destilación bajo presión reducida, seguido por dilución con acetato de etilo (30 mL); se le agregó una solución acuosa saturada de carbonato ácido de sodio (20 mL) y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-60%), para producir el compuesto deseado

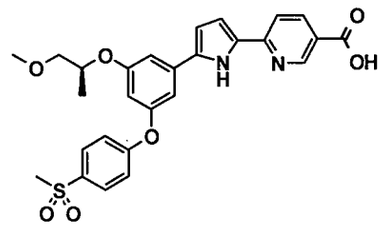
como un sólido amarillo (124 mg, rendimiento de 45%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 2.55 (3H, s), 3.07 (3H, s), 3.42 (3H, s), 3.52 (1H, dd, J = 3.9, 10.2 Hz), 3.61 (1H, dd, J = 5.9, 10.2 Hz), 4.58 (1H, m), 6.55 (1H, t, J = 2.0 Hz), 6.59 (1H, dd, J = 2.8, 3.9 Hz), 6.81 (1H, dd, J = 2.4, 3.9 Hz), 6.88 (1H, t, J = 2.0 Hz), 7.04 (1H, t, J = 2.0 Hz), 7.14 (2H, d, J = 9.0 Hz), 7.91 (2H, d, J = 9.0 Hz), 8.28 (1H, brs), 8.76 (1H, d, J = 1.6 Hz), 9.62 (1H, brs).

MS (ESI) m/z: 494.17511 $(M+H)^+$.

EJEMPLO 11

Acido 6-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il) nicotínico



(11a) 6-[1-(t-Butoxicarbonil)-1H-pirrol-2-il]nicotinato de metilo

Se disolvió 6-bromonicotinato de metilo (650 mg, 3.01 mmol), disponible comercialmente, y ácido 1-(t-butoxicarbonil)pirrol-2-borónico (960 mg, 4.34 mmol), disponible comercialmente, en 1,2-dimetoxietano (30 mL) y se les agregó acetato de paladio (II) (34.0 mg, 0.151 mmol), trifenilfosfina (158 mg, 0.602 mol) y una solución acuosa de carbonato de potasio (2M, 4.5 mL, 9.00 mmol), seguido por agitación a 100°C durante 15 horas bajo una

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atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) y acetato de etilo (30 mL), y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-20%), para producir el compuesto deseado como un sólido amarillo (835 mg, rendimiento de 92%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.39 (9H, s), 3.95 (3H, s), 6.26 (1H, t, J = 3.5 Hz), 6.53 (1H, m), 7.39 (1H, m), 7.47 (1H, dd, J = 0.8, 8.2 Hz), 8.27 (1H, dd, J = 2.4, 8.2 Hz), 9.19 (1H, dd, J = 0.8, 2.4 Hz).

(11b) 6-[5-Bromo-1-(t-butoxicarbonil)-1H-pirrol-2-il]nicotinato de metilo

El 6-[1-(t-butoxicarbonil)-1H-pirrol-2-il]nicotinato de metilo (835 mg, 2.76 mmol) sintetizado en el ejemplo (11a) se disolvió en tetrahidrofurano (30 mL) y se enfrió a 0°C. Se le agregó N-bromosuccinimida (492 mg, 2.76 mmol), y se agitó a temperatura ambiente durante 19 horas bajo una atmósfera de nitrógeno. Se le agregó agua (30 mL) y se extrajo con éter dietílico (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-30%), para producir el compuesto deseado

como un aceite amarillo pálido (712 mg, rendimiento de 68%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.54 (9H, s), 3.94 (3H, s), 6.30 (1H, d, J = 3.5 Hz), 6.62 (1H, d, J = 3.5 Hz), 7.51 (1H, brd, J = 8.6 Hz), 8.23 (1H, dd, J = 2.0, 8.6 Hz), 9.07 (1H, m).

(11c) 6-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)nicotinato de etilo

El 2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-4,4,5,5-tetrametil-1,3,2-dioxaborolano (398 mg, 0.890 mmol) sintetizado en el ejemplo (1e), y el 6-[5-bromo-1-(t-butoxicarbonil)-1H-pirrol-2-il]nicotinato de metilo (403 mg, 0.493 mmol) sintetizado en el ejemplo (11b), se disolvieron en un disolvente mixto de tolueno (20 mL) y etanol (8 mL) y se les agregó complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano (40 mg, 0.049 mmol) y una solución acuosa de carbonato de potasio (3M, 0.60 mL, 1.80 mmol), seguido por agitación a 100°C durante 20 horas bajo una atmósfera de nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) y se extrajo con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada; subsiguientemente se secó sobre sulfato de magnesio anhidro y el disolvente se removió por destilación bajo presión reducida.

El residuo resultante se disolvió en diclorometano (10 mL) y se enfrió a 0°C. Se le agregó a gotas ácido trifluoroacético (10 mL) con agitación y bajo una atmósfera de nitrógeno. Después de agitar a temperatura ambiente durante 30 minutos, el disolvente se removió por destilación bajo

presión reducida, seguido por dilución con acetato de etilo (30 mL); se le agregó una solución acuosa saturada de carbonato ácido de sodio (20 mL), y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-60%), para producir el compuesto deseado como un sólido amarillo (173 mg, rendimiento de 35%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 1.42 (3H, t, J = 7.0 Hz), 3.07 (3H, s), 3.42 (3H, s), 3.52 (1H, dd, J = 3.9, 10.2 Hz), 3.61 (1H, dd, J = 6.3, 10.2 Hz), 4.41 (2H, q, J = 7.0 Hz), 4.58 (1H, m), 6.55 (1H, t, J = 2.0 Hz), 6.60 (1H, dd, J = 2.0, 3.9 Hz), 6.85 (1H, dd, J = 2.0, 3.9 Hz), 7.06 (1H, t, J = 2.0 Hz), 7.14 (2H, d, J = 9.0 Hz), 7.57 (1H, dd, J = 0.8, 8.6 Hz), 7.90 (2H, d, J = 9.0 Hz), 8.21 (1H, dd, J = 2.0, 8.6 Hz), 9.06 (1H, dd, J = 0.8, 2.0 Hz), 9.94 (1H, brs), m).

MS (ESI) m/z: 551.18403 $(M+H)^+$.

(11d) Acido 6-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)nicotínico

El 6-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)nicotinato de etilo (42.0 mg, 0.076 mmol) sintetizado en el ejemplo (11c) se disolvió en etanol (4 mL). Se le agregó una solución acuosa de hidróxido de sodio (5M, 2 mL) y se agitó a 70°C durante 2 horas. Después de enfriar a temperatura ambiente , se le agregó ácido clorhídrico (2M, 5 mL) y

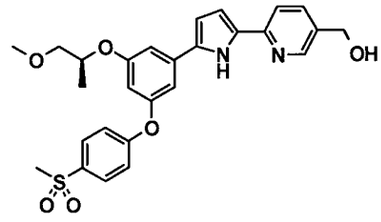
acetato de etilo (10 mL), y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida para producir el compuesto deseado como un sólido amarillo pálido (39.6 mg, rendimiento de 99%).

^{1}H-RMN (DMSO, 400 MHz): δ 1.26 (3H, d, J = 6.3 Hz), 3.20 (3H, s), 3.31 (3H, s), 3.45-3.55 (2H, m), 4.83 (1H, m), 6.58 (1H, brs), 6.80 (1H, brs), 7.01 (1H, brs), 7.22 (2H, d, J = 9.0 Hz), 7.31 (1H, brs), 7.45 (1H, brs), 7.88 (1H, d, J = 8.6 Hz), 7.93 (2H, d, J = 9.0 Hz), 8.18 (1H, J = 8.6 Hz), 9.00 (1H, s), 11.92 (1H, brs).

MS (ESI) m/z: 523.15247 $(M+H)^+$.

EJEMPLO 12

[6-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)piridin-3-il]metanol



Se suspendió hidruro de litio y aluminio (12 mg, 0.316 mmol) en tetrahidrofurano (2 mL). El 6-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)nicotinato de etilo (56.0 mg, 0.102 mmol) sintetizado en el ejemplo (11c) se disolvió en tetrahidrofurano (2 mL),

seguido por su adición gota a gota a 0°C bajo una atmósfera de nitrógeno. Después de agitar a 0°C durante 30 minutos, se le agregó lenta y secuencialmente agua (12 μL) y una solución acuosa de hidróxido de sodio (5M, 48 μL), gota a gota. Después de filtración a través de Celite, el disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-100%), para producir el compuesto deseado como un sólido amarillo pálido (33 mg, rendimiento de 64%).

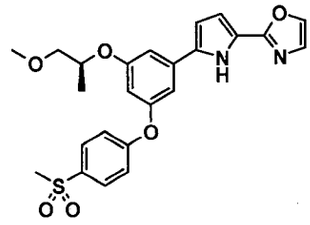
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 3.06 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 3.9, 10.2 Hz), 3.60 (1H, dd, J = 5.9, 10.2 Hz), 4.57 (1H, m), 4.69 (2H, brs), 6.52 (1H, brt, J = 2.0 Hz), 6.57 (1H, m), 6.74 (1H, m), 6.90 (1H, brt, J = 2.0 Hz), 7.06 (1H, brt, J = 2.0 Hz), 7.13 (2H, d, J = 8.6 Hz), 7.55 (1H, brd, J = 8.2 Hz), 7.69 (1H, brd, J = 8.2 Hz), 7.89 (2H, d, J = 8.6 Hz), 8.41 (1H, brs), 10.00 (1H, brs).

MS (ESI) m/z: 509.17476 $(M+H)^+$.

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EJEMPLO 13

2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-1,3-oxazol



(13a) 1-Bromo-3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]benceno

El 3-bromo-5-[4-(metilsulfonil)fenoxi]fenol (4.86 g, 14.2 mmol) sintetizado en el ejemplo (1c) se disolvió en tolueno (100 mL), y se le agregó (R)-(-)-1-metoxi-2-propanol (1.77 mL, 18.1 mmol) y trifenilfosfina (4.10 g, 15.6 mmol), seguido por enfriamiento a 0°C. Bajo una atmósfera de nitrógeno, se le agregó a gotas azodicarboxilato de dietilo (solución en tolueno al 40%, 7.75 mL, 17.1 mmol) durante 10 minutos, y se agitó a 0°C durante 30 minutos, seguido por aumento natural de la temperatura y agitación a temperatura ambiente durante la noche. Se le agregó agua (100 mL) y acetato de etilo (100 mL), y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-40%), para producir el compuesto deseado como un aceite amarillo pálido (5.06 g, rendimiento de 86%).

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^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.28 (3H, d, J = 6.3 Hz), 3.05 (3H, s), 3.37 (3H, s), 3.46 (1H, dd, J = 3.9, 10.2 Hz), 3.54 (1H, dd, J = 6.3, 10.2 Hz), 4.49 (1H, m), 6.56 (1H, d, J = 2.0 Hz), 6.77 (1H, d, J = 2.0 Hz), 6.93 (1H, d, J = 2.0 Hz), 7.10 (2H, d, J = 9.0 Hz), 7.89 (2H, d, J = 9.0 Hz).

(13b) 2-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-1-carboxilato de t-butilo

El 1-bromo-3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]benceno (2.38 g, 5.73 mmol) sintetizado en el ejemplo (13a), y ácido 1-(t-butoxicarbonil)pirrol-2-borónico (1.45 g, 6.87 mmol), se disolvieron en un disolvente mixto de 1,2-dimetoxietano (50 mL) y agua (6 mL) y se les agregó acetato de paladio (II) (40 mg, 0.178 mmol), trifenilfosfina (180 mg, 0.686 mmol) y carbonato de potasio (2.38 g, 17.2 mmol), seguido por agitación a 90°C durante 18 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (30 mL) y acetato de etilo (50 mL), y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-40%), para producir el compuesto deseado como un aceite pardo (2.71 g, rendimiento de 94%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 1.44 (9H, s), 3.05 (3H, s), 3.41 (3H, s), 3.49 (1H, dd, J = 4.3, 10.2 Hz), 3.58 (1H, dd, J =

6.3, 10.2 Hz), 4.53 (1H, m), 6.19-6.23 (2H, m), 6.61 (1H, t, J = 2.4 Hz), 6.63 (1H, dd, J = 1.6, 2.0 Hz), 6.79 (1H, dd, J = 1.6, 2.4 Hz), 7.15 (2H, d, J = 9.0 Hz), 7.31 (1H, dd, J = 2.0, 3.2 Hz), 7.88 (2H, d, J = 9.0 Hz).

(13c) 2-Bromo-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-1-carboxilato de t-butilo

El 2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-1-carboxilato de t-butilo (2.70 g, 5.38 mmol) sintetizado en el ejemplo (13b) se disolvió en tetrahidrofurano (50 mL), y se enfrió a 0°C. Después de agregar N-bromosuccinimida (960 mg, 5.38 mmol) con agitación bajo una atmósfera de nitrógeno, se agitó a temperatura ambiente durante 4 horas. Se le agregó agua (50 mL) y se extrajo con acetato de etilo (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-40%), para producir el compuesto deseado como un aceite pardo (2.93 g, rendimiento de 94%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J = 6.3 Hz), 1.42 (9H, s), 3.05 (3H, s), 3.39 (3H, s), 3.48 (1H, dd, J = 4.3, 10.2 Hz), 3.57 (1H, dd, J = 6.3, 10.2 Hz), 4.53 (1H, m), 6.21 (1H, d, J = 3.5 Hz), 6.30 (1H, d, J = 3.5 Hz), 6.57 (1H, t, J = 2.4 Hz), 6.61 (1H, d, J = 2.4 Hz), 6.75 (1H, d, J = 2.4 Hz), 7.12 (2H, d, J = 9.0 Hz), 7.89 (2H, d, J = 9.0 Hz).

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(13d) 2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-1,3-oxazol

El 2-bromo-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-1-carboxilato de t-butilo (102.9 mg, 0.177 mmol) sintetizado en el ejemplo (13c) se disolvió en tolueno (5 mL), y se le agregó 2-(tri-n-butilestanil)oxazol (133.7 mg, 0.373 mmol) y tetrakis(trifenilfosfina) paladio (20.5 mg, 0.0177 mmol), seguido por calentamiento a reflujo durante 18 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) y se extrajo con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 35%-55%), para producir 2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-5-(1,3-oxazol-2-il)-1H-pirrol-1-carboxilato de t-butilo.

Este se disolvió en diclorometano (1 mL) y se le agregó ácido trifluoroacético (2 mL), seguido por agitación a temperatura ambiente durante 2 horas; subsiguientemente el disolvente se removió por destilación bajo presión reducida. El residuo se diluyó con acetato de etilo (20 mL), se lavó con una solución acuosa saturada de carbonato ácido de sodio, seguido por lavado adicional con salmuera saturada, y se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente

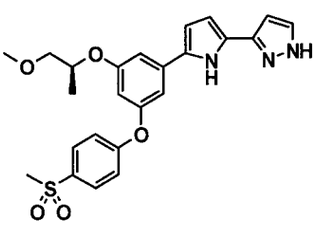
de elución: acetato de etilo/hexano = 65%), para producir el compuesto deseado como un sólido amarillo pálido (15.6 mg, rendimiento de 19%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ ppm 1.34 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 4.3, 10.2 Hz), 3.60 (1H, dd, J = 6.3, 10.2 Hz), 4.56-4.60 (1H, m), 6.55-6.57 (2H, m), 6.84-6.86 (2H, m), 7.02 (1H, t, J = 1.7 Hz), 7.13 (1H, s), 7.15 (2H, d, J = 8.6 Hz), 7.61 (1H, s), 7.91 (2H, d, J = 9.0 Hz), 9.52 (1H, brs).

MS (ESI) m/z: 469.14163 $(M+H)^+$.

EJEMPLO 14

3-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-1H-pirazol



El 2-bromo-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-1-carboxilato de t-butilo (375 mg, 0.446 mmol) sintetizado en el ejemplo (13c) y ácido 1H-pirazol-3-ilborónico (120 mg, 1.00 mmol), disponible comercialmente, se disolvió en un disolvente mixto de 1,2-dimetoxietano (20 mL) y agua (5 mL), se le agregó complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano (28 mg, 0.034 mmol) y una solución acuosa de carbonato de potasio (3M, 0.65 mL, 1.95

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mmol), y se agitó a 100°C durante 7 días bajo una atmósfera de nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente, se le agregó agua (10 mL) y se extrajo con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-80%), para producir el compuesto deseado como un sólido amarillo pálido (106 mg, rendimiento de 35%).

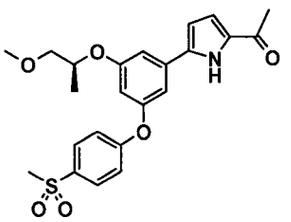
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 3.9, 10.2 Hz), 3.60 (1H, dd, J = 6.3, 10.2 Hz), 4.57 (1H, m), 6.549-6.55 (4H, m), 6.83 (1H, brs), 7.00 (1H, brs), 7.14 (2H, d, J = 9.0 Hz), 7.57 (1H, d, J = 2.4 Hz), 7.90 (2H, d, J = 9.0 Hz), 9.30 (1H, brs).

MS (ESI) m/z: 468.15954 $(M+H)^+$.

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EJEMPLO 15

1-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)etanona



(15a) 1-(5-Bromo-1H-pirrol-2-il)etanona

Se disolvió 2-acetilpirrol (2.00 g, 18.3 mmol) en un disolvente mixto de tetrahidrofurano (100 mL) y metanol (50 mL), y se le agregó N-bromosuccinimida (3.26 g, 18.3 mmol) con agitación a temperatura ambiente, bajo una atmósfera de nitrógeno. Después de agitar 1 hora, el disolvente se removió por destilación bajo presión reducida. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (200 mL), y se extrajo con acetato de etilo (300 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-20%), para producir el compuesto deseado como un sólido blanco (770 mg, rendimiento de 22%).

^{1}H-RMN ($CDCl_3$, 400 MHz): 2.40 (3H, s), 6.24 (1H, dd, J = 2.4, 4.0 Hz), 6.80 (1H, dd, J = 2.9, 4.0 Hz), 9.37 (1H, brs).

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(15b) 2-Acetil-5-bromo-1H-pirrol-1-carboxilato de t-butilo

La 1-(5-bromo-1H-pirrol-2-il)etanona (770 mg, 4.1 mmol) sintetizada en el ejemplo (15a) se disolvió en diclorometano (30 mL), y se le agregó trietilamina (0.57 mL, 4.1 mmol) y 4-dimetilaminopiridina (500 mg, 4.1 mmol). Se disolvió dicarbonato de di-t-butilo (930 mg, 4.3 mmol) en diclorometano (10 mL) y la solución se le agregó, seguido por agitación a temperatura ambiente durante 3 horas bajo una atmósfera de nitrógeno. La solución de reacción se diluyó con diclorometano (200 mL), se lavó con ácido clorhídrico 1N, solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-20%), para producir el producto deseado como un sólido blanco (538 mg, rendimiento de 46%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.64 (9H, s), 2.40 (3H, s), 6.24 (1H, d, J = 3.9 Hz), 6.82 (1H, d, J = 3.9 Hz).

(15c) 1-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)etanona

El 2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-4,4,5,5-tetrametil-1,3,2-dioxaborolano (146 mg, 0.33 mmol) sintetizado en el ejemplo (1e), y el 2-acetil-5-bromo-1H-pirrol-1-carboxilato de t-butilo (141 mg, 0.49 mmol) sintetizado en el ejemplo (15b), se disolvieron en un disolvente mixto de tolueno (3 mL) y etanol (1.3 mL) y se les agregó complejo

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de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano (13 mg, 0.016 mmol) y una solución acuosa de carbonato de potasio (2M, 0.41 mL, 0.83 mmol), y se agitó a 100°C durante 1.5 horas bajo una atmósfera de nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) y se extrajo con acetato de etilo (60 mL). La capa orgánica se lavó con salmuera saturada; subsiguientemente se secó sobre sulfato de magnesio anhidro y el disolvente se removió por destilación bajo presión reducida.

El residuo resultante se disolvió en diclorometano (2 mL) y se le agregó ácido trifluoroacético (1 mL, 13.0 mmol), seguido por agitación a temperatura ambiente durante 1 hora bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida, se le agregó una solución acuosa saturada de carbonato ácido de sodio (30 mL), y se extrajo con acetato de etilo (70 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-50%), para producir el compuesto deseado como un sólido amarillo pálido (95 mg, rendimiento de 66%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz,), 2.44 (3H, s), 3.07 (3H, s), 3.41 (3H, s), 3.51 (1H, dd, J = 4.0, 10.2 Hz), 3.59 (1H, dd, J = 6.2, 10.2 Hz), 4.56-4.59 (1H, m), 6.53 (1H, dd, J = 2.9, 3.5 Hz), 6.62 (1H, t, J = 2.0 Hz), 6.86 (1H, t, J = 1.6 Hz), 6.93 (1H, dd, J = 2.5, 3.9 Hz), 7.02 (1H, s),

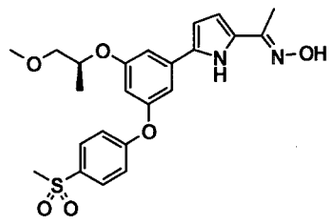
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7.14 (2H, d, J = 8.9 Hz), 7.91 (2H, d, J = 8.8 Hz), 9.64 (1H, brs).

MS (ESI) m/z: 444.14808 $(M+H)^+$.

EJEMPLO 16

Oxima de (1E)-1-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)etanona



La 1-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)etanona (117 mg, 0.26 mmol) sintetizada en el ejemplo (15c) se disolvió en metanol (6 mL), y se le agregó clorhidrato de hidroxilamina (37 mg, 0.53 mmol) y acetato de sodio (26 mg, 0.32 mmol), seguido por calentamiento a reflujo durante 6 horas bajo una atmósfera de nitrógeno. La solución de reacción se diluyó con diclorometano (60 mL), se lavó con agua y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-50%), para producir el producto deseado como un sólido blanco (50 mg, rendimiento de 41%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.2 Hz), 2.19 (3H,

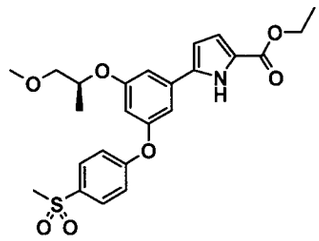
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s), 3.06 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 4.1,10.2 Hz), 3.58 (1H, dd, J = 6.1, 10.2 Hz), 4.52-4.57 (1H, m), 6.47 (2H, d, J = 2.7 Hz), 6.53 (1H, t, J = 2.0 Hz), 6.79 (1H, t, J = 1.5 Hz), 6.89 (1H, brs), 6.95 (1H, t, J = 1.8 Hz), 7.13 (2H, d, J = 8.8 Hz), 7.90 (2H, d, J = 8.8 Hz), 9.03 (1H, brs)

MS (ESI) m/z: 459.15898 $(M+H)^+$.

EJEMPLO 17

5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxilato de etilo



(17a) 5-Bromo-1H-pirrol-2-carboxilato de etilo

Se disolvió 1H-pirrol-2-carboxilato de etilo (5.10 g, 30.7 mmol), disponible comercialmente, en un disolvente mixto de tetrahidrofurano (120 mL) y metanol (60 mL), y se enfrió a 0°C. Se le agregó N-bromosuccinimida (6.52 g, 30.7 mmol), y se agitó a temperatura ambiente durante 18 horas bajo una atmósfera de nitrógeno. Se le agregó agua (150 mL) y acetato de etilo (200 mL) y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente

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de elución: acetato de etilo/hexano = 5%-30%), para producir el compuesto deseado como un sólido blanco (3.20 g, rendimiento de 40%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.36 (3H, t, J = 7.1 Hz), 4.32 (2H, q, J = 7.1 Hz), 6.21 (1H, dd, J = 2.7, 3.9 Hz), 6.82 (1H, dd, J = 2.7, 3.9 Hz), 9.21 (1H, brs).

(17b) 5-Bromo-1H-pirrol-1,2-dicarboxilato de 1-t-butilo-2-etilo

El 5-bromo-1H-pirrol-2-carboxilato de etilo (3.20 g, 14.7 mmol) sintetizado en el ejemplo (17a) se disolvió en diclorometano (100 mL), se le agregó dicarbonato de di-t-butilo (3.85 g, 17.6 mmol), trietilamina (2.70 mL, 19.4 mmol) y 4-dimetilaminopiridina (180 mg, 1.47 mmol), y se agitó a temperatura ambiente durante 1 hora bajo una atmósfera de nitrógeno. Se le agregó agua (100 mL) y se extrajo con diclorometano (100 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-20%), para producir el compuesto deseado como un aceite incoloro (4.37 g, rendimiento de 94%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, t, J = 7.0 Hz), 1.63 (9H, s), 4.30 (2H, q, J = 7.0 Hz), 6.23 (1H, d, J = 3.9 Hz), 6.83 (1H, d, J = 3.9 Hz).

(17c) 5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-1,2-dicarboxilato de 1-t-butilo-2-etilo

El 2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-

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fenil}-4,4,5,5-tetrametil-1,3,2-dioxaborolano (8.73 g, 18.9 mmol) sintetizado en el ejemplo (1e), y el 5-bromo-1H-pirrol-1,2-dicarboxilato de 1-t-butilo-2-etilo (8.37 g, 26.3 mmol) sintetizado en el ejemplo (17b), se disolvieron en un disolvente mixto de tolueno (180 mL) y etanol (77 mL), y se le agregó complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano (770 mg, 0.94 mmol) y una solución acuosa de carbonato de potasio (2M, 23.7 mL, 47.2 mmol), y se agitó a 100°C durante 1 hora bajo una atmósfera de nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente, se le agregó agua (200 mL) y se extrajo con acetato de etilo (400 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-50%), para producir el compuesto deseado como un aceite amarillo pálido (9.44 g, rendimiento de 84%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J = 6.3 Hz), 1.35 (3H, t, J = 7.0 Hz), 1.46 (9H, s), 3.05 (3H, s), 3.39 (3H, s), 3.48 (1H, dd, J = 4.3, 10.2 Hz), 3.57 (1H, dd, J = 5.9, 10.2 Hz), 4.32 (2H, q, J = 7.0 Hz), 4.53 (1H, m), 6.22 (1H, d, J = 3.9 Hz), 6.65 (1H, m), 6.73 (1H, m), 6.88 (1H, m), 6.89 (1H, d, J = 3.9 Hz), 7.12 (1H, d, J = . 9.0 Hz), 7.89 (2H, d, J = 9.0 Hz).

(17d) 5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-carboxilato de etilo

El 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-

fenil}-1H-pirrol-1,2-dicarboxilato de 1-t-butilo-2-etilo (9.44 g, 16.5 mmol) sintetizado en el ejemplo (17c) se disolvió en diclorometano (90 mL) y se enfrió a 0°C. Se le agregó a gotas ácido trifluoroacético (45 mL) con agitación y bajo una atmósfera de nitrógeno, y se agitó a temperatura ambiente durante 1 hora. El disolvente se removió por destilación bajo presión reducida, seguido por dilución con acetato de etilo (300 mL); se le agregó una solución acuosa saturada de carbonato ácido de sodio (200 mL) y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-50%), para producir el compuesto deseado como un sólido amarillo pálido (6.34 g, rendimiento de 81%).

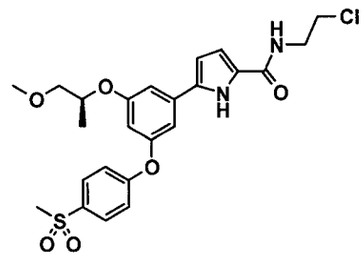
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 1.37 (2H, t, J = 7.0 Hz), 3.07 (3H, s), 3.41 (3H, s), 3.51 (1H, dd, J = 3.9, 10.2 Hz), 3.60 (1H, dd, J = 6.3, 10.2 Hz), 4.34 (2H, q, J = 7.0 Hz), 4.58 (1H, m), 6.51 (1H, dd, J = 2.5, 4.0 Hz), 6.58 (1H, m), 6.86 (1H, m), 6.93 (1H, dd, J = 2.5, 4.0 Hz), 7.01 (1H, m), 7.13 (2H, d, J = 8.8 Hz), 7.91 (2H, d, J = 8.8 Hz), 9.41 (1H, brs).

MS (ESI) m/z: 474.16048 $(M+H)^+$.

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EJEMPLO 18

N-(2-Cloroetil)-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida



(18a) Acido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-carboxílico

El 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-carboxilato de etilo (4.36 g, 9.2 mmol) sintetizado en el ejemplo (17d) se disolvió en etanol (100 mL), y se le agregó una solución acuosa de hidróxido de sodio 4N (23 mL, 92 mmol), seguido por calentamiento a reflujo durante 1 hora bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó ácido clorhídrico 2N (45 mL) para neutralizarla, y el disolvente se removió por destilación bajo presión reducida. La solución se acidificó con ácido clorhídrico 1N y se extrajo con acetato de etilo (300 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida para producir el producto deseado como un sólido blanco (4.06 g, rendimiento de 99%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz,), 3.07 (3H,

s), 3.46 (3H, s), 3.55 (1H, dd, J = 4.2, 10.4 Hz), 3.66 (1H, dd, J = 6.3, 10.5 Hz), 4.70-4.75 (1H, m), 6.53 (1H, dd, J = 2.6, 3.9 Hz), 6.59 (1H, t, J = 2.0 Hz), 6.91 (1H, t, J = 1.6 Hz,), 7.04 (1H, dd, J = 2.3, 3.9 Hz), 7.25 (1H, m), 7.14 (2H, d, J = 8.9 Hz), 7.91 (2H, d, J = 8.8 Hz), 10.13 (1H, brs).

(18b) N-(2-Cloroetil)-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-carboxílico (150 mg, 0.34 mmol) sintetizado en el ejemplo (18a), clorhidrato de 2-cloroetilamina (78 mg, 0.68 mmol) y 4-dimetilaminopiridina (41 mg, 0.34 mmol), se disolvieron en diclorometano (15 mL) y se les agregó WSCI·HCl (71 mg, 0.37 mmol) a temperatura ambiente, y se agitó durante 2 horas bajo una atmósfera de nitrógeno. La solución de reacción se diluyó con diclorometano (150 mL), se lavó con ácido clorhídrico 1N, solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-60%), para producir el producto deseado como un sólido blanco (105 mg, rendimiento de 62%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 4.0, 10.3 Hz), 3.59 (1H, dd, J = 6.1,10.4 Hz), 3.70 (2H, t, J = 5.4 Hz), 3.77 (2H, t, J = 5.4 Hz), 4.55-4.59 (1H, m), 6.26-6.29 (1H, brm), 6.50 (1H, dd, J = 2.9, 3.9 Hz), 6.58 (1H, t, J = 2.2 Hz), 6.63 (1H, dd,

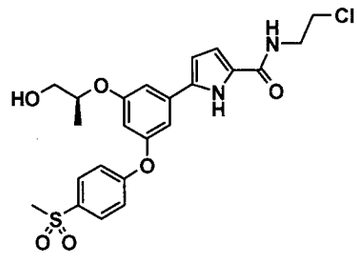
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J = 2.5, 3.8 Hz), 6.83 (1H, t, J = 1.7 Hz), 6.99 (1H, t, J = 2.0 Hz), 7.14 (2H, d, J = 8.8 Hz), 7.91 (2H, d, J = 8.8 Hz), 9.52 (1H, brs).

MS (ESI) m/z: 507.13566 $(M+H)^+$.

EJEMPLO 19

N-(2-Cloroetil)-5-{3-[(1S)-2-hidroxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida



La N-(2-cloroetil)-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida (88 mg, 0.17 mmol) sintetizada en el ejemplo (18b) se disolvió en diclorometano (5 mL) y se enfrió a -78°C, y se le agregó una solución de tribromuro de boro en diclorometano 1.0 mol/L (0.19 mL, 0.19 mmol) bajo una atmósfera de nitrógeno. La temperatura se aumentó naturalmente y la solución se agitó a temperatura ambiente durante 30 minutos; subsiguientemente se le agregó una solución acuosa saturada de carbonato ácido de sodio para neutralizar la solución de reacción y se extrajo con diclorometano (60 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo

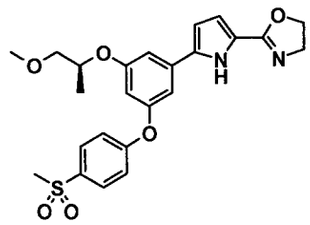
resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-80%), para producir el producto deseado como un sólido blanco (55 mg, rendimiento de 64%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.31 (3H, d, J = 6.3 Hz), 2.1 (1H, brm), 3.08 (3H, s), 3.70 (2H, t, J = 5.2 Hz), 3.76-3.80 (4H, m), 4.52-4.56 (1H, m), 6.27-6.30 (1H, brm), 6.50 (1H, dd, J = 2.9, 3.8 Hz), 6.57 (1H, t, J = 2.1 Hz), 6.64 (1H, dd, J = 2.3, 3.9 Hz), 6.85 (1H, t, J = 1.7 Hz), 6.98 (1H, t, J = 1.8 Hz), 7.14 (2H, d, J = 8.8 Hz), 7.91 (2H, d, J = 8.8 Hz), 9.56 (1H, brs).

MS (FAB) m/z: 493 $(M+H)^+$.

EJEMPLO 20

2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol



La N-(2-cloroetil)-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida (177 mg, 0.349 mmol) sintetizada en el ejemplo (18b) se disolvió en tetrahidrofurano (5 mL) y se enfrió a 0°C. Se le agregó hidruro de sodio (40 mg, 0.917 mmol) y la temperatura se elevó a temperatura ambiente, seguido por agitación durante 19 horas. Después de que la solución de reacción se enfrió a 0°C, se le

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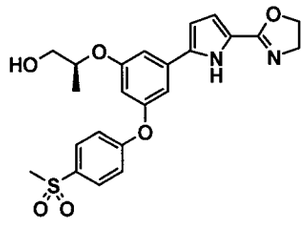
agregó agua (5 mL) y se extrajo con acetato de etilo (10 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-100%), para producir el compuesto deseado como un sólido blanco (118 mg, rendimiento de 72%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 3.9, 10.2 Hz), 3.59 (1H, dd, J = 6.3, 10.2 Hz), 3.98 (2H, t, J = 9.4 Hz), 4.40 (2H, t, J = 9.4 Hz), 4.56 (1H, m), 6.50 (1H, d, J = 3.9 Hz), 6.56 (1H, brt, J = 2.0 Hz), 6.75 (1H, d, J = 3.9 Hz), 6.83 (1H, brt, J = 2.0 Hz), 7.00 (1H, brt, J = 2.0 Hz), 7.13 (2H, d, J = 9.0 Hz), 7.90 (2H, d, J = 9.0 Hz).

MS (ESI) m/z: 471.16050 $(M+H)^+$.

EJEMPLO 21

(2S)-2-{3-[5-(4,5-Dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[4-(metilsulfonil)fenoxi]fenoxi}propan-1-ol



El 2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-

fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol (3.17 g, 6.74 mmol) sintetizado en el ejemplo 20 se disolvió en diclorometano (100 mL) y se enfrió a -78°C; se le agregó una solución de tribromuro de boro en diclorometano 1.0 mol/l (7.07 mL, 7.07 mmol) bajo una atmósfera de nitrógeno. La temperatura se elevó naturalmente, seguido por agitación a temperatura ambiente durante 30 minutos; subsiguientemente se le agregó una solución acuosa saturada de carbonato ácido de sodio para neutralizar la solución de reacción, y se extrajo con diclorometano (200 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se lavó con acetato de etilo (100 mL) y etanol (50 mL), para producir el producto deseado como un sólido blanco (1.96 g, rendimiento de 64%).

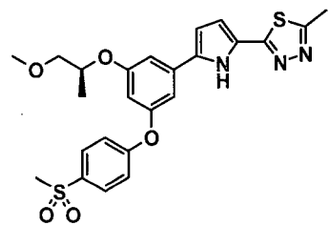
^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.29 (3H, d, J = 6.3 Hz), 3.06 (3H, s), 3.79 (2H, d, J = 5.9 Hz), 4.00 (2H, t, J = 9.3 Hz), 4.42 (2H, t, J = 9.4 Hz), 4.58-4.63 (1H, m), 6.40 (1H, t, J = 2.2 Hz), 6.47 (1H, d, J = 3.9 Hz), 6.75 (1H, d, J = 3.8 Hz), 6.79 (1H, t, J = 1.7 Hz), 6.94 (1H, t, J = 1.8 Hz), 7.09 (2H, d, J = 8.8 Hz), 7.88 (2H, d, J = 8.8 Hz).

MS (ESI) m/z: 457.14357 $(M+H)^+$.

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EJEMPLO 22

2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-5-metil-1,3,4-tiadiazol



(22a) N'-Acetil-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carbohidrazida

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-carboxílico (114.5 mg, 0.257 mmol) sintetizado en el ejemplo (18a) se disolvió en N,N-dimetilformamida (4 mL), y se le agregó acetohidrazida (39.4 mg, 0.531 mmol), HATU (150.1 mg, 0.395 mol) y N,N-diisopropiletilamina (70 μL, 0.40 mmol), y se agitó a temperatura ambiente durante 20 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó agua (20 mL) y se extrajo con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-100%), para producir el compuesto deseado como un sólido blanco (73.0 mg, rendimiento de 57%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.29 (3H, d, J = 6.3 Hz), 1.99 (3H,

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s), 3.06 (3H, s), 3.40 (3H, s), 3.49 (1H, dd, J = 3.9, 10.2 Hz), 3.57 (1H, dd, J = 6.3, 10.2 Hz), 4.58-4.63 (1H, m), 6.46 (1H, dd, J = 2.7, 3.9 Hz), 6.53 (1H, s), 6.78 (1H, dd, J = 2.4, 3.9 Hz), 6.86 (1H, s), 7.10 (2H, d, J = 9.0 Hz), 7.13 (1H, s), 7.88 (2H, d, J = 8.6 Hz), 8.63 (1H, brs), 9.08 (1H, brs), 10.20 (1H, brs).

MS (ESI) m/z: 524.14725 $(M+Na)^+$.

(22b) 2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5-metil-1,3,4-tiadiazol

La N'-acetil-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-carbohidrazida (58.1 mg, 0.116 mmol) sintetizada en el ejemplo (22a) se disolvió en tolueno (4 mL), se le agregó 2,4-disulfuro de 2,4-bis-(4-metoxifenil)-1,3-ditia-2,4-difosfoetano (63.5 mg, 0.157 mmol) y piridina (20 μL, 0.25 mmol), y se agitó a 90°C durante 5 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) a la solución de reacción, y se extrajo con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 40%-80%), para producir el compuesto deseado como un sólido amarillo pálido (50.6 mg, rendimiento de 87%).

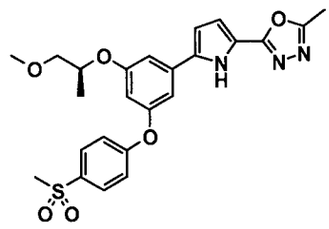
^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.34 (3H, d, J = 6.4 Hz), 2.77 (3H, s), 3.07 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 4.4, 10.3 Hz), 3.60 (1H, dd, J = 6.4, 10.3 Hz), 4.57-4.61 (1H, m), 6.55 (1H, t, J = 3.4 Hz), 6.58 (1H, t, J = 1.9

Hz), 6.67 (1H, dd, J = 2.4, 3.9 Hz), 6.87 (1H, t, J = 1.7 Hz), 7.03 (1H, s), 7.14 (2H, d, J = 8.8 Hz), 7.91 (2H, d, J = 8.8 Hz), 9.74 (1H, brs).

MS (ESI) m/z: 500.12981 $(M+H)^+$.

EJEMPLO 23)

2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-5-metil-1,3,4-oxadiazol



La N'-acetil-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-carbohidrazida (86.5 mg, 0.172 mmol) sintetizada en el ejemplo (22a) se disolvió en acetonitrilo (5 mL), y se le agregó hidróxido de (metoxicarbonilsulfamoil)trietilamonio (60.7 mg, 0.258 mmol) y trietilamina (36 μL, 0.26 mmol), y se agitó a 80°C durante 3 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) a la solución de reacción, y se extrajo con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-75%), para producir el compuesto deseado como un

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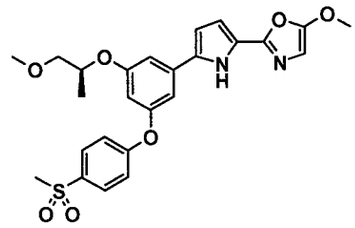
sólido blanco (49.1 mg, rendimiento de 59%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 2.58 (3H, s), 3.08 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 3.9, 10.2 Hz), 3.60 (1H, dd, J = 6.3, 10.2 Hz), 4.55-4.61 (1H, m), 6.57-6.60 (2H, m), 6.85-6.87 (2H, m), 7.02 (1H, s), 7.14 (2H, d, J = 8.6 Hz), 7.91 (2H, d, J = 8.6 Hz), 9.65 (1H, brs).

MS (ESI) m/z: 484.15505 $(M+H)^+$.

EJEMPLO 24

5-Metoxi-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-1,3-oxazol



(24a) N-[(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)carbonil]glicinato de metilo

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-carboxílico (275 mg, 0.617 mmol) sintetizado en el ejemplo (18a) se disolvió en diclorometano (10 mL), y se le agregó clorhidrato del éster metílico de glicina (120 mg, 0.956 mmol), WSCI·HCl (180 mg, 0.939 mmol) y 4-dimetilaminopiridina (150 mg, 1.23 mmol), seguido por agitación a temperatura ambiente durante 2 horas bajo una atmósfera de nitrógeno. Se le agregó ácido clorhídrico 1N (10 mL) y la solución se separó con diclorometano

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(15 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-60%), para producir el producto deseado como un sólido blanco (270 mg, rendimiento de 85%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 3.9, 10.2 Hz), 3.59 (1H, dd, J = 6.3, 10.2 Hz), 3.78 (3H, s), 4.56 (1H, m), 6.48 (1H, brt, J = 3.9 Hz), 6.54-6.58 (2H, m), 6.69 (1H, dd, J = 2.4, 3.9 Hz), 6.89 (1H, t, J = 2.0 Hz), 7.02 (1H, t, J = 2.0 Hz), 7.12 (2H, d, J = 8.6 Hz), 7.89 (2H, d, J = 8.9 Hz), 10.11 (1H, brs).

(24b) 5-Metoxi-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-1,3-oxazol

El N-[(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)carbonil]glicinato de metilo (270 mg, 0.523 mmol) sintetizado en el ejemplo (24a) se disolvió en acetonitrilo (10 mL), y se le agregó trifenilfosfina (410 mg, 1.56 mmol), trietilamina (0.22 mL, 1.58 mmol) y tetracloruro de carbono (0.33 mL, 3.42 mmol), seguido por agitación a temperatura ambiente durante 15 horas bajo una atmósfera de nitrógeno. Se le agregó agua (10 mL) y la solución se separó con acetato de etilo (15 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en

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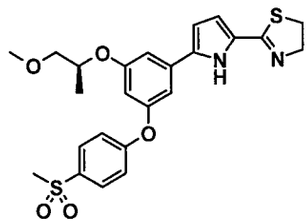
columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-40%), para producir el producto deseado como un sólido anaranjado (162 mg, rendimiento de 62%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 3.9, 10.2 Hz), 3.59 (1H, dd, J = 6.3, 10.2 Hz), 3.92 (3H, s), 4.55 (1H, m), 6.08 (1H, s), 6.51-6.55 (2H, m), 6.70 (1H, dd, J = 2.4, 3.9 Hz), 6.83 (1H, t, J = 2.0 Hz), 6.99 (1H, t, J = 2.0 Hz), 7.12 (2H, d, J = 9.0 Hz), 7.90 (2H, d, J = 9.0 Hz), 9.77 (1H, brs).

MS (ESI) m/z: 499.15601 $(M+H)^+$.

EJEMPLO 25

2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-tiazol



(25a) 2-(Tritiltio)etanoamina

Se disolvió ácido clorhídrico 2-aminoetanotiol (5.16 g, 45.4 mmol) en diclorometano (80 mL), y se le agregó ácido trifluoroacético (7.0 mL, 90.8 mmol) y cloruro de trifenilmetilo (13.29 g, 47.7 mmol), seguido por agitación a temperatura ambiente durante 1 hora. Se le agregó una solución acuosa de hidróxido de sodio 1N (150 mL) y se extrajo con diclorometano (500 mL). La

capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y al residuo resultante se le agregó metanol (100 mL); el subproducto depositado se removió por filtración. Se le agregó ácido clorhídrico 1N (300 mL) para hacer ácida la solución, y el depósito se filtró. Después de que el subproducto se lavó con diclorometano (50 mL) para removerlo, la solución se hizo alcalina con una solución acuosa de hidróxido de sodio 1N, y se extrajo con diclorometano (600 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida para producir el producto deseado como un sólido blanco (8.77 g, rendimiento de 60%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.33 (2H, t, J = 6.6 Hz), 2.59 (2H, t, J = 6.6 Hz), 7.19-7.23 (3H, m), 7.26-7.30 (6H, m), 7.41-7.44 (6H, m).

(25b) 5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-N-[2-(tritiltio)etil]-1H-pirrol-2-carboxamida

Al ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxílico (940 mg, 2.1 mmol) sintetizado en el ejemplo (18a), se le agregó la 2-(tritiltio)etanoamina (1.01 g, 3.17 mmol) sintetizada en el ejemplo (25a) y 4-dimetilaminopiridina (13 mg, 0.1 mmol), seguido por disolución en diclorometano (50 mL); subsiguientemente se le agregó WSCI·HCl (445 mg, 2.3 mmol) a temperatura ambiente y se agitó durante 1 hora bajo una atmósfera de nitrógeno. La

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solución de reacción se diluyó con diclorometano (150 mL), se lavó con ácido clorhídrico 1N, solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-55%), para producir el producto deseado como un sólido blanco (1.08 g, rendimiento de 69%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 2.50 (2H, t, J = 6.5 Hz), 3.07 (3H, s), 3.27 (2H, dt, J = 5.9, 6.2 Hz), 3.42 (3H, s), 3.51 (1H, dd, J = 4.0, 10.4 Hz), 3.59 (1H, dd, J = 5.9, 10.4 Hz), 4.55-4.59 (1H, m), 5.99 (1H, brm), 6.48 (1H, dd, J = 2.8, 3.9 Hz), 6.53 (1H, dd, J = 2.5, 3.9 Hz), 6.57 (1H, t, J = 2.3 Hz), 6.81 (1H, t, J = 2.2 Hz), 6.98 (1H, t, J = 2.1 Hz), 7.14 (2H, d, J = 8.9 Hz), 7.19-7.30 (9H, m), 7.42 (6H, dd, J = 1.6, 7.3 Hz), 7.91 (2H, d, J = 8.9 Hz), 9.41 (1H, brs).

(25c) 2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-tiazol

Se disolvió óxido de trifenilfosfina (2.41 g, 8.7 mmol) en diclorometano (20 mL) y se le agregó lentamente, gota a gota, anhídrido trifluorometanosulfónico (0.73 mL, 4.3 mmol), a 0°C. Después de agitar 10 minutos se le agregó una solución de 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-N-[2-(tritiltio)etil]-1H-pirrol-2-carboxamida, sintetizada en el ejemplo (25b), en diclorometano (15 mL). Después de que la solución de reacción se agitó a temperatura ambiente durante 30 minutos, el disolvente

1125

se removió por destilación bajo presión reducida, se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con acetato de etilo (200 mL). La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-80%), para producir el producto deseado como un sólido blanco (636 mg, rendimiento de 90%).

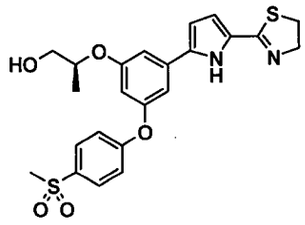
^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.39 (2H, t, J = 8.4 Hz), 3.41 (3H, s), 3.50 (1H, dd, J = 3.9, 10.3 Hz), 3.59 (1H, dd, J = 5.9, 10.3 Hz), 4.33 (2H, t, J = 8.7 Hz), 4.55-4.59 (1H, m), 6.50 (1H, d, J = 3.9 Hz), 6.56 (1H, t, J = 2.5 Hz), 6.64 (1H, d, J = 3.9 Hz), 6.83 (1H, t, J = 2.0 Hz), 7.00 (1H, t, J = 2.4 Hz), 7.13 (2H, d, J = 8.8 Hz), 7.90 (2H, d, J = 8.8 Hz).

MS (ESI) m/z: 487.13595 $(M+H)^+$.

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EJEMPLO 26

(2S)-2-{3-[5-(4,5-Dihidro-1,3-tiazol-2-il)-1H-pirrol-2-il]-5-[4-(metilsulfonil)fenoxi]fenoxi}propan-1-ol



El 2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-tiazol (88 mg, 0.18 mmol) sintetizado en el ejemplo (25c), se disolvió en diclorometano (5 mL) y se enfrió a -78°C; se le agregó una solución de tribromuro de boro en diclorometano 1.0 mol/l (0.22 mL, 0.22 mmol) bajo una atmósfera de nitrógeno. Después de que la temperatura se elevó naturalmente y la solución se agitó a temperatura ambiente durante 1 hora, subsiguientemente se le agregó una solución acuosa saturada de carbonato ácido de sodio para neutralizar la solución de reacción, seguido por extracción con diclorometano (60 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 40%-100%), para producir el producto deseado como un sólido amarillo pálido (46 mg, rendimiento de 54%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.29 (3H, d, J = 6.4 Hz), 3.27 (3H,

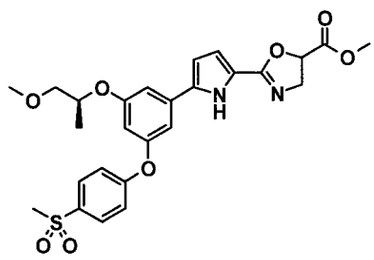
1127

s), 3.40 (2H, t, J = 8.1 Hz), 3.76-3.78 (2H, m), 4.33 (2H, t, J = 8.2 Hz), 4.55-4.59 (1H, m), 6.47 (1H, d, J = 2.4 Hz), 6.49 (1H, d, J = 3.7 Hz), 6.65 (1H, d, J = 3.7 Hz), 6.82 (1H, s), 6.96 (1H, s), 7.11 (2H, d, J = 8.7 Hz), 7.90 (2H, d, J = 8.7 Hz).

MS (ESI) m/z: 473.12049 $(M+H)^+$.

EJEMPLO 27

2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol-5-carboxilato de metilo



(27a) 2-Hidroxi-3-{[(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)carbonil]amino}propanoato de metilo

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-carboxílico (420 mg, 0.943 mmol) sintetizado en el ejemplo (18a) se disolvió en diclorometano (10 mL), y se le agregó clorhidrato del éster metílico de DL-isoserina (300 mg, 1.93 mmol), WSCI·HCl (270 mg, 1.41 mmol) y 4-dimetilaminopiridina (230 mg, 1.88 mmol), seguido por agitación a temperatura ambiente durante 1.5 horas bajo una atmósfera de nitrógeno. Se le agregó ácido clorhídrico 1N (10 mL) y la solución se separó

1128

con diclorometano (15 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-80%), para producir el producto deseado como un sólido blanco (400 mg, rendimiento de 78%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 3.9, 10.2 Hz), 3.60 (1H, dd, J = 6.3, 10.2 Hz), 3.72-3.85 (2H, m), 3.80 (3H, s), 4.38 (1H, brt, J = 4.7 Hz), 4.58 (1H, m), 6.43 (1H, brs), 6.47 (1H, m), 6.56 (1H, t, J = 2.0 Hz), 6.63 (1H, dd, J = 2.4, 3.9 Hz), 6.86 (1H, t, J = 2.0 Hz), 7.01 (1H, t, J = 2.0 Hz), 7.12 (2H, d, J = 9.0 Hz), 7.90 (2H, d, J = 9.0 Hz), 9.85 (1H, brs).

(27b) 2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol-5-carboxilato de metilo

El 2-hidroxi-3-{[(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)carbonil]amino}propanoato de metilo (686 mg, 1.26 mmol) sintetizado en el ejemplo (27a) se disolvió en tetrahidrofurano (15 mL), y se le agregó anhídrido metanosulfónico (330 mg, 1.89 mmol) y trietilamina (0.53 mL, 3.80 mmol), seguido por agitación a temperatura ambiente durante 19 horas bajo una atmósfera de nitrógeno. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (10 mL), y la solución se separó con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de

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magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-70%), para producir el producto deseado como un sólido blanco (586 mg, rendimiento de 88%).

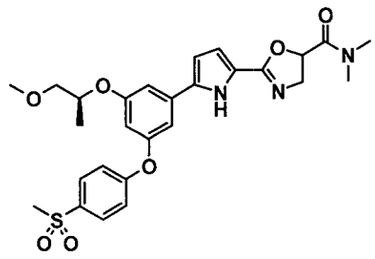
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 3.9, 10.2 Hz), 3.60 (1H, dd, J = 6.3, 10.2 Hz), 4.10 (1H, dd, J = 7.0, 14.5 Hz), 4.30 (1H, dd, J = 10.6, 14.5 Hz), 4.56 (1H, m), 5.07 (1H, dd, J = 7.0, 10.6 Hz), 6.52 (1H, d, J = 3.9 Hz), 6.57 (1H, t, J = 2.0 Hz), 6.83 (1H, t, J = 2.0 Hz), 6.86 (1H, d, J = 3.9 Hz), 7.00 (1H, t, J = 2.0 Hz), 7.14 (2H, d, J = 9.0 Hz), 7.90 (2H, d, J = 9.0 Hz), 9.66 (1H, brs).

MS (ESI) m/z: 529.16412 $(M+H)^+$.

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EJEMPLO 28

2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-N,N-dimetil-4,5-dihidro-1,3-oxazol-5-carboxamida



(28a) Acido 2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol-5-carboxílico

El 2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol-5-carboxilato de metilo (60.5 mg, 0.114 mmol) sintetizado en el ejemplo (27b) se disolvió en etanol (4 mL). Se le agregó una solución acuosa de hidróxido de sodio (5M, 2 mL) y se agitó a 70°C durante 2.5 horas. Después de enfriar a temperatura ambiente, se le agregó ácido clorhídrico (2M, 5 mL) y acetato de etilo (10 mL) y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida para producir el compuesto deseado como un sólido amarillo pálido (69.3 mg, rendimiento de ~100%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.42 (3H, s), 3.55-3.63 (2H, m), 4.28-4.44 (2H, m), 4.78 (1H, m), 5.49 (1H, brs), 6.60-6.68 (2H, m), 7.10 (1H, brs), 7.14 (2H, d, J = 8.3 Hz), 7.26 (1H, m),

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7.39 (1H, brd, J = 8.3 Hz), 7.89 (2H, d, J = 8.3 Hz), 13.10 (1H, brs).

MS (ESI) m/z: 515.14638 $(M+H)^+$.

(28b) 2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-N,N-dimetil-4,5-dihidro-1,3-oxazol-5-carboxamida

El ácido 2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol-5-carboxílico (154 mg, 0.299 mmol) sintetizado en el ejemplo (28a) se disolvió en diclorometano (10 mL), y se le agregó clorhidrato de dimetilamina (75.0 mg, 0.920 mmol), WSCI·HCl (115 mg, 0.600 mmol) y 4-dimetilaminopiridina (110 mg, 0.900 mmol), seguido por agitación a temperatura ambiente durante 2 días bajo una atmósfera de nitrógeno. Se le agregó agua (10 mL) y la solución se separó con diclorometano (15 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 70%-100%), para producir el producto deseado como un sólido blanco (107 mg, rendimiento de 66%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.02 (3H, s), 3.07 (3H, s), 3.15 (3H, s), 3.42 (3H, s), 3.50 (1H, dd, J = 3.9, 10.2 Hz), 3.60 (1H, dd, J = 5.9, 10.2 Hz), 4.19 (1H, ddd, J = 1.2, 10.2, 14.1 Hz), 4.33 (1H, brdd, J = 7.8, 14.1 Hz), 4.57 (1H, m), 5.27 (1H, dd, J = 7.8, 10.2 Hz), 6.50 (1H, d, J = 3.9 Hz), 6.56 (1H, d, J = 2.0 Hz), 6.78 (1H, d, J = 3.9 Hz), 6.83 (1H, t, J = 2.0 Hz), 7.01 (1H, d, J = 2.0 Hz), 7.13 (2H, d, J = 8.6 Hz), 7.90 (2H, d, J =

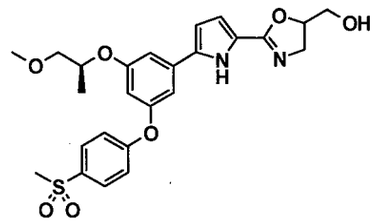
1132

8.9 Hz), 9.80 (1H, brs).

MS (ESI) m/z: 542.19865 $(M+H)^+$.

EJEMPLO 29

[2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol-5-il]metanol



Se suspendió hidruro de litio y aluminio (17.0 mg, 0.448 mmol) en tetrahidrofurano (2 mL). El 2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol-5-carboxilato de metilo (77.0 mg, 0.146 mmol) sintetizado en el ejemplo (27b) se disolvió en tetrahidrofurano (2 mL), seguido por su adición a gotas a 0°C y bajo una atmósfera de nitrógeno. Después de agitar a 0°C durante 30 minutos, se le agregó secuencialmente agua (17 μL) y una solución acuosa de hidróxido de sodio (5M, 68 μL) lentamente, gota a gota. Después de filtración a través de Celite, el disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-100%), para producir el compuesto deseado como un sólido blanco (54.1 mg, rendimiento de 74%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.29-1.33 (3H, m), 3.06 (3H, s),

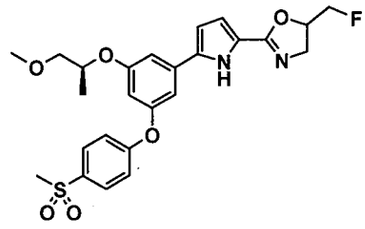
1133

3.41 (3H, s), 3.49 (1H, m), 3.58 (1H, m), 3.63-3.76 (2H, m), 3.83 (1H, m), 3.97 (1H, m), 4.59 (1H, m), 4.76 (1H, m), 6.46 (1H, m), 6.54 (1H, brs), 6.72 (1H, m), 6.69 (1H, brs), 7.05 (1H, m), 7.13 (2H, d, J = 8.8 Hz), 7.89 (2H, d, J = 8.8 Hz).

MS (ESI) m/z: 501.17097 $(M+H)^+$.

EJEMPLO 30

5-(Fluorometil)-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol



El [2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol-5-il]metanol (100 mg, 0.20 mmol) sintetizado en el ejemplo 29 se disolvió en diclorometano (5 mL), y se le agregó trifluoruro de bis(2-metoxietil)aminoazufre (81 μL, 0.44 mmol) a 0°C. Después de agitar a temperatura ambiente durante 6 horas, se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con diclorometano (60 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de

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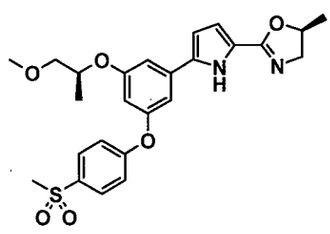
etilo/hexano = 80%-100%), para producir el producto deseado como un sólido blanco (61 mg, rendimiento de 61%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 4.1,10.3 Hz), 3.59 (1H, dd, J = 6.3, 10.3 Hz), 3.82 (1H, dd, J = 7.4, 14.5 Hz), 4.10 (1H, ddd, J = 1.4, 10.1, 14.6 Hz), 4.49 (1H, ddd, J = 5.5, 10.5, 37.9 Hz), 4.54-4.58 (1H, m), 4.62 (1H, ddd, J = 3.0, 10.6, 33.3 Hz), 4.85-4.96 (1H, m), 6.51 (1H, d, J = 3.9 Hz), 6.57 (1H, t, J = 2.1 Hz), 6.80 (1H, d, J = 3.6 Hz), 6.81 (1H, t, J = 1.9 Hz), 6.98 (1H, t, J = 1.8 Hz), 7.13 (2H, d, J = 8.9 Hz), 7.91 (2H, d, J = 8.9 Hz)

MS (ESI) m/z: 503.16398 $(M+H)^+$.

EJEMPLO 31

(5S)-2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol



(31a) N-[(2R)-2-Hidroxipropil]-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-carboxílico (204 mg, 0.458 mmol) sintetizado en el ejemplo (18a) se disolvió en diclorometano (10 mL), y se le agregó (R)-(-)-1-

amino-2-propanol (72.0μ mL, 0.914 mmol), WSCI·HCl (130 mg, 0.678 mmol) y 4-dimetilaminopiridina (115 mg, 0.941 mmol), seguido por agitación a temperatura ambiente durante 18 horas bajo una atmósfera de nitrógeno. Se le agregó ácido clorhídrico 1N (10 mL) y la solución se separó con diclorometano (15 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 60%-100%), para producir el producto deseado como un sólido blanco (191 mg, rendimiento de 83%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.21 (3H, d, J = 6.3 Hz), 1.31 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.24 (3H, s), 3.41 (3H, s), 3.51 (1H, dd, J = 3.9, 10.2 Hz), 3.57 (1H, m), 3.59 (1H, dd, J = 6.3, 10.2 Hz), 3.98 (1H, m), 4.56 (1H, m), 6.47 (1H, dd, J = 2.7, 3.9 Hz), 6.50 (1H, brs), 6.55 (1H, t, J = 2.0 Hz), 6.64 (1H, dd, J = 2.4, 3.9 Hz), 6.87 (1H, t, J = 2.0 Hz), 7.00 (1H, t, J = 2.0 Hz), 7.12 (2H, d, J = 9.0 Hz), 7.89 (2H, d, J = 9.0 Hz), 10.09 (1H, brs).

(31b) (5S)-2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol

La N-[(2R)-2-hidroxipropil]-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida (191 mg, 0.380 mmol) sintetizada en el ejemplo (31a) se disolvió en tetrahidrofurano (10 mL), y se le agregó ácido metanosulfónico anhidro (100 mg, 0.574 mmol) y trietilamina (0.16 mL, 1.15 mmol), seguido por agitación a temperatura ambiente durante

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18 horas bajo una atmósfera de nitrógeno. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (10 mL) y la solución se separó con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-70%), para producir el producto deseado como un sólido blanco (136 mg, rendimiento de 74%).

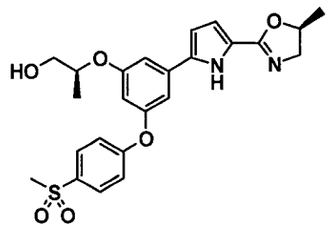
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 1.42 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 4.3, 10.2 Hz), 3.52 (1H, dd, J = 7.4, 14.1 Hz), 3.59 (1H, dd, J = 6.3, 10.2 Hz), 4.06 (1H, dd, J = 9.4, 14.1 Hz), 4.57 (1H, m), 4.82 (1H, m), 6.50 (1H, d, J = 3.9 Hz), 6.55 (1H, t, J = 2.0 Hz), 6.75 (1H, d, J = 3.9 Hz), 6.83 (1H, t, J = 2.0 Hz), 7.00 (1H, t, J = 2.0 Hz), 7.13 (2H, d, J = 9.0 Hz), 7.90 (2H, d, J = 9.0 Hz).

MS (ESI) m/z: 485.17394 $(M+H)^+$.

1137

EJEMPLO 32

(2S)-2-(3-{5-[(5S)-5-Metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[4-(metilsulfonil)fenoxi]fenoxi)propan-1-ol



El (5S)-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol (280 mg, 0.58 mmol) sintetizado en el ejemplo(31b) se disolvió en diclorometano (10 mL) y se enfrió a -78°C; se le agregó una solución de tribromuro de boro en diclorometano 1.0 mol/l (0.61 mL, 0.61 mmol) bajo una atmósfera de nitrógeno. Después de que la temperatura se elevó naturalmente y la solución se agitó a temperatura ambiente durante 30 minutos, se le agregó una solución acuosa saturada de carbonato ácido de sodio para neutralizar la solución de reacción, seguido por extracción con diclorometano (60 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo), para producir el producto deseado como un sólido blanco (222 mg, rendimiento de 82%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.28 (3H, d, J = 6.3 Hz), 1.43 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.55 (1H, dd, J = 7.3, 13.9 Hz), 3.79 (2H, d, J = 5.4

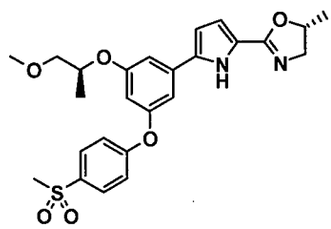
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Hz), 4.09 (1H, dd, J = 9.2, 14.0 Hz), 4.60-4.64 (1H, m), 4.81-4.87 (1H, m), 6.36 (1H, t, J = 2.3 Hz), 6.46 (1H, d, J = 3.9 Hz), 6.75 (1H, d, J = 3.9 Hz), 6.91 (1H, t, J = 1.9 Hz), 7.08 (2H, d, J = 8.9 Hz), 7.88 (2H, d, J = 8.9 Hz).

MS (ESI) m/z: 471.15892 $(M+H)^+$.

EJEMPLO 33

(5R)-2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol



(33a) N-[(2S)-2-Hidroxipropil]-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-carboxílico (305 mg, 0.685 mmol) sintetizado en el ejemplo (18a) se disolvió en diclorometano (10 mL), y se le agregó (S)-(+)-1-amino-2-propanol (110μ mL, 1.40 mmol), WSCI·HCl (200 mg, 1.04 mmol) y 4-dimetilaminopiridina (170 mg, 1.39 mmol), seguido por agitación a temperatura ambiente durante 16 horas bajo una atmósfera de nitrógeno. Se le agregó ácido clorhídrico 1N (10 mL) y la solución se separó con diclorometano (15 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por

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destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 60%-100%), para producir el producto deseado como un sólido blanco (285 mg, rendimiento de 83%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.24 (3H, d, J = 6.3 Hz), 1.33 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.28 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 3.9, 10.2 Hz), 3.56-3.65 (2H, m), 4.01 (1H, m), 4.58 (1H, m), 6.35 (1H, brt, J = 5.5 Hz), 6.49 (1H, dd, J = 2.7, 3.9 Hz), 6.57 (1H, t, J = 2.0 Hz), 6.62 (1H, dd, J = 2.4, 3.9 Hz), 6.84 (1H, t, J = 2.0 Hz), 7.00 (1H, t, J = 2.0 Hz), 7.13 (2H, d, J = 8.6 Hz), 7.90 (2H, d, J = 8.6 Hz), 9.66 (1H, brs).

(33b) (5R)-2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol

La N-[(2S)-2-hidroxipropil]-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida (285 mg, 0.567 mmol) sintetizada en el ejemplo (33a) se disolvió en tetrahidrofurano (10 mL), y se le agregó ácido metanosulfónico anhidro (130 mg, 0.746 mmol) y trietilamina (0.24 mL, 1.72 mmol), seguido por agitación a temperatura ambiente durante 21 horas bajo una atmósfera de nitrógeno. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (10 mL) y la solución se separó con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución:

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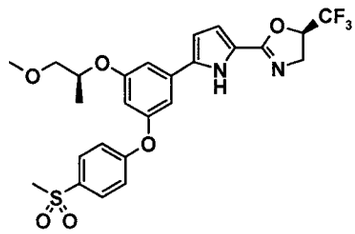
acetato de etilo/hexano = 30%-70%), para producir el producto deseado como un sólido blanco (155 mg, rendimiento de 56%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J = 6.3 Hz), 1.41 (3H, d, J = 6.3 Hz), 3.06 (3H, s), 3.40 (3H, s), 3.50 (1H, dd, J = 3.9, 10.2 Hz), 3.51 (1H, dd, J = 8.2, 14.1 Hz), 3.58 (1H, dd, J = 5.9, 10.2 Hz), 4.04 (1H, dd, J = 9.4, 14.1 Hz), 4.56 (1H, m), 4.80 (1H, m), 6.50 (1H, d, J = 3.9 Hz), 6.55 (1H, t, J = 2.0 Hz), 6.74 (1H, d, J = 3.9 Hz), 6.84 (1H, t, J = 2.0 Hz), 7.00 (1H, t, J = 2.0 Hz), 7.12 (2H, d, J = 9.0 Hz), 7.89 (2H, d, J = 9.0 Hz).

MS (ESI) m/z: 485.17398 $(M+H)^+$.

EJEMPLO 34

(5R)-2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-5-(trifluorometil)-4,5-dihidro-1,3-oxazol



(34a) 5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-N-[(2S)-3,3,3-trifluoro-2-hidroxipropil]-1H-pirrol-2-carboxamida

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-carboxílico (408 mg, 0.94 mmol) sintetizado en el ejemplo (18a), (2S)-3-amino-1,1,1-trifluoro-2-propanol (177 mg, 1.37 mmol) y 4-dimetilaminopiridina (224 mg, 1.87 mmol), se disolvieron en diclorometano

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(20 mL) y se les agregó WSCI·HCl (193 mg, 1.01 mmol) a temperatura ambiente, seguido por agitación durante 2 horas bajo una atmósfera de nitrógeno. La solución de reacción se diluyó con diclorometano (200 mL), se lavó con ácido clorhídrico 1N, solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-70%), para producir el producto deseado como una sustancia amorfa blanca (339 mg, rendimiento de 67%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.31 (3H, d, J = 6.3 Hz), 3.08 (3H, s), 3.42 (3H, s), 3.52 (1H, dd, J = 3.9, 10.3 Hz), 3.60 (1H, dd, J = 6.2, 10.2 Hz), 3.58-3.65 (1H, m), 3.85 (1H, ddd, J = 2.7, 6.6, 14.9 Hz), 4.08-4.15 (1H, brm), 4.53-4.60 (1H, m), 4.74 (1H, d, J = 5.5 Hz), 6.37 (1H, t, J = 6.1 Hz), 6.50 (1H, dd, J = 3.0, 4.0 Hz), 6.58 (1H, t, J = 2.2 Hz), 6.67 (1H, dd, J = 2.7, 4.0 Hz), 6.84 (1H, t, J = 1.7 Hz), 6.99 (1H, t, J = 2.0 Hz), 7.13 (2H, d, J = 8.9 Hz), 7.91 (2H, d, J = 8.9 Hz), 9.82 (1H, brs).

(34b) (5R)-2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5-(trifluorometil)-4,5-dihidro-1,3-oxazol

La 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]-fenil}-N-[(2S)-3,3,3-trifluoro-2-hidroxipropil]-1H-pirrol-2-carboxamida (339 mg, 0.61 mmol) sintetizada en el ejemplo (34a) se disolvió en tetrahidrofurano (10 mL), y se le agregó trietilamina (0.51 mL, 3.66 mmol) y ácido metanosulfónico

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anhidro (296 mg, 1.71 mmol) a 0°C, seguido por calentamiento a 120°C durante 30 horas. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con acetato de etilo (60 mL). Después de lavar con salmuera saturada, se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-50%), para producir el producto deseado como un sólido blanco (328 mg, rendimiento de 84%).

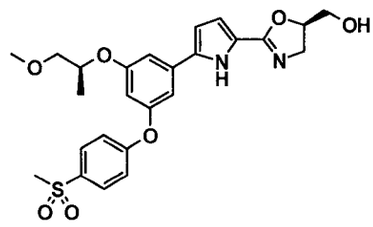
^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.08 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 3.9, 10.4 Hz), 3.59 (1H, dd, J = 6.3, 10.1 Hz), 4.15 (1H, dd, J = 6.5, 15.4 Hz), 4.22 (1H, dd, 10.0, 15.4 Hz), 4.55-4.59 (1H, m), 4.88-4.92 (1H, m), 6.52 (1H, dd, J = 2.4,4.0 Hz), 6.58 (1H, t, J = 2.2 Hz), 6.82 (1H, t, J = 1.8 Hz), 6.84 (1H, dd, J = 2.3, 3.9 Hz), 6.98 (1H, t, J = 2.0 Hz), 7.13 (2H, d, J = 8.8 Hz), 7.91 (2H, d, J = 8.8 Hz), 9.25 (1H, brs).

MS (ESI) m/z: 539.14603 $(M+H)^+$.

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EJEMPLO 35

[(5R)-2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol-5-il]metanol



(35a) N-[(2S)-2,3-Dihidroxipropil]-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxílico (338 mg, 0.759 mmol) sintetizado en el ejemplo (18a) se disolvió en diclorometano (10 mL), y se le agregó (S)-(-)-3-amino-1,2-propanodiol (105 mg, 1.15 mmol), WSCI·HCl (220 mg, 1.15 mmol) y 4-dimetilaminopiridina (185 mg, 1.51 mmol), seguido por agitación a temperatura ambiente durante 3 días bajo una atmósfera de nitrógeno. Se le agregó ácido clorhídrico 1N (10 mL) y la solución se separó con diclorometano (15 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 70%-100%), para producir el producto deseado como un sólido blanco (265 mg, rendimiento de 68%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.07 (3H,

s), 3.42 (3H, s), 3.51 (1H, dd, J = 3.9, 10.2 Hz), 3.553-3.64 (4H, m), 3.85 (1H, m), 4.57 (1H, m), 6.38 (1H, m), 6.50 (1H, dd, J = 2.7, 3.9 Hz), 6.58 (1H, t, J = 2.0 Hz), 6.64 (1H, dd, J = 2.4, 3.9 Hz), 6.84 (1H, t, J = 2.0 Hz), 7.00 (1H, t, J = 2.0 Hz), 7.13 (2H, d, J = 9.0 Hz), 7.91 (2H, d, J = 9.0 Hz), 9.59 (1H, brs).

(35b) N-{(2S)-2-Hidroxi-3-[(triisopropilsilil)oxi]propil}-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida

La N-[(2S)-2,3-dihidroxipropil]-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida (265 mg, 0.514 mmol) sintetizada en el ejemplo (35a) se disolvió en diclorometano (10 mL), y se le agregó cloruro de triisopropilsililo (0.12 mL, 0.691 mmol), trietilamina (0.21 mL, 1.51 mmol) y 4-dimetilaminopiridina (6.0 mg, 0.049 mmol), seguido por agitación a temperatura ambiente durante 24 horas bajo una atmósfera de nitrógeno. Se le agregó agua (10 mL) y la solución se separó con diclorometano (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-50%), para producir el producto deseado como un sólido blanco (177 mg, rendimiento de 51%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.04-1.13 (21H, m), 1.32 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.21 (1H, d, J = 4.3 Hz), 3.38 (1H, m), 3.42 (3H, s), 3.51 (1H, dd, J = 3.9, 10.2 Hz), 3.60 (1H, dd, J = 6.3, 10.2 Hz), 3.67 (1H, dd, J = 6.3, 9.8 Hz), 3.73 (1H, m), 3.76 (1H, dd, J = 5.0, 9.8 Hz), 3.86 (1H, m), 4.58

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(1H, m), 6.43 (1H, brt, J = 5.9 Hz), 6.48 (1H, dd, J = 2.8, 3.9 Hz), 6.56 (1H, t, J = 2.0 Hz), 6.61 (1H, dd, J = 2.4, 3.9 Hz), 6.85 (1H, t, J = 2.0 Hz), 7.00 (1H, t, J = 2.0 Hz), 7.13 (2H, d, J = 8.6 Hz), 7.90 (2H, d, J = 8.6 Hz), 9.80 (1H, brs).

(35c) (5S)-2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5-{[(triisopropilsilil)oxi]metil}-4,5-dihidro-1,3-oxazol

La N-{(2S)-2-hidroxi-3-[(triisopropilsilil)oxi]propil}-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida (177 mg, 0.262 mmol) sintetizada en el ejemplo (35b) se disolvió en tetrahidrofurano (10 mL), y se le agregó ácido metanosulfónico anhidro (70.0 mg, 0.402 mmol) y trietilamina (0.22 mL, 1.58 mmol), seguido por agitación a 70°C durante 3 días bajo una atmósfera de nitrógeno. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (10 mL) y la solución se separó con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-60%), para producir el producto deseado como un aceite amarillo (180 mg, rendimiento de ~100%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.02-1.10 (21H, m), 1.33 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 4.3, 10.2 Hz), 3.59 (1H, dd, J = 6.3, 10.2 Hz), 3.82-3.90 (3H, m), 4.00 (1H, dd, J = 9.8, 14.1 Hz), 4.58 (1H, m), 4.75 (1H, m), 6.49 (1H, d, J = 3.9 Hz), 6.55 (1H, t, J = 2.0 Hz), 6.73 (1H, d, J = 3.9 Hz), 6.83 (1H, t, J = 2.0 Hz), 7.00 (1H, t, J = 2.0 Hz), 7.13 (2H,

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d, J = 9.0 Hz), 7.90 (2H, d, J = 9.0 Hz), 9.59 (1H, brs).

(35d) [(5R)-2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol-5-il]metanol

El (5S)-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5-{[(triisopropilsilil)oxi]metil}-4,5-dihidro-1,3-oxazol (180 mg, 0.262 mmol) sintetizado en el ejemplo (35c) se disolvió en tetrahidrofurano (10 mL), y se le agregó fluoruro de tetrabutilamonio (solución en tetrahidrofurano 1M, 0.53 mL, 0.53 mmol), seguido por agitación a temperatura ambiente durante 30 minutos bajo una atmósfera de nitrógeno. Se le agregó agua (10 mL) y se extrajo con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 60%-100%), para producir el compuesto deseado como un sólido blanco (103 mg, rendimiento de 79%).

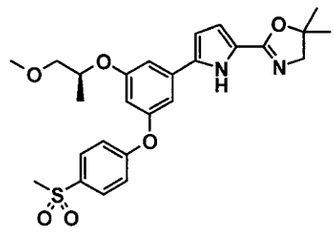
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.27 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.42 (3H, s), 3.49 (1H, dd, J = 3.9, 10.2 Hz), 3.58 (1H, dd, J = 6.3, 10.2 Hz), 3.67 (1H, dd, J = 5.1, 12.5 Hz), 3.74 (1H, dd, J = 7.4, 14.5 Hz), 3.84 (1H, dd, J = 3.1, 12.5 Hz), 4.00 (1H, dd, J = 9.8, 14.5 Hz), 4.54 (1H, m), 4.78 (1H, m), 6.46 (1H, d, J = 3.9 Hz), 6.55 (1H, t, J = 2.0 Hz), 6.71 (1H, d, J = 3.9 Hz), 6.85 (1H, t, J = 2.0 Hz), 6.98 (1H, t, J = 2.0 Hz), 7.14 (2H, d, J = 8.6 Hz), 7.90 (2H, d, J = 9.0 Hz), 9.59 (1H, brs).

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MS (ESI) m/z: 501.16898 $(M+H)^+$.

EJEMPLO 36

2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-5,5-dimetil-4,5-dihidro-1,3-oxazol



(36a) N-(2-Hidroxi-2-metilpropil)-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-carboxílico (300 mg, 0.673 mmol) sintetizado en el ejemplo (18a) se disolvió en diclorometano (10 mL), y se le agregó 1-amino-2-metil-2-propanol (150 mg, 1.68 mmol), WSCI·HCl (185 mg, 0.965 mmol) y 4-dimetilaminopiridina (165 mg, 1.35 mmol), seguido por agitación a temperatura ambiente durante 17 horas, bajo una atmósfera de nitrógeno. Se le agregó ácido clorhídrico 1N (10 mL) y la solución se separó con diclorometano (15 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de

etilo/hexano = 60%-100%), para producir el producto deseado como un sólido blanco (307 mg, rendimiento de 88%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.26 (6H, s), 1.32 (3H, d, J = 6.3 Hz), 3.07 (3H, s), 3.41 (3H, s), 3.41 (2H, m), 3.51 (1H, dd, J = 3.9, 10.2 Hz), 3.59 (1H, dd, J = 6.3, 10.2 Hz), 4.58 (1H, m), 4.46 (1H, brs), 6.48 (1H, dd, J = 2.7, 3.9 Hz), 6.56 (1H, t, J = 2.0 Hz), 6.65 (1H, dd, J = 2.4, 3.9 Hz), 6.86 (1H, t, J = 2.0 Hz), 7.00 (1H, t, J = 2.0 Hz), 7.12 (2H, d, J = 9.0 Hz), 7.90 (2H, d, J = 9.0 Hz), 9.86 (1H, brs).

(36b) 2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5,5-dimetil-4,5-dihidro-1,3-oxazol

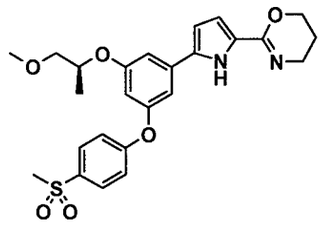
La N-(2-hidroxi-2-metilpropil)-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida (307 mg, 0.594 mmol) sintetizada en el ejemplo (36a) se disolvió en tetrahidrofurano (10 mL), y se le agregó ácido metanosulfónico anhidro (160 mg, 0.918 mmol) y trietilamina (0.25 mL, 1.79 mmol), seguido por agitación a temperatura ambiente durante 4 días bajo una atmósfera de nitrógeno. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (10 mL) y la solución se separó con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-70%), para producir el producto deseado como un sólido blanco (187 mg, rendimiento de 63%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 1.47 (6H, s), 3.07 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 3.9, 10.2 Hz), 3.59 (1H, dd, J = 6.3, 10.2 Hz), 3.69 (1H, s), 4.57 (1H, m), 6.50 (1H, d, J = 3.9 Hz), 6.55 (1H, t, J = 2.0 Hz), 6.74 (1H, d, J = 3.9 Hz), 6.83 (1H, t, J = 2.0 Hz), 7.00 (1H, t, J = 2.0 Hz), 7.13 (2H, d, J = 9.0 Hz), 7.90 (2H, d, J = 9.0 Hz).

MS (ESI) m/z: 499.18990 $(M+H)^+$.

EJEMPLO 37

2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-il)-5,6-dihidro-4H-1,3-oxazina



(37a) N-(3-Hidroxipropil)-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-carboxílico (250 mg, 0.561 mmol) sintetizado en el ejemplo (18a) se disolvió en diclorometano (10 mL), y se le agregó 3-amino-1-propanol (90.0 µL, 1.18 mmol), WSCI·HCl (165 mg, 0.861 mmol) y 4-dimetilaminopiridina (140 mg, 1.15 mmol), seguido por agitación a temperatura ambiente durante 16 horas bajo una atmósfera de nitrógeno. Se le agregó ácido clorhídrico 1N (10 mL) y la solución se separó con diclorometano (15

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mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 60%-100%), para producir el producto deseado como un sólido blanco (216 mg, rendimiento de 77%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 1.78 (2H, m), 3.07 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 3.9, 10.2 Hz), 3.56-3.62 (3H, m), 3.71 (2H, m), 4.58 (1H, m), 6.32 (1H, brs), 6.49 (1H, dd, J = 2.7, 3.9 Hz), 6.56-6.60 (2H, m), 6.84 (1H, t, J = 2.0 Hz), 6.99 (1H, t, J = 2.0 Hz), 7.13 (2H, d, J = 9.0 Hz), 7.91 (2H, d, J = 9.0 Hz), 9.63 (1H, brs).

(37b) 2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[4-(metilsulfonil)-fenoxi]fenil}-1H-pirrol-2-il)-5,6-dihidro-4H-1,3-oxazina

La N-(3-hidroxipropil)-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[4-(metilsulfonil)fenoxi]fenil}-1H-pirrol-2-carboxamida (216 mg, 0.430 mmol) sintetizada en el ejemplo (37a) se disolvió en tetrahidrofurano (10 mL), y se le agregó ácido metanosulfónico anhidro (115 mg, 0.660 mmol) y trietilamina (0.18 mL, 1.29 mmol), seguido por agitación a temperatura ambiente durante 4 días, y a 80°C durante 17 horas, bajo una atmósfera de nitrógeno. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (10 mL), y la solución se separó con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión

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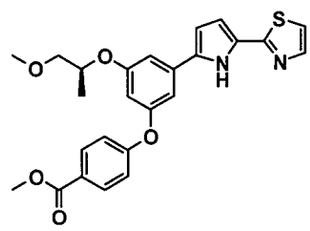
reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-90%), para producir el producto deseado como un sólido pardusco pálido (150 mg, rendimiento de 72%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 1.98 (2H, m), 3.06 (3H, s), 3.41 (3H, s), 3.48-3.54 (3H, m), 3.59 (1H, dd, J = 6.3, 10.2 Hz), 4.32 (2H, brt, J = 5.5 Hz), 4.56 (1H, m), 6.46 (1H, d, J = 3.9 Hz), 6.53 (1H, t, J = 2.0 Hz), 6.62 (1H, d, J = 3.9 Hz), 6.82 (1H, t, J = 2.0 Hz), 6.99 (1H, t, J = 2.0 Hz), 7.12 (2H, d, J = 9.0 Hz), 7.89 (2H, d, J = 9.0 Hz).

MS (ESI) m/z: 485.17572 $(M+H)^+$.

EJEMPLO 38

4-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzoato de metilo



(38a) 1-Bromo-3-metoxi-5-[(1S)-2-metoxi-1-metiletoxi]benceno

El 3-bromo-5-metoxifenol (7.60 g, 37.4 mmol) sintetizado en el ejemplo (1a) se disolvió en tolueno (100 mL), y se le agregó R-(-)-1-metoxi-2-propanol (4.40 mL, 44.9 mmol) y trifenilfosfina (13.8 g, 52.6 mmol), seguido por la adición, gota a gota, de azodicarboxilato de dietilo (solución en tolueno

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2.2 mol/l, 24 mL, 52.8 mmol) a 0°C, y agitación a temperatura ambiente durante 1.5 horas, bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida, se le agregó éter dietílico (100 mL) y el depósito se filtró para removerlo. El licor madre se destiló bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-20%), para producir el compuesto deseado como un líquido incoloro (9.22 g, rendimiento de 89%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.30 (3H, d, J = 6.3 Hz), 3.40 (3H, s), 3.47 (1H, dd, J = 10.6, 4.3 Hz), 3.55 (1H, dd, J = 10.4, 6.1 Hz), 3.76 (3H, s), 4.46-4.52 (1H, m), 6.42 (1H, t, J = 2.2 Hz), 6.65 (1H, dd, J = 2.3, 1.6 Hz), 6.69 (1H, t, J = 2.0 Hz).

MS (EI) m/z: 274 $(M)^+$.

(38b) 3-Bromo-5-[(1S)-2-metoxi-1-metiletoxi]fenol

El 1-bromo-3-metoxi-5-[(1S)-2-metoxi-1-metiletoxi]benceno (9.21 g, 33.5 mmol) sintetizado en el ejemplo (38a) se disolvió en 1-metil-2-pirrolidona (100 mL), y se le agregó tiometóxido de sodio (2.75 g, 37.3 mmol), seguido por agitación a 130°C durante 3 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó ácido clorhídrico 2N (500 mL) y se extrajo con éter dietílico (300 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en

1153

columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-25%), para producir el compuesto deseado como un líquido incoloro (8.30 g, rendimiento de 95%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.29 (3H, d, J = 6.3 Hz), 3.41 (3H, s), 3.46 (1H, dd, J = 10.2, 4.3 Hz), 3.55 (1H, dd, J = 10.6, 5.9 Hz), 4.45-4.51 (1H, m), 4.96 (1H, br s), 6.36 (1H, t, J = 2.0 Hz), 6.59 (1H, t, J = 2.0 Hz), 6.68 (1H, t, J = 2.0 Hz).

MS (EI) m/z: 260 $(M)^+$.

(38c) 3-[(1S)-2-Metoxi-1-metiletoxi]-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenol

El 3-bromo-5-[(1S)-2-metoxi-1-metiletoxi]fenol (8.30 g, 31.8 mmol) sintetizado en el ejemplo (38b) se disolvió en N,N-dimetilformamida (100 mL), y se le agregó bis(pinacolato)diboro (10.50 g, 41.3 mmol), complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano (810 mg, 0.992 mmol) y acetato de potasio (15.50 g, 158 mmol), seguido por agitación a 90°C durante 3 horas bajo una atmósfera de nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente, se le agregó agua (500 mL) y se extrajo con éter dietílico (300 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-30%), para producir el compuesto deseado como un aceite pardusco (8.75 g, rendimiento

1154

de 89%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.26 (3H, d, J = 4.1 Hz), 1.33 (12H, s), 3.41 (1H, s), 3.47 (1H, dd, J = 10.2, 4.7 Hz), 3.57 (1H, dd, J = 10.6, 5.9 Hz), 4.52-4.58 (1H, m), 4.80 (1H, brs), 6.55 (1H, t, J = 2.4 Hz), 6.83 (1H, d, J = 2.4 Hz), 6.95 (1H, d, J = 2.4 Hz).

MS (FAB) m/z: 309 $(M+H)^+$.

(38d) 2-{3-Hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo

El 3-[(1S)-2-metoxi-1-metiletoxi]-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenol (3.30 g, 10.7 mmol) sintetizado en el ejemplo (38c), y el 2-bromo-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (4.10 g, 12.5 mmol) sintetizado en el ejemplo (1g), se disolvieron en un disolvente mixto de 1,4-dioxano (100 mL) y agua (25 mL) y se les agregó complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano (400 mg, 0.490 mmol) y carbonato de potasio (7.20 g, 52.1 mmol), seguido por agitación a 50°C durante 4 horas bajo una atmósfera de nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente, se le agregó agua (200 mL) y se extrajo con acetato de etilo (400 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 25%-40%), para producir el compuesto deseado como un aceite amarillo pálido (3.72 g,

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rendimiento de 81%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.24-1.29 (12H, m), 3.40 (3H, s), 3.47 (1H, dd, J = 4.4, 10.3 Hz), 3.57 (1H, dd, J = 5.9, 10.3 Hz), 4.48-4.54 (1H, m), 5.74 (1H, brs), 6.19 (1H, brs), 6.39-6.44 (2H, brs), 6.55 (1H, brs), 6.60 (1H, d, J = 3.9 Hz), 7.31 (1H, d, J = 3.0 Hz), 7.81 (1H, d, J = 3.4 Hz).

(38e) 2-{3-[4-(Metoxicarbonil)fenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo

El 2-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (117 mg, 0.272 mmol) sintetizado en el ejemplo (38d) se disolvió en diclorometano (20 mL), y se le agregó ácido 4-metoxicarbonilfenil-borónico (100 mg, 0.556 mmol), acetato de cobre (II) (80 mg, 0.440 mmol), trietilamina (0.20 mL, 1.435 mmol) y tamices moleculares de 4A (100 mg), seguido por agitación a temperatura ambiente durante 3 días bajo una atmósfera de nitrógeno. El depósito de esta solución de reacción se filtró por Celite. Este licor madre se destiló bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 15%-25%), para producir el compuesto deseado como un aceite amarillo (70 mg, rendimiento de 46%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (12H, m), 3.40 (3H, s), 3.48 (1H, dd, J = 10.2, 4.3 Hz), 3.57 (1H, dd, J = 10.2, 5.9 Hz), 3.90 (3H, s), 4.48-4.58 (1H, m), 6.25 (1H, d, J = 3.5 Hz), 6.58 (1H, d, J = 3.5 Hz), 6.63 (1H, t, J = 2.4 Hz), 6.70 (1H, dd, J = 2.4, 1.2 Hz), 6.84 (1H, dd, J = 2.4, 1.6 Hz), 7.04 (2H, d, J = 9.0 Hz), 7.33 (1H, d, J = 3.1 Hz), 7.80 (1H, d, J = 3.5 Hz), 8.00 (2H, d, J

= 9.0 Hz).

(38f) 4-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi} benzoato de metilo

El 2-{3-[4-(metoxicarbonil)fenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (70 mg, 0.124 mmol) sintetizado en el ejemplo (38e), se disolvió en diclorometano (1.0 mL). Se le agregó a gotas ácido trifluoroacético (2.0 mL) con agitación y bajo una atmósfera de nitrógeno; se agitó a temperatura ambiente durante 2 horas. El disolvente se removió por destilación bajo presión reducida, seguido por dilución con acetato de etilo (30 mL); se le agregó una solución acuosa saturada de carbonato ácido de sodio (20 mL) y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-50%), para producir el compuesto deseado como un líquido amarillo pálido (65 mg, rendimiento de ~100%).

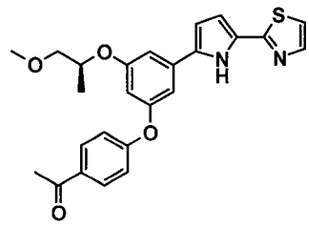
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.42 (3H, s), 3.52 (1H, dd, J = 3.9, 10.2 Hz), 3.60 (1H, dd, J = 5.9, 10.2 Hz), 3.91 (3H, s), 4.60-4.70 (1H, m), 6.56-6.59 (2H, m), 6.86 (1H, brs), 6.93 (1H, brs), 7.05 (2H, d, J = 9.0 Hz), 7.15 (1H, brs), 7.70 (1H, brs), 8.02 (2H, d, J = 9.0 Hz).

MS (ESI) m/z: 465.19025 $(M+H)^+$.

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EJEMPLO 39

1-(4-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}fenil)etanona



(39a) 2-{3-(4-Acetilfenoxi)-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo

El 2-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (92 mg, 0.214 mmol) sintetizado en el ejemplo (38d) se disolvió en diclorometano (10 mL), y se le agregó ácido 4-acetilfenilborónico (70 mg, 0.427 mmol), acetato de cobre (II) (60 mg, 0.330 mmol), trietilamina (0.15 mL, 1.08 mmol) y tamices moleculares de 4A (90 mg), seguido por agitación a temperatura ambiente durante 1 día bajo una atmósfera de nitrógeno. El depósito de esta solución de reacción se filtró por Celite. Este licor madre se destiló bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 15%-25%), para producir el compuesto deseado como un aceite amarillo (73 mg, rendimiento de 62%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (12H, m), 2.57 (3H, s), 3.40 (3H, s), 3.48 (1H, dd, J = 10.2, 4.3 Hz), 3.57 (1H, dd, J = 10.2, 5.9 Hz), 4.53-4.54 (1H, m), 6.26 (1H, d, J = 3.9 Hz), 6.59 (1H, d, J = 3.5 Hz), 6.63 (1H, t, J =

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2.3 Hz), 6.71 (1H, t, J = 1.8 Hz), 6.85 (1H, dd, J = 2.2, 1.4 Hz), 7.06 (2H, dt, J = 9.4, 2.4 Hz), 7.30 (1H, d, J = 3.1 Hz), 7.80 (1H, d, J = 3.1 Hz), 7.94 (2H, dt, J = 9.4, 2.4 Hz).

(39b) 1-(4-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}fenil)etanona

El 2-{3-(4-acetilfenoxi)-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (73 mg, 0.133 mmol) sintetizado en el ejemplo (39a) se disolvió en diclorometano (1.0 mL). Se le agregó a gotas ácido trifluoroacético (2.0 mL) con agitación y bajo una atmósfera de nitrógeno, y se agitó a temperatura ambiente durante 2.5 horas. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-40%), para producir el compuesto deseado como un líquido amarillo pálido (56 mg, rendimiento de 94%).

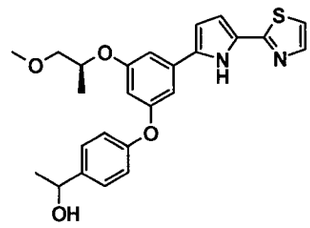
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 2.59 (3H, s), 3.42 (3H, s), 3.52 (1H, dd, J = 10.3, 3.9 Hz), 3.59 (1H, dd, J = 10.3, 5.9 Hz), 4.61-4.68 (1H, m), 6.54-6.59 (2H, m), 6.82 (1H, d, J = 2.9 Hz), 6.91 (1H, s), 7.06-7.11 (3H, br m), 7.18-7.20 (1H, br m), 7.68-7.70 (1H, br m), 7.96 (2H, d, J = 8.8 Hz), 10.51 (1H, br s).

MS (ESI) m/z: 449.15388 $(M+H)^+$.

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EJEMPLO 40

1-(4-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}fenil)etanol



La 1-(4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}fenil)etanona (30 mg, 0.067 mmol) sintetizada en el ejemplo (39b) se disolvió en un disolvente mixto de tetrahidrofurano (3.0 mL) y metanol (1.0 mL), y se le agregó borohidruro de sodio (10 mg, 0.264 mmol), seguido por agitación a temperatura ambiente durante 3 horas bajo una atmósfera de nitrógeno. A esta solución de reacción, se le agregó una solución acuosa saturada de cloruro de amonio (10 mL) y se extrajo con acetato de etilo (10 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 40%-60%), para producir el compuesto deseado como un sólido blanco (27.5 mg, rendimiento de 91%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 1.53 (3H, d, J = 6.3 Hz), 3.42 (3H, s), 3.49 (1H, dd, J = 9.4, 5.1 Hz), 3.59 (1H, dd, J = 10.2, 5.9 Hz), 4.52-4.59 (1H, m), 4.92 (1H, q, J = 6.3 Hz), 6.47-6.52 (2H, m),

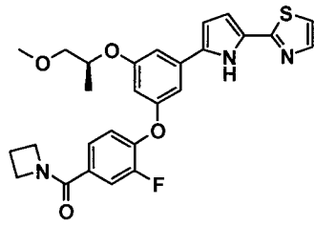
1160

6.72 (1H, t, J = 2.7 Hz), 6.92 (1H, s), 7.04 (2H, d, J = 8.2 Hz), 7.16 (1H, d, J = 3.1 Hz), 7.37 (2H, d, J = 9.0 Hz), 7.67 (1H, d, J = 3.1 Hz), 9.72 (1H, br s).

MS (ESI) m/z: 451.16915 $(M+H)^+$.

EJEMPLO 41

2-(5-{3-[4-(Azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol



(41a) 1-(3,4-Difluorobenzoil)azetidina

Se disolvió ácido 3,4-difluorobenzoico (3.00 g, 19.0 mmol), disponible comercialmente, en diclorometano (50 mL), y se le agregó N,N-dimetilformamida (0.10 mL), seguido por la adición a gotas de cloruro de oxalilo (1.98 mL, 22.8 mmol) y agitación a temperatura ambiente durante la noche, bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se disolvió en diclorometano (100 mL) y se le agregó clorhidrato de azetidina (2.27 g, 24.2 mmol) y trietilamina (6.60 mL, 47.4 mmol), seguido por agitación a temperatura ambiente durante 4.5 horas bajo una atmósfera de nitrógeno. Se le agregó ácido clorhídrico 0.5N (100 mL) y se extrajo con diclorometano (100 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se

secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 40%-50%), para producir el compuesto deseado como un líquido incoloro (600 mg, rendimiento de 16%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.37 (2H, m), 4.23 (2H, t, J = 7.4 Hz), 4.32 (2H, t, J = 7.4 Hz), 7.20 (1H, m), 7.40 (1H, m), 7.50 (1H, m).

(41b) 2-(5-{3-[4-(Azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol

El 2-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (70 mg, 0.163 mmol) sintetizado en el ejemplo (38d), y la 1-(3,4-difluorobenzoil)azetidina (68 mg, 0.345 mmol) sintetizada en el ejemplo (41a), se disolvieron en sulfóxido de dimetilo (3.0 mL) y se les agregó hidruro de sodio (60%, 25 mg, 0.63 mmol), seguido por agitación a 100°C durante 5 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó ácido clorhídrico 2N (30 mL) y se extrajo con éter dietílico (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 60%-80%), para producir el compuesto deseado como un sólido amarillo (54 mg, rendimiento de 65%).

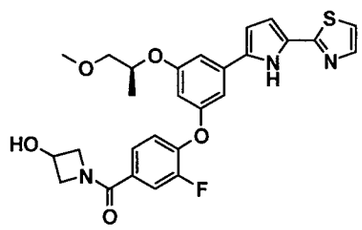
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^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 2.38 (2H, m), 3.41 (3H, s), 3.50 (1H, dd, J = 3.9, 10.2 Hz), 3.58 (1H, dd, J = 6.3, 10.2 Hz), 4.20-4.26 (2H, brs), 4.33-4.40 (2H, brs), 4,57 (1H, m), 6.49-6.52 (2H, m), 6.71 (1H, dd, J = 2.4, 3.9 Hz), 6.82 (1H, dd, J = 1.6, 2.4 Hz), 6.94 (1H, dd, J = 1.6, 2.4 Hz), 7.07 (1H, t, J = 8.2 Hz), 7.16 (1H, d, J = 3.5 Hz), 7.40 (1H, ddd, J = 1.2, 2.4, 8.6 Hz), 7.52 (1H, dd, J = 2.0, 11.0 Hz), 7.68 (1H, d, J = 3.2 Hz), 9.62 (1H, brs).

MS (ESI) m/z: 508.17094 $(M+H)^+$.

EJEMPLO 42

1-(3-Fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzoil)azetidin-3-ol



(42a) 1-(3,4-Difluorobenzoil)-3-(tetrahidro-2H-piran-2-iloxi)-azetidina

Se disolvió ácido 3,4-difluorobenzoico (1.00 g, 6.33 mmol), disponible comercialmente, en metanol (10 mL), y se le agregó clorhidrato de 3-hidroxiazetidina (830 mg, 7.58 mmol), cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio n-hidratado (2.10 g, 7.59 mmol) y N-metilmorfolina (0.85 mL, 2.83 mmol), seguido por agitación a temperatura

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ambiente durante 2.5 horas bajo una atmósfera de nitrógeno. El material insoluble se removió por filtración en Celite y el disolvente se removió por destilación bajo presión reducida. El residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-70%).

El compuesto resultante se disolvió en diclorometano (20 mL) y se le agregó 3,4-dihidro-2H-pirano (1.00 mL, 11.1 mmol) y p-toluenosulfonato de piridinio (250 mg, 0.99 mmol), seguido por agitación a temperatura ambiente durante la noche bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó trietilamina (0.5 mL), el disolvente se removió por destilación bajo presión reducida, y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 35%-50%), para producir el compuesto deseado como un líquido incoloro (2.24 g, rendimiento de ~100%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.48-1.65 (4H, br m), 1.68-1.89 (2H, br m), 3.46-3.55 (2H, br m), 3.83-3.88 (2H, br m), 4.02-4.47 (2H, br m), 4.55-4.66 (2H, br m), 7.18-7.21 (1H, m), 7.38-7.42 (1H, m), 7.47-7.52 (1H, m).

(42b) 2-(5-{3-(2-Fluoro-4-{[3-(tetrahidro-2H-piran-2-iloxi)azetidin-1-il]carbonil}fenoxi)-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol

El 2-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (150 mg, 0.348 mmol) sintetizado en el ejemplo (38d), y la 1-(3,4-difluorobenzoil)-3-(tetrahidro-2H-piran-2-iloxi)azetidina (220 mg, 0.740 mmol) sintetizada en el ejemplo (42a), se

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disolvieron en sulfóxido de dimetilo (5.0 mL) y se les agregó hidruro de sodio (60%, 70 mg, 1.75 mmol), seguido por agitación a 100°C durante 1.5 horas, bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó salmuera saturada (30 mL) y se extrajo con acetato de etilo (30 mL). Subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 65%-85%), para producir el compuesto deseado como un sólido blanco (158 mg, rendimiento de 75%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 1.48-1.90 (6H, m), 3.41 (3H, s), 3.46-3.55 (2H, m), 3.50 (1H, dd, J = 10.2, 4.3 Hz), 3.59 (1H, dd, J = 10.4, 6.1 Hz), 3.80-3.89 (2H, m), 4.40-4.64 (4H, m), 6.51-6.52 (2H, m), 6.72 (1H, dd, J = 3.5, 2.7 Hz), 6.82 (1H, br s), 6.94 (1H, br s), 7.06 (1H, t, J = 8.4 Hz), 7.17 (1H, d, J = 3.5 Hz), 7.34-7.44 (1H, m), 7.52 (1H, dd, J = 10.0, 5.0 Hz), 7.68 (1H, d, J = 3.1 Hz), 9.52 (1H, br s).

MS (ESI) m/z: 608.22267 $(M+H)^+$.

(42c) 1-(3-Fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzoil)azetidin-3-ol

El 2-(5-{3-(2-fluoro-4-{[3-(tetrahidro-2H-piran-2-iloxi)azetidin-1-il]carbonil}fenoxi)-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol (110 mg, 0.181 mmol) sintetizado en el ejemplo (42b) se disolvió en metanol (10 mL), y se le agregó ácido 10-alcanforsulfónico (20 mg, 0.086 mmol),

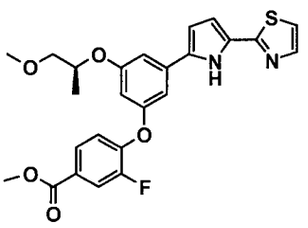
seguido por agitación a temperatura ambiente durante la noche bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó trietilamina (0.1 mL) y el disolvente se removió por destilación bajo presión reducida. El residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 90%-100%), para producir el compuesto deseado como un sólido amarillo (62 mg, rendimiento de 65%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 2.28 (1H, br s), 3.41 (3H, s), 3.50 (1H, dd, J = 10.4, 4.1 Hz), 3.59 (1H, dd, J = 10.2, 5.9 Hz), 4.08 (1H, br s), 4.23 (1H, br s), 4.45-4.58 (2H, m), 4.52-4.60 (1H, m), 4.71-4.80 (2H, m), 6.50-6.53 (2H, m), 6.73 (1H, dd, J = 3.5, 2.7 Hz), 6.83 (1H, t, J = 1.8 Hz), 6.95-6.97 (1H, m), 7.06 (1H, t, J = 8.2 Hz), 7.17 (1H, d, J = 3.1 Hz), 7.37-7.40 (1H, m), 7.50-7.53 (1H, m), 7.68 (1H, d, J = 3.1 Hz), 9.61 (1H, br s).

MS (ESI) m/z: 524.16841 $(M+H)^+$.

EJEMPLO 43

3-Fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzoato de metilo



El 2-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-

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il)-1H-pirrol-1-carboxilato de t-butilo (485 mg, 1.127 mmol) sintetizado en el ejemplo (38d), y 3,4-difluorobenzoato de metilo (540 mg, 3.137 mmol), disponible comercialmente, se disolvieron en sulfóxido de dimetilo (10 mL) y se les agregó hidruro de sodio (60%, 180 mg, 4.50 mmol), seguido por agitación a 100°C durante 2.5 horas, bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (50 mL) y se extrajo con éter dietílico (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-30%), para producir el compuesto deseado como un sólido blanco (97 mg, rendimiento de 18%).

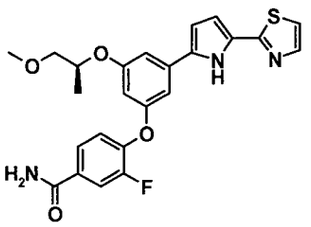
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J = 6.3 Hz), 3.39 (3H, s), 3.48 (1H, dd, J = 10.2, 3.9 Hz), 3.57 (1H, dd, J = 10.2, 5.9 Hz), 3.91 (3H, s), 4.51-4.59 (1H, m), 6.49-6.52 (2H, m), 6.71 (1H, dd, J = 3.9, 2.3 Hz), 6.82-6.85 (1H, br m), 6.98 (1H, br s), 7.05 (1H, t, J = 8.2 Hz), 7.15 (1H, d, J = 3.1 Hz), 7.66 (1H, d, J = 3.1 Hz), 7.78 (1H, d, J = 9.8 Hz), 7.85 (1H, dd, J = 11.1, 2.2 Hz), 9.78-9.87 (1H, m).

MS (ESI) m/z: 483.13782 $(M+H)^+$.

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EJEMPLO 44

3-Fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzamida



(44a) Acido 3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzoico

El 3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzoato de metilo (611 mg, 1.42 mmol) sintetizado en el ejemplo 43 se disolvió en metanol (18 mL), y se le agregó agua (3 mL) e hidróxido de litio monohidratado (298 mg, 7.10 mmol), seguido por agitación a 60°C durante 4 horas, bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó agua (50 mL) y se extrajo dos veces con acetato de etilo (40 mL), seguido por secado sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-75%), para producir el compuesto deseado como un sólido blanco (519 mg, rendimiento de 88%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.38 (3H, d, J = 6.3 Hz), 3.45 (3H, s), 3.55 (1H, dd, J = 10.2, 4.3 Hz), 3.64 (1H, dd, J = 10.2, 5.9 Hz), 4.60-4.67 (1H, m), 6.63 (1H, dd, J = 3.9, 2.7 Hz), 6.74 (1H, t, J = 2.2 Hz), 6.84 (1H, dd, J

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= 3.9, 2.3 Hz), 6.99 (1H, t, J = 8.2 Hz), 7.16-7.14 (2H, m), 7.41 (1H, t, J = 1.8 Hz), 7.55 (1H, dt, J = 8.6, 1.0 Hz), 7.61 (1H, d, J = 3.1 Hz), 7.72 (1H, dd, J = 10.6, 2.0 Hz), 11.85 (1H, s).

(44b) 3-Fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzamida

El ácido 3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzoico (40.0 mg, 0.163 mmol) sintetizado en el ejemplo (44a) se disolvió en diclorometano (5 mL), y se le agregó una solución acuosa de amoniaco al 28% (0.50 mL), WSCI·HCl (19.6 mg, 0.102 mmol) y HOBt·H_2O (13.1 mg, 0.086 mmol), seguido por agitación a temperatura ambiente durante 7 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó agua (10 mL) y se extrajo con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-75%), para producir el compuesto deseado como un sólido blanco (11.3 mg, rendimiento de 28%).

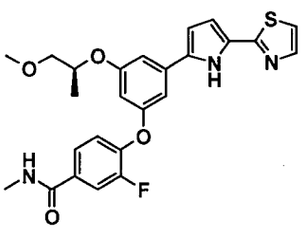
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.42 (3H, s), 3.51 (1H, dd, J = 10.3, 5.4 Hz), 3.59 (1H, dd, J = 10.3, 5.9 Hz), 4.54-4.61 (1H, m), 6.51-6.54 (2H, m), 6.73 (1H, dd, J = 3.4, 2.4 Hz), 6.84 (1H, s), 6.97 (1H, s), 7.09 (1H, t, J = 8.1 Hz), 7.18 (1H, d, J = 2.9 Hz), 7.53 (1H, d, J = 8.8 Hz), 7.67-7.73 (2H, m), 9.60 (1H, br s).

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MS (ESI) m/z: 468.13800 $(M+H)^+$.

EJEMPLO 45

3-Fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-N-metilbenzamida



El ácido 3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzoico (40.0 mg, 0.163 mmol) sintetizado en el ejemplo (44a) se disolvió en tetrahidrofurano (5 mL), y se le agregó clorhidrato de metilamina (17.3 mg, 0.256 mmol), HATU (64.5 mg, 0.170 mmol) y N,N-diisopropiletilamina (89 μL, 0.51 mmol), seguido por agitación a temperatura ambiente durante 4 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó salmuera saturada (15 mL) y se extrajo dos veces con acetato de etilo (15 mL), seguido por secado sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-55%), para producir el compuesto deseado como un sólido amarillo pálido (41 mg, rendimiento de ~100%).

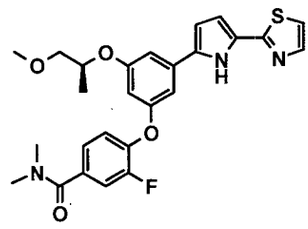
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 3.03 (3H, d, J = 4.7 Hz), 3.41 (3H, s), 3.50 (1H, dd, J = 10.2, 3.9 Hz), 3.58 (1H, dd, J =

10.2, 6.3 Hz), 4.52-4.60 (1H, m), 6.49-6.53 (2H, m), 6.72 (1H, dd, J = 3.9, 2.3 Hz), 6.79 (1H, t, J = 2.0 Hz), 6.94 (1H, t, J = 2.0 Hz), 7.08 (1H, t, J = 8.0 Hz), 7.17 (1H, d, J = 3.5 Hz), 7.47 (1H, d, J = 8.6 Hz), 7.65 (1H, dd, J = 10.9, 2.0 Hz), 7.68 (1H, d, J = 3.9 Hz), 9.48 (1H, br s).

MS (ESI) m/z: 482.15436 $(M+H)^+$.

EJEMPLO 46

3-Fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-N,N-dimetilbenzamida



El ácido 3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzoico (40.0 mg, 0.163 mmol) sintetizado en el ejemplo (44a) se disolvió en tetrahidrofurano (5 mL), y se le agregó clorhidrato de dimetilamina (20.1 mg, 0.246 mmol), HATU (64.5 mg, 0.170 mmol) y N,N-diisopropiletilamina (89 μL, 0.51 mmol), seguido por agitación a temperatura ambiente durante 4 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó salmuera saturada (15 mL) y se extrajo dos veces con acetato de etilo (15 mL), seguido por secado sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente

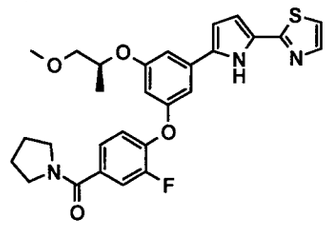
de elución: acetato de etilo/hexano = 0%-75%), para producir el compuesto deseado como un sólido amarillo pálido (45 mg, rendimiento de 99%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 3.02-3.14 (6H, br m), 3.41 (3H, s), 3.50 (1H, dd, J = 10.2, 3.9 Hz), 3.58 (1H, dd, J = 10.2, 5.9 Hz), 4.52-4.61 (1H, m), 6.49-6.54 (2H, m), 6.73 (1H, dd, J = 3.7, 1.9 Hz), 6.85 (1H, t, J = 1.6 Hz), 6.95 (1H, t, J = 1.6 Hz), 7.08 (1H, t, J = 8.0 Hz), 7.16-7.20 (2H, m), 7.29 (1H, dd, J = 10.8, 1.8 Hz), 7.68 (1H, d, J = 3.1 Hz), 9.65 (1H, br s).

MS (ESI) m/z: 496.17025 $(M+H)^+$.

EJEMPLO 47

2-(5-{3-[2-Fluoro-4-(pirrolidin-1-ilcarbonil)fenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol



El ácido 3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzoico (40.0 mg, 0.085 mmol) sintetizado en el ejemplo (44a) se disolvió en tetrahidrofurano (5 mL), y se le agregó pirrolidina (21 μL, 0.26 mmol), HATU (64.9 mg, 0.171 mmol) y N,N-diisopropiletilamina (89 μL, 0.51 mmol), seguido por agitación a temperatura ambiente durante 20 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó

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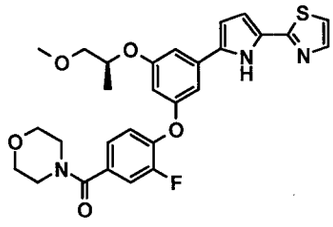
salmuera saturada (15 mL) y se extrajo dos veces con acetato de etilo (15 mL), seguido por secado sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-75%), para producir el compuesto deseado como un sólido blanco (32 mg, rendimiento de 72%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.29 (3H, d, J = 6.3 Hz), 1.84-1.98 (4H, m), 3.38 (3H, s), 3.41-3.49 (3H, m), 3.55 (1H, dd, J = 10.2, 5.9 Hz), 3.61 (2H, t, J = 6.8 Hz), 4.48-4.56 (1H, m), 6.46-6.49 (2H, m), 6.68 (1H, dd, J = 3.9, 2.7 Hz), 6.78 (1H, t, J = 1.8 Hz), 6.89 (1H, t, J = 2.0 Hz), 7.04 (1H, t, J = 8.2 Hz), 7.13 (1H, d, J = 3.1 Hz), 7.25-7.29 (1H, m), 7.38 (1H, dd, J = 10.9, 2.0 Hz), 7.64 (1H, d, J = 3.5 Hz), 9.51 (1H, br s).

MS (ESI) m/z: 522.18695 $(M+H)^+$.

EJEMPLO 48

4-(3-Fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzoil)morfolina



El ácido 3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzoico (49.0 mg, 0.105 mmol) sintetizado en el

ejemplo (44a) se disolvió en tetrahidrofurano (5 mL), y se le agregó morfolina (22 μL, 0.26 mmol), HATU (64.5 mg, 0.170 mmol) y N,N-diisopropiletilamina (89 μL, 0.51 mmol), seguido por agitación a temperatura ambiente durante 4 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó salmuera saturada (15 mL) y se extrajo dos veces con acetato de etilo (15 mL), seguido por secado sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-75%), para producir el compuesto deseado como un sólido amarillo pálido (39 mg, rendimiento de 70%).

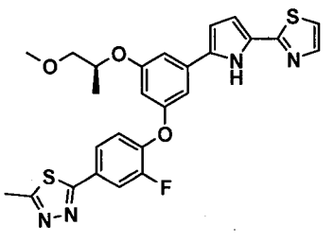
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.42 (3H, s), 3.51 (1H, dd, J = 10.2, 4.3 Hz), 3.59 (1H, dd, J = 10.2, 5.9 Hz), 3.72 (8H, br s), 4.52-4.61 (1H, m), 6.49-6.54 (2H, m), 6.72 (1H, dd, J = 3.7, 2.5 Hz), 6.82 (1H, t, J = 1.8 Hz), 6.93 (1H, t, J = 1.8 Hz), 7.09 (1H, t, J = 8.2 Hz), 7.16-7.19 (2H, m), 7.30 (1H, dd, J = 10.6, 2.0 Hz), 7.69 (1H, d, J = 3.1 Hz), 9.45 (1H, br s).

MS (ESI) m/z: 538.18048 $(M+H)^+$.

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EJEMPLO 49

2-(3-Fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}fenil)-5-metil-1,3,4-tiadiazol



(49a) N'-Acetil-3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzohidrazida

El ácido 3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzoico (84 mg, 0.179 mmol) sintetizado en el ejemplo (44a) se disolvió en diclorometano (5.0 mL), y se le agregó acetohidrazida (40 mg, 0.540 mmol), HATU (200 mg, 0.526 mmol) y N,N-diisopropiletilamina (0.15 mL, 0.861 mmol), seguido por agitación a temperatura ambiente durante la noche, bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo), para producir el compuesto deseado como un sólido blanco (110 mg, rendimiento de ~100%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.44 (3/2H, d, J = 6.3 Hz), 1.49 (3/2H, d, J = 6.3 Hz), 2.05 (3H, s), 3.46 (3H, s), 3.55 (1H, dd, J = 10.8, 4.1 Hz), 3.65 (1H, dd, J = 10.0, 6.1 Hz), 4.58-4.69 (1H, m), 6.69 (1H, d, J = 2.3 Hz), 6.73 (1H, s), 6.77 (1H, d, J = 2.7 Hz), 7.12 (1H, br s), 7.16 (1H, br s), 7.29 (1H,

br s), 7.34 (1H, br s), 7.37 (1H, br s), 7.45 (1H, d, J = 8.2 Hz), 7.62 (1H, br s), 11.51 (1H, br s), 11.79 (1H, br s), 12.56 (1H, br s).

MS (ESI) m/z: 547.14358 $(M+Na)^+$.

(49b) 2-(3-Fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}fenil)-5-metil-1,3,4-tiadiazol

La N'-acetil-3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzohidrazida (40 mg, 0.076 mmol) sintetizada en el ejemplo (49a) se disolvió un disolvente mixto de tolueno (4.0 mL) y acetonitrilo (2.0 mL), y se le agregó 2,4-disulfuro de 2,4-bis-(4-metoxifenil)-1,3-ditia-2,4-difosfoetano (45 mg, 0.111 mmol) y piridina (0.03 mL, 0.372 mmol), seguido por agitación a 100°C durante 4 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, el disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 60%-80%), para producir el compuesto deseado como un sólido amarillo (28 mg, rendimiento de 70%).

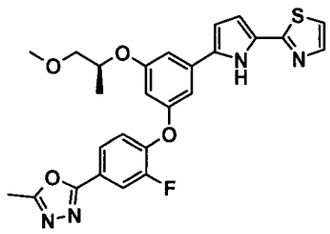
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 2.83 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 10.3, 4.4 Hz), 3.60 (1H, dd, J = 10.3, 5.9 Hz), 4.57-4.63 (1H, m), 6.54-6.54 (2H, m), 6.77 (1H, s), 6.87 (1H, s), 7.00 (1H, s), 7.14-7.17 (2H, m), 7.64 (1H, dd, J = 8.3, 1.0 Hz), 7.68 (1H, d, J = 3.4 Hz), 7.84 (1H, dd, J = 11.2, 2.0 Hz), 10.01 (1H, br s).

MS (ESI) m/z: 523.12785 $(M+H)^+$.

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EJEMPLO 50

2-(3-Fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}fenil)-5-metil-1,3,4-oxadiazol



La N'-acetil-3-fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}benzohidrazida (45 mg, 0.086 mmol) sintetizada en el ejemplo (49a) se disolvió en acetonitrilo (3.0 mL), y se le agregó hidróxido de (metoxicarbonilsulfamoil)trietilamonio (50 mg, 0.210 mmol) y trietilamina (0.05 mL, 0.359 mmol), seguido por agitación a 100°C durante 1 día bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 80%-100%), para producir el compuesto deseado como un líquido incoloro (26 mg, rendimiento de 60%).

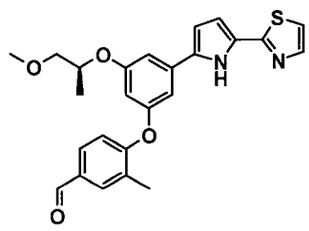
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 2.63 (3H, s), 3.42 (3H, s), 3.50 (1H, dd, J = 10.2, 4.3 Hz), 3.60 (1H, dd, J = 10.2, 5.9 Hz), 4.54-4.62 (1H, m), 6.50-6.55 (2H, m), 6.72 (1H, dd, J = 3.5, 2.0 Hz), 6.86 (1H, s), 6.99 (1H, s), 7.12-7.19 (2H, m), 7.67 (1H, d, J = 3.1 Hz), 7.78 (1H, d, J = 9.0 Hz), 7.87 (1H, dd, J = 10.8, 1.4 Hz), 9.94 (1H, br s).

MS (ESI) m/z: 507.14909 $(M+H)^+$.

1177

EJEMPLO 51

4-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-3-metilbenzaldehído



El 2-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (150 mg, 0.348 mmol) sintetizado en el ejemplo (38d), y 4-fluoro-3-metilbenzaldehído (0.14 mL, 1.148 mmol), disponible comercialmente, se disolvieron en sulfóxido de dimetilo (5.0 mL) y se les agregó hidruro de sodio (60%, 40 mg, 1.00 mmol), seguido por agitación a 100°C durante 4 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó una solución acuosa saturada de cloruro de amonio (30 mL), y se extrajo con éter dietílico (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 25%-30%), para producir el compuesto deseado como un sólido amarillo (84 mg, rendimiento de 54%).

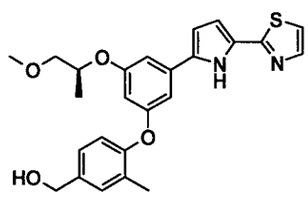
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 2.39 (3H, s), 3.42 (3H, s), 3.50 (1H, dd, J = 10.2, 3.9 Hz), 3.60 (1H, dd, J = 10.4, 6.1 Hz),

4.55-4.64 (1H, m), 6.50 (1H, t, J = 2.2 Hz), 6.53 (1H, dd, J = 3.7, 2.9 Hz), 6.74 (1H, t, J = 2.5 Hz), 6.83 (1H, t, J = 2.0 Hz), 6.96 (1H, d, J = 8.2 Hz), 7.00-7.02 (1H, m), 7.17 (1H; d, J = 3.1 Hz), 7.65 (1H, d, J = 2.3 Hz), 7.68 (1H, d, J = 3.1 Hz), 7.81 (1H, d, J = 1.2 Hz), 9.90 (1H, br s), 9.92 (1H, s).

MS (ESI) m/z: 449.15343 $(M+H)^+$.

EJEMPLO 52

(4-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-3-metilfenil)metanol



El 4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-3-metilbenzaldehído (32 mg, 0.071 mmol) sintetizado en el ejemplo 51 se disolvió en metanol (3.0 mL), y se le agregó borohidruro de sodio (5 mg, 0.132 mmol), seguido por agitación a 0°C durante 4 horas bajo una atmósfera de nitrógeno. La solución de reacción se llevó a temperatura ambiente, se le agregó una solución acuosa saturada de cloruro de amonio (10 mL) y se extrajo con acetato de etilo (10 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente

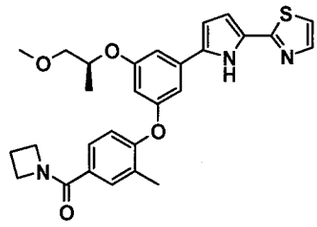
de elución: acetato de etilo/hexano = 50%-75%), para producir el compuesto deseado como un sólido blanco (26 mg, rendimiento de 81%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 2.26 (3H, s), 3.41 (3H, s), 3.49 (1H, dd, J = 10.2, 4.3 Hz), 3.58 (1H, dd, J = 10.2, 5.9 Hz), 4.51-4.60 (1H, m), 4.67 (2H, br s), 6.40 (1H, t, J = 2.2 Hz), 6.49 (1H, dd, J = 3.5, 2.7 Hz), 6.70-6.72 (2H, m), 6.86 (1H, dd, J = 3.5, 1.6 Hz), 6.96 (1H, d, J = 8.2 Hz), 7.15 (1H, d, J = 3.5 Hz), 7.19 (1H, dd, J = 8.2, 2.0 Hz), 7.28 (1H, d, J = 2.3 Hz), 7.66 (1H, d, J = 3.5 Hz), 9.72 (1H, br s).

MS (ESI) m/z: 451.16757 $(M+H)^+$.

EJEMPLO 53

2-(5-{3-[4-(Azetidin-1-ilcarbonil)-2-metilfenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol



(53a) Acido 4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-3-metilbenzoico

El 4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-3-metilbenzaldehído (50 mg, 0.11 mmol) sintetizado en el ejemplo 51 se disolvió en un disolvente mixto de t-butanol (5.0 mL) y agua (2.0 mL), y se le agregó 2-metil-2-buteno (0.15 mL, 1.42 mmol) y fosfato diácido de sodio

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dihidratado (80 mg, 0.51 mmol), seguido por la adición lenta de clorito de sodio (25 mg, 0.28 mmol) a 0°C y agitación a 0°C durante 2 horas, bajo una atmósfera de nitrógeno. Se le agregó una solución acuosa de sulfito ácido de sodio (5 mL) a 0°C y se agitó a temperatura ambiente durante 10 minutos. Se le agregó una solución acuosa de sulfito ácido de sodio (15 mL) y se extrajo con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida para producir el compuesto deseado como un sólido amarillo (58 mg, rendimiento de ~100%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 2.33 (3H, s), 3.41 (3H, s), 3.52 (1H, dd, J = 10.6, 4.3 Hz), 3.60 (1H, dd, J = 10.2, 5.9 Hz), 4.62-4.71 (1H, m), 6.54-6.57 (2H, m), 6.85-6.87 (2H, m), 7.08-7.16 (2H, m), 7.15 (1H, d, J = 3.5 Hz), 7.64 (1H, s), 7.64 (1H, d, J = 3.5 Hz), 7.87 (1H, s).

(53b) 2-(5-{3-[4-(Azetidin-1-ilcarbonil)-2-metilfenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol

El ácido 4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-3-metilbenzoico (58 mg, 0.125 mmol) sintetizado en el ejemplo (53a) y clorhidrato de azetidina (29 mg, 0.310 mmol) se disolvieron en diclorometano (10.0 mL) y se les agregó HATU (95 mg, 0.250 mmol) y N,N-diisopropiletilamina (0.15 mL, 0.861 mmol), seguido por agitación a temperatura ambiente durante la noche bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente

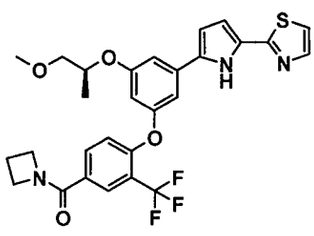
de elución: acetato de etilo/hexano = 75%-90%), para producir el compuesto deseado como un sólido amarillo (58 mg, rendimiento de 92%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 2.30 (3H, s), 2.31-2.39 (2H, m), 3.41 (3H, s), 3.49 (1H, dd, J = 10.4, 4.1 Hz), 3.59 (1H, dd, J = 10.2, 5.9 Hz), 4.22-4.25 (2H, br m), 4.33-4.36 (2H, br m), 4.52-4.60 (1H, m), 6.43 (1H, t, J = 2.3 Hz), 6.50 (1H, dd, J = 3.7, 2.9 Hz), 6.72 (1H, dd, J = 3.9, 2.3 Hz), 6.76 (1H, t, J = 1.8 Hz), 6.90 (1H, s), 6.92-6.93 (1H, m), 7.16 (1H, d, J = 3.1 Hz), 7.42 (1H, dd, J = 8.2, 2.0 Hz), 7.59 (1H, d, J = 1.6 Hz), 7.67 (1H, d, J = 3.1 Hz), 9.73 (1H, br s).

MS (ESI) m/z: 504.19979 $(M+H)^+$.

EJEMPLO 54

2-(5-{3-[4-(Azetidin-1-ilcarbonil)-2-(trifluorometil)fenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol



(54a) 1-[4-Fluoro-3-(trifluorometil)benzoil]azetidina

Se disolvió ácido 4-fluoro-3-(trifluorometil)benzoico (230 mg, 1.10 mmol), disponible comercialmente, en diclorometano (50 mL), y se le agregó clorhidrato de azetidina (120 mg, 1.28 mmol), HATU (550 mg, 1.45 mmol) y N,N-diisopropiletilamina (0.50 mL, 2.87 mmol), seguido por agitación a

temperatura ambiente durante 4 horas bajo una atmósfera de nitrógeno. Se le agregó ácido clorhídrico 0.5N (100 mL) y se extrajo con diclorometano (100 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 60%-80%), para producir el compuesto deseado como un líquido incoloro (211 mg, rendimiento de 78%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.35-2.43 (2H, m), 4.25 (2H, t, J = 7.6 Hz), 4.33 (2H, t, J = 7.4 Hz), 7.83-7.87 (1H, m), 7.93 (1H, dd, J = 6.6, 2.0 Hz).

(54b) 2-(5-{3-[4-(Azetidin-1-ilcarbonil)-2-(trifluorometil)fenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol

El 2-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (119 mg, 0.276 mmol) sintetizado en el ejemplo (38d), y la 1-[4-fluoro-3-(trifluorometil)benzoil]azetidina (145 mg, 0.587 mmol) sintetizada en el ejemplo (54a), se disolvieron en sulfóxido de dimetilo (8.0 mL) y se les agregó hidruro de sodio (60%, 39 mg, 0.97 mmol), seguido por agitación a 100°C durante 2 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente

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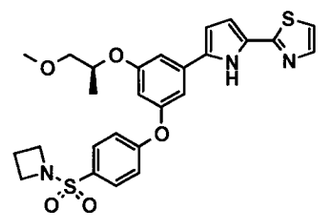
se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 45%-60%), para producir el compuesto deseado como un sólido amarillo (105 mg, rendimiento de 68%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 2.34-2.42 (2H, m), 3.42 (3H, s), 3.50 (1H, dd, J = 10.2, 4.3 Hz), 3.60 (1H, dd, J = 10.2, 5.9 Hz), 4.25 (2H, t, J = 6.8 Hz), 4.36 (2H, t, J = 6.6 Hz), 4.56-4.60 (1H, m), 6.54-6.55 (2H, m), 6.73 (1H, dd, J = 3.7, 2.5 Hz), 6.87 (1H, t, J = 1.6 Hz), 6.99 (1H, d, J = 8.6 Hz), 7.03 (1H, t, J = 1.8 Hz), 7.17 (1H, d, J = 3.1 Hz), 7.68 (1H, d, J = 3.1 Hz), 7.74 (1H, dd, J = 8.6, 2.3 Hz), 8.00 (1H, d, J = 2.0 Hz), 9.73 (1H, br s).

MS (ESI) m/z: 558.16727 $(M+H)^+$.

EJEMPLO 55

2-(5-{3-[4-(Azetidin-1-ilsulfonil)fenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol



(55a) 1-[(4-Fluorofenil)sulfonil]azetidina

Se suspendió en agua (8 mL) cloruro de 4-fluorofenilsulfonilo (225 mg, 1.15 mmol), disponible comercialmente, y se le agregó clorhidrato de

azetidina (90.0 mg, 0.96 mmol) y carbonato de potasio (293 mg, 2.12 mmol), seguido por agitación a temperatura ambiente durante 16 horas. A la solución de reacción se le agregó agua (15 mL), seguido por extracción dos veces con éter dietílico (15 mL) y lavado con salmuera saturada (15 mL), seguido por secado sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida, seguido por secado al vacío, para producir el compuesto deseado como un sólido blanco (170 mg, rendimiento de 82%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.10-2.17 (2H, m), 3.82 (4H, t, J = 7.8 Hz), 7.28-7.30 (2H, m), 7.88-7.92 (2H, m).

(55b) 2-(5-{3-[4-(Azetidin-1-ilsulfonil)fenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol

El 2-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (60.0 mg, 0.139 mmol) sintetizado en el ejemplo (38d), y la 1-[(4-fluorofenil)sulfonil]azetidina (60.0 mg, 0.279 mmol) sintetizada en el ejemplo (55a), se disolvieron en N-metilpirrolidona (5.0 mL) y se les agregó hidruro de sodio (60%, 24 mg, 0.60 mmol), seguido por agitación a 100°C durante 6 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) y se extrajo con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-35%), para producir el

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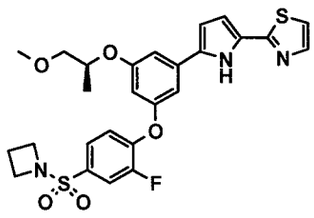
compuesto deseado como un sólido blanco (42 mg, rendimiento de 57%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.37 (3H, d, J = 6.8 Hz), 2.12-2.18 (2H, m), 3.45 (3H, s), 3.54 (1H, dd, J = 10.3, 4.4 Hz), 3.64 (1H, dd, J = 10.0, 6.1 Hz), 3.83 (4H, t, J = 7.6 Hz), 4.59-4.65 (1H, m), 6.57 (1H, t, J = 3.4 Hz), 6.60 (1H, t, J = 2.0 Hz), 6.76 (1H, t, J = 3.7 Hz), 6.92 (1H, s), 7.07 (1H, s), 7.18 (2H, d, J = 8.3 Hz), 7.21 (1H, d, J = 2.9 Hz), 7.71 (1H, d, J = 2.9 Hz), 7.84 (2H, d, J = 8.8 Hz), 9.76 (1H, br s).

MS (ESI) m/z: 526.14773 $(M+H)^+$.

EJEMPLO 56

2-(5-{3-[4-(Azetidin-1-ilsulfonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol



(56a) 1-[(3,4-Difluorofenil)sulfonil]azetidina

Se disolvió en diclorometano (5 mL) cloruro de 3,4-difluorofenilsulfonilo (117 µL, 0.87 mmol), disponible comercialmente, y se le agregó clorhidrato de azetidina (68 mg, 0.73 mmol) y trietilamina (203 µL, 1.45 mmol), seguido por agitación a temperatura ambiente durante 2 horas. A la solución de reacción se le agregó agua (15 mL) y se extrajo dos veces con diclorometano (15 mL). Se lavó con salmuera saturada (15 mL), seguido por

secado sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-50%), para producir el compuesto deseado como un aceite incoloro (132 mg, rendimiento de 78%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.10-2.18 (2H, m), 3.82 (4H, t, J = 7.6 Hz), 7.35-7.41 (1H, m), 7.66-7.62 (1H, m), 7.72-7.68 (1H, m).

(56b) 2-(5-{3-[4-(Azetidin-1-ilsulfonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-1,3-tiazol

El 2-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (65.0 mg, 0.151 mmol) sintetizado en el ejemplo (38d), y la 1-[(3,4-difluorofenil)sulfonil]azetidina (42.3 mg, 0.181 mmol) sintetizada en el ejemplo (56a), se disolvieron en N-metilpirrolidona (5.0 mL) y se les agregó hidruro de sodio (55%, 20 mg, 0.45 mmol), seguido por agitación a 100°C durante 4 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó una solución acuosa saturada de cloruro de amonio (20 mL) y se extrajo con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó dos veces por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-35%), para producir el compuesto deseado como un sólido blanco (35.6 mg, rendimiento de 43%).

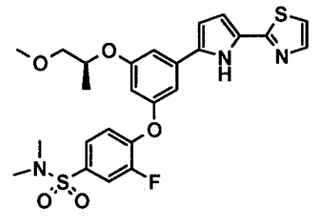
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^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 2.11-2.20 (2H, m), 3.42 (3H, s), 3.51 (1H, dd, J = 10.4, 4.1 Hz), 3.60 (1H, dd, J = 10.4, 6.1 Hz), 3.84 (4H, t, J = 7.6 Hz), 4.55-4.63 (1H, m), 6.53-6.56 (2H, m), 6.73 (1H, dd, J = 3.9, 2.3 Hz), 6.89 (1H, t, J = 2.0 Hz), 7.03 (1H, t, J = 1.8 Hz), 7.14 (1H, t, J = 8.0 Hz), 7.18 (1H, d, J = 3.5 Hz), 7.57 (1H, d, J = 8.6 Hz), 7.67-7.71 (2H, m), 9.79 (1H, br s).

MS (ESI) m/z: 544.13720 $(M+H)^+$.

EJEMPLO 57

3-Fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-N,N-dimetilbencenosulfonamida



(57a) 3,4-Difluoro-N,N-dimetilbencenosulfonamida

Se disolvió cloruro de 3,4-difluorofenilsulfonilo (117 µL, 0.87 mmol) en diclorometano (5 mL), y se le agregó clorhidrato de dimetilamina (59 mg, 0.73 mmol) y trietilamina (203 µL, 1.45 mmol), seguido por agitación a temperatura ambiente durante 2 horas. A la solución de reacción se le agregó agua (15 mL), seguido por extracción dos veces con diclorometano (15 mL) y lavado con salmuera saturada (15 mL), seguido por secado sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida, seguido

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por secado al vacío, para producir el compuesto deseado como un aceite incoloro (41.0 mg, rendimiento de 26%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.74 (6H, s), 7.32-7.38 (1H, m), 7.59-7.55 (1H, m), 7.61-7.66 (1H, m).

(57b) 3-Fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-N,N-dimetilbencenosulfonamida

El 2-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (65.0 mg, 0.151 mmol) sintetizado en el ejemplo (38d), y la 3,4-difluoro-N,N-dimetilbencenosulfonamida (40.1 mg, 0.181 mmol) sintetizada en el ejemplo (57a), se disolvieron en N-metilpirrolidona (5.0 mL) y se les agregó hidruro de sodio (55%, 20 mg, 0.45 mmol), seguido por agitación a 100°C durante 4 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó una solución acuosa saturada de cloruro de amonio (20 mL) y se extrajo con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-35%), para producir el compuesto deseado como un sólido blanco (31.0 mg, rendimiento de 39%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 2.76 (6H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 10.4, 4.1 Hz), 3.60 (1H, dd, J = 10.4, 6.1 Hz), 4.55-4.62 (1H, m), 6.53-6.55 (2H, m), 6.73 (1H, dd, J = 3.7, 2.5 Hz), 6.87 (1H,

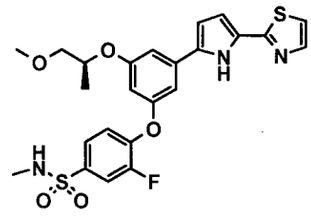
1789

t, J = 1.8 Hz), 7.02 (1H, t, J = 1.8 Hz), 7.12 (1H, t, J = 8.0 Hz), 7.18 (1H, d, J = 3.5 Hz), 7.52-7.49 (1H, m), 7.63 (1H, dd, J = 9.8, 2.0 Hz), 7.68 (1H, d, J = 3.1 Hz), 9.79 (1H, s).

MS (ESI) m/z: 532.13886 $(M+H)^+$.

EJEMPLO 58

3-Fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-N-metilbencenosulfonamida



(58a) 3,4-Difluoro-N-metilbencenosulfonamida

Se disolvió cloruro de 3,4-difluorofenilsulfonilo (117 μL, 0.87 mmol), disponible comercialmente, en diclorometano (5 mL), y se le agregó clorhidrato de metilamina (49 mg, 0.73 mmol) y trietilamina (203 μL, 1.45 mmol), seguido por agitación a temperatura ambiente durante 2 horas. A la solución de reacción se le agregó agua (15 mL), se extrajo dos veces con diclorometano (15 mL) y se lavó con salmuera saturada (15 mL), seguido por secado sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida, seguido por secado al vacío, para producir el compuesto deseado como un aceite incoloro (44.7 mg, rendimiento de 30%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.70 (3H, d, J = 5.5 Hz), 4.43 (1H,

br s), 7.36-7.30 (1H, m), 7.64-7.68 (1H, m), 7.69-7.74 (1H, m).

(58b) 3-Fluoro-4-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-N-metilbencenosulfonamida

El 2-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (60.0 mg, 0.139 mmol) sintetizado en el ejemplo (38d), y la 3,4-difluoro-N-metilbencenosulfonamida (47.4 mg, 0.229 mmol) sintetizada en el ejemplo (58a), se disolvieron en N,N-dimetilformamida (5.0 mL) y se les agregó carbonato de potasio (77.0 mg, 0.557 mmol), seguido por agitación a 100°C durante 19 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) y se extrajo con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-25%), para producir el compuesto deseado como un sólido blanco (21.1 mg, rendimiento de 30%).

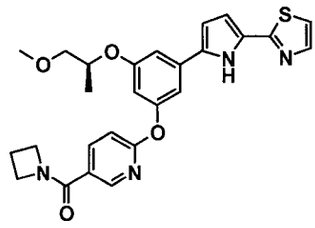
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (4H, d, J = 5.9 Hz), 2.69 (3H, d, J = 5.4 Hz), 3.42 (3H, s), 3.51 (1H, dd, J = 10.3, 4.4 Hz), 3.60 (1H, dd, J = 10.3, 5.9 Hz), 4.55-4.61 (1H, m), 5.22 (1H, s), 6.55 (2H, dt, J = 8.3, 2.7 Hz), 6.74 (1H, t, J = 2.9 Hz), 6.89 (1H, s), 7.01 (1H, t, J = 1.7 Hz), 7.12 (1H, t, J = 8.1 Hz), 7.16-7.18 (1H, m), 7.56-7.61 (2H, m), 7.69 (1H, d, J = 9.8 Hz), 9.96 (1H, br s).

MS (ESI) m/z: 518.12006 $(M+H)^+$.

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EJEMPLO 59

5-(Azetidin-1-ilcarbonil)-2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}piridina



(59a) 5-(Azetidin-1-ilcarbonil)-2-cloropiridina

Se disolvió ácido 6-cloronicotínico (160 mg, 1.01 mmol), disponible comercialmente, en diclorometano (5 mL), y se le agregó clorhidrato de azetidina (130 mg, 1.39 mmol), HATU (420 mg, 1.10 mmol) y N,N-diisopropiletilamina (0.50 mL, 2.87 mmol), seguido por agitación a temperatura ambiente durante la noche bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 40%-50%), para producir el compuesto deseado como un líquido incoloro (210 mg, rendimiento de ~100%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.40 (2H, m), 4.25 (2H, t, J = 7.6 Hz), 4.35 (2H, t, J = 7.6 Hz), 7.40 (1H, dd, J = 0.8, 8.6 Hz), 7.97 (1H, dd, J = 2.4, 8.2 Hz), 8.62 (1H, dd, J = 0.8, 2.4 Hz).

(59b) 5-(Azetidin-1-ilcarbonil)-2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}piridina

El 2-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-

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il)-1H-pirrol-1-carboxilato de t-butilo (84 mg, 0.195 mmol) sintetizado en el ejemplo (38d), y la 5-(azetidin-1-ilcarbonil)-2-cloropiridina (110 mg, 0.559 mmol) sintetizada en el ejemplo (59a), se disolvieron en sulfóxido de dimetilo (3.0 mL) y se les agregó hidruro de sodio (60%, 30 mg, 0.75 mmol), seguido por agitación a 100°C durante 2 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó ácido clorhídrico 2N (30 mL), y se extrajo con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 75%-90%), para producir el compuesto deseado como un sólido amarillo (56 mg, rendimiento de 59%).

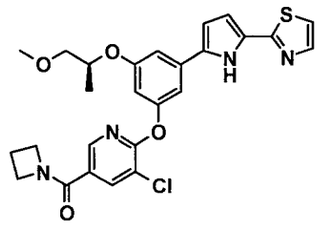
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 2.38 (2H, m), 3.42 (3H, s), 3.50 (1H, dd, J = 4.3, 10.2 Hz), 3.60 (1H, dd, J = 5.9, 10.2 Hz), 4.24 (2H, t, J = 7.4 Hz), 4.36 (2H, t, J = 6.6 Hz), 4,57 (1H, m), 6.54 (1H, dd, J = 2.7, 3.9 Hz), 6.64 (1H, t, J = 2.3 Hz), 6.73 (1H, dd, J = 2.4, 3.9 Hz), 6.97 (2H, m), 7.07 (1H, t, J = 1.8 Hz), 7.16 (1H, d, J = 3.5 Hz), 7.67 (1H, d, J = 3.1 Hz), 8.07 (1H, dd, J = 2.7, 8.6 Hz), 8.45 (1H, d, J = 2.4 Hz), 9.85 (1H, brs).

MS (ESI) m/z: 491.17450 $(M+H)^+$.

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EJEMPLO 60

5-(Azetidin-1-ilcarbonil)-3-cloro-2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}piridina



(60a) 5-(Azetidin-1-ilcarbonil)-2,3-dicloropiridina

Se disolvió ácido 5,6-dicloronicotínico (200 mg, 1.04 mmol), disponible comercialmente, en diclorometano (5.0 mL), y se le agregó clorhidrato de azetidina (125 mg, 1.34 mmol), HATU (440 mg, 1.16 mmol) y N,N-diisopropiletilamina (0.45 mL, 2.58 mmol), seguido por agitación a temperatura ambiente durante 5 horas bajo una atmósfera de nitrógeno. Se le agregó ácido clorhídrico 0.5N (30 mL) y se extrajo con diclorometano (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 60%-80%), para producir el compuesto deseado como un líquido incoloro (162 mg, rendimiento de 67%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.38-2.46 (2H, m), 4.25 (2H, t, J = 7.6 Hz), 4.37 (2H, t, J = 7.6 Hz), 8.10 (1H, d, J = 2.3 Hz), 8.51 (1H, d, J = 2.3 Hz).

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(60b) 5-(Azetidin-1-ilcarbonil)-3-cloro-2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}piridina

El 2-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (70 mg, 0.163 mmol) sintetizado en el ejemplo (38d), y la 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina (75 mg, 0.325 mmol) sintetizada en el ejemplo (60a), se disolvieron en sulfóxido de dimetilo (5.0 mL) y se les agregó hidruro de sodio (60%, 30 mg, 0.75 mmol), y se agitó a 100°C durante 3.5 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 85%-100%), para producir el compuesto deseado como un sólido amarillo (58 mg, rendimiento de 68%).

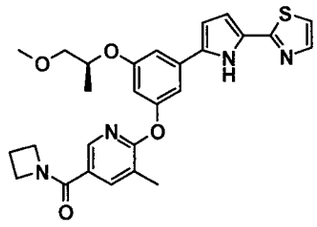
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.35 (3H, d, J = 5.9 Hz), 2.34-2.42 (2H, m), 3.42 (3H, s), 3.51 (1H, dd, J = 10.6, 4.7 Hz), 3.61 (1H, dd, J = 10.4, 5.7 Hz), 4.21-4.27 (2H, m), 4.34-4.37 (2H, m), 4.56-4.59 (1H, m), 6.54 (1H, t, J = 2.9 Hz), 6.66 (1H, t, J = 1.8 Hz), 6.72 (1H, t, J = 2.9 Hz), 6.96 (1H, s), 7.05 (1H, s), 7.16 (1H, dd, J = 3.3, 0.6 Hz), 7.68 (1H, dd, J = 3.3, 0.6 Hz), 8.16 (1H, dd, J = 2.0, 0.8 Hz), 8.26 (1H, dd, J = 1.8, 1.0 Hz), 9.57 (1H, br s).

MS (ESI) m/z: 525.13929 $(M+H)^+$.

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EJEMPLO 61

5-(Azetidin-1-ilcarbonil)-2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-3-metilpiridina



(61a) 5-(Azetidin-1-ilcarbonil)-2-cloro-3-metilpiridina

Se disolvió ácido 6-cloro-5-metilnicotínico (200 mg, 1.29 mmol) en diclorometano (7.0 mL), y se le agregó clorhidrato de azetidina (160 mg, 1.71 mmol), HATU (1000 mg, 2.63 mmol) y N,N-diisopropiletilamina (0.69 mL, 3.96 mmol), seguido por agitación a temperatura ambiente durante la noche bajo una atmósfera de nitrógeno. Se le agregó ácido clorhídrico 0.5N (30 mL) y se extrajo con diclorometano (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 60%-75%), para producir el compuesto deseado como un líquido incoloro (160 mg, rendimiento de 64%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.32 (3H, s), 2.36-2.42 (2H, m), 4.24 (2H, t, J = 7.6 Hz), 4.35 (2H, t, J = 7.6 Hz), 7.95 (1H, dd, J = 9.3, 1.0 Hz), 8.26 (1H, d, J = 1.0 Hz).

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(61b) 5-(Azetidin-1-ilcarbonil)-2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-3-metilpiridina

El 2-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (59 mg, 0.137 mmol) sintetizado en el ejemplo (38d), y la 5-(azetidin-1-ilcarbonil)-2-cloro-3-metilpiridina (45 mg, 0.232 mmol) sintetizada en el ejemplo (61a), se disolvieron en sulfóxido de dimetilo (3.0 mL) y se les agregó hidruro de sodio (60%, 25 mg, 0.63 mmol), seguido por agitación a 80°C durante 4.5 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 60%-80%), para producir el compuesto deseado como un sólido amarillo (50 mg, rendimiento de 72%).

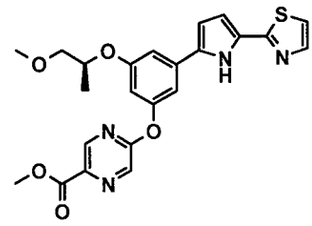
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.35 (3H, d, J = 6.3 Hz), 2.32-2.38 (2H, m), 2.40 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 10.2, 4.3 Hz), 3.60 (1H, dd, J = 10.2, 5.9 Hz), 4.23 (2H, t, J = 7.2 Hz), 4.34 (2H, t, J = 6.6 Hz), 4.56-4.58 (1H, m), 6.53 (1H, dd, J = 3.9, 2.7 Hz), 6.63 (1H, t, J = 2.0 Hz), 6.72 (1H, dd, J = 3.9, 2.3 Hz), 6.92 (1H, t, J = 1.8 Hz), 7.00 (1H, dd, J = 3.9, 1.6 Hz), 7.16 (1H, d, J = 3.1 Hz), 7.67 (1H, d, J = 3.1 Hz), 7.94 (1H, dd, J = 2.3, 0.8 Hz), 8.22 (1H, d, J = 2.3 Hz), 9.46 (1H, br s).

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MS (ESI) m/z: 505.19091 $(M+H)^+$.

EJEMPLO 62

5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}pirazin-2-carboxilato de metilo



(62a) 5-Hidroxipirazin-2-carboxilato de metilo

Se disolvió ácido 5-hidroxipirazin-2-carboxílico (1.00 g, 7.14 mmol) en metanol (5 mL), y se le agregó una solución de ácido clorhídrico 4N /dioxano (25 mL), seguido por agitación a 60°C durante 1.5 horas y calentamiento a reflujo a 80°C durante 2.5 horas. La solución de reacción se llevó de vuelta a temperatura ambiente y el disolvente se removió por destilación bajo presión reducida; al residuo resultante se le agregó acetato de etilo (20 mL) para suspenderlo. El precipitado resultante se filtró y se lavó con acetato de etilo, seguido por secado al vacío, para producir el compuesto deseado como un sólido anaranjado-pardo (673 mg, rendimiento de 61%).

^{1}H-RMN (CD_3OD, 400 MHz): δ 3.31 (1H, s), 3.85 (3H, s), 8.00 (1H, d, J = 1.2 Hz), 8.13 (1H, d, J = 1.2 Hz).

(62b) 5-Cloropirazin-2-carboxilato de metilo

El 5-hidroxipirazin-2-carboxilato de metilo (673 mg, 4.37 mmol)

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sintetizado en el ejemplo (62a) se disolvió en oxicloruro de fósforo (6.1 mL) y se le agregaron unas gotas de N,N-dimetilformamida, seguido por calentamiento a reflujo durante 2 horas bajo una atmósfera de nitrógeno. La solución de reacción se vació en agua de hielo y se extrajo tres veces con cloroformo (30 mL). La capa orgánica se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada (100 mL de cada una), y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida para producir el compuesto deseado como un sólido gris (611 mg, rendimiento de 81%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 4.05 (3H, s), 8.71 (1H, d, J = 1.6 Hz), 9.10 (1H, d, J = 1.2 Hz).

(62c) 5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}pirazin-2-carboxilato de metilo

El 2-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de metilo (200 mg, 0.464 mmol) sintetizado en el ejemplo (38d), y el 5-cloropirazin-2-carboxilato de metilo (120 mg, 0.695 mmol) sintetizado en el ejemplo (62b), se disolvieron en N,N-dimetilformamida (10 mL) y se les agregó carbonato de potasio (257 mg, 1.86 mmol), seguido por agitación a 80°C durante 7 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (40 mL) y se extrajo con acetato de etilo (40 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el

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residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-50%). El sólido amarillo resultante se disolvió en diclorometano (2 mL) y se le agregó ácido trifluoroacético (4 mL), seguido por agitación a temperatura ambiente durante 1.5 horas. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio (40 mL) y se extrajo dos veces con acetato de etilo (40 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-50%), para producir el compuesto deseado como un sólido amarillo (164 mg, rendimiento de 93%).

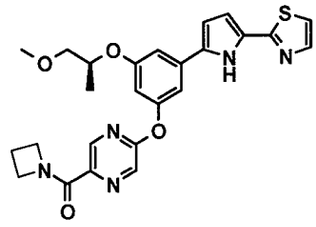
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.35 (3H, d, J = 6.3 Hz), 3.42 (3H, s), 3.52 (1H, dd, J = 10.2, 4.3 Hz), 3.60 (1H, dd, J = 10.2, 5.9 Hz), 4.02 (3H, s), 4.56-4.63 (1H, m), 6.55 (1H, dd, J = 3.9, 2.7 Hz), 6.67 (1H, t, J = 2.2 Hz), 6.75 (1H, dd, J = 3.9, 2.3 Hz), 6.98 (1H, t, J = 1.8 Hz), 7.10 (1H, t, J = 1.8 Hz), 7.18 (1H, d, J = 3.5 Hz), 7.68 (1H, d, J = 3.1 Hz), 8.51 (1H, d, J = 1.2 Hz), 8.87 (1H, d, J = 1.2 Hz), 9.74 (1H, br s).

MS (ESI) m/z: 467 $(M+H)^+$.

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EJEMPLO 63

2-(Azetidin-1-ilcarbonil)-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}pirazina



(63a) Acido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}pirazin-2-carboxílico

El 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}pirazin-2-carboxilato de metilo (423 mg, 0.907 mmol) sintetizado en el ejemplo (62c) se disolvió en metanol (10 mL), y se le agregó agua (2 mL) e hidróxido de litio monohidratado (76.2 mg, 1.82 mmol), seguido por agitación a 50°C durante 1 hora bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó agua (30 mL) y se extrajo dos veces con acetato de etilo (30 mL), seguido por secado sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: diclorometano/metanol = 0%-10%), para producir el compuesto deseado como un sólido amarillo pálido (269 mg, rendimiento de 66%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.38 (3H, d, J = 6.3 Hz), 3.44 (3H, s), 3.54 (1H, dd, J = 10.2, 4.3 Hz), 3.63 (1H, dd, J = 10.2, 5.9 Hz), 4.60-4.65 (1H, m), 6.62 (1H, dd, J = 3.9, 2.3 Hz), 6.71 (1H, t, J = 2.2 Hz), 6.82 (1H, dd, J

= 3.9, 2.3 Hz), 7.16-7.18 (2H, m), 7.37 (1H, s), 7.67 (1H, d, J = 3.5 Hz), 8.54 (1H, d, J = 1.2 Hz), 8.81 (1H, s), 11.30 (1H, br s).

(63b) 2-(Azetidin-1-ilcarbonil)-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}pirazina

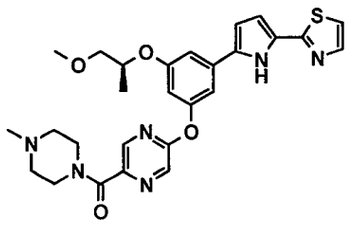
El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}pirazin-2-carboxílico (28.0 mg, 0.062 mmol) sintetizado en el ejemplo (63a) se disolvió en tetrahidrofurano (3 mL), y se le agregó clorhidrato de azetidina (17.4 mg, 0.186 mmol), HATU (35.3 mg, 0.093 mmol) y N,N-diisopropiletilamina (65 μL, 0.37 mmol), seguido por agitación a temperatura ambiente durante 28 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó agua (15 mL) y se extrajo con acetato de etilo (15 mL), seguido por secado sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por TLC preparativa (disolvente de desarrollo: metanol/diclorometano = 15%), para producir el compuesto deseado como un sólido blanco (29.1 mg, rendimiento de 96%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.35 (3H, d, J = 5.9 Hz), 2.35-2.41 (2H, m), 3.42 (3H, s), 3.51 (1H, dd, J = 10.3, 3.9 Hz), 3.60 (1H, dd, J = 10.3, 5.9 Hz), 4.26 (2H, t, J = 7.8 Hz), 4.54-4.60 (1H, m), 4.69 (2H, t, J = 7.8 Hz), 6.54 (1H, t, J = 3.2 Hz), 6.65 (1H, s), 6.73 (1H, t, J = 2.9 Hz), 6.95 (1H, s), 7.06 (1H, t, J = 1.7 Hz), 7.17 (1H, d, J = 2.9 Hz), 7.67 (1H, d, J = 3.4 Hz), 8.31 (1H, s), 8.88 (1H, s), 9.69 (1H, br s).

MS (ESI) m/z: 492.16821 $(M+H)^+$.

EJEMPLO 64

2-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-5-[(4-metilpiperazin-1-il)carbonil]pirazina



El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}pirazin-2-carboxílico (40.4 mg, 0.089 mmol) sintetizado en el ejemplo (63a) se disolvió en tetrahidrofurano (5 mL), y se le agregó 1-metilpiperazina (30 μL, 0.27 mmol), HATU (67.9 mg, 0.18 mmol) y N,N-diisopropiletilamina (93 μL, 0.54 mmol), seguido por agitación a temperatura ambiente durante 12 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó agua (15 mL) y se extrajo con acetato de etilo (15 mL), seguido por secado sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/diclorometano = 0%-5%), para producir el compuesto deseado como un sólido amarillo pálido (47 mg, rendimiento de 98%).

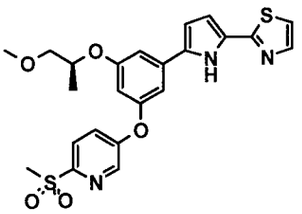
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.35 (3H, d, J = 6.3 Hz), 2.37 (3H, s), 2.50 (2H, br s), 2.56 (2H, br s), 3.42 (3H, s), 3.52 (1H, dd, J = 10.2, 4.3 Hz), 3.61 (1H, dd, J = 10.4, 6.1 Hz), 3.75 (2H, br s), 3.85 (2H, br s), 4.54-4.62 (1H, m), 6.54 (1H, t, J = 3.3 Hz), 6.65 (1H, t, J = 2.0 Hz), 6.73 (1H, dd, J = 3.9, 2.3

Hz), 6.95 (1H, t, J = 1.8 Hz), 7.06 (1H, t, J = 1.8 Hz), 7.17 (1H, d, J = 3.1 Hz), 7.68 (1H, d, J = 3.1 Hz), 8.35 (1H, d, J = 1.2 Hz), 8.56 (1H, d, J = 1.2 Hz), 9.59 (1H, br s).

MS (ESI) m/z: 535.21022 $(M+H)^+$.

EJEMPLO 65

5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-2-(metilsulfonil)piridina



(65a) 5-Bromo-2-(metiltio)piridina

Se disolvió 2,5-dibromo-piridina (6.01 g, 25.4 mmol), disponible comercialmente, en N,N-dimetilformamida (50 mL), y se le agregó tiometóxido de sodio (2.20 g, 31.4 mmol), seguido por agitación a 0°C durante 3.5 horas bajo una atmósfera de nitrógeno. La solución de reacción se llevó de vuelta a temperatura ambiente, se le agregó agua (250 mL) y se extrajo con éter dietílico (250 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 3%-5%), para producir el compuesto deseado como

un sólido blanco (4.90 g, rendimiento de 94%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.54 (3H, s), 7.08 (1H, d, J = 8.2 Hz), 7.58 (1H, dd, J = 8.6, 2.3 Hz), 8.49 (1H, d, J = 2.0 Hz).

(65b) 5-Fluoro-2-(metilsulfonil)piridina

La 5-bromo-2-(metiltio)piridina (4.90 g, 24.0 mmol) sintetizada en el ejemplo (65a) se disolvió en tetrahidrofurano (100 mL), y se le agregó a gotas n-butil-litio (solución en hexano 1.57 mol/L, 17.0 mL, 26.7 mmol) a -78°C, seguido por agitación a -78°C durante 1 hora bajo una atmósfera de nitrógeno. Se disolvió N-fluorobencenosulfonimida (11.0 g, 34.9 mmol) en tetrahidrofurano (25 mL), seguido por su adición, gota a gota, a la solución de reacción a -78°C, y se agitó a -78°C durante 2 horas bajo una atmósfera de nitrógeno. La solución de reacción se llevó de vuelta a temperatura ambiente y se agitó durante 1.5 horas. Se le agregó una solución acuosa saturada de cloruro de amonio (200 mL) y se extrajo con éter dietílico (300 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión ligeramente reducida.

El residuo resultante se disolvió en cloruro de metileno (150 mL), y se le agregó lentamente ácido m-cloroperbenzoico (65%, 16.5 g, 62.1 mmol) a 0°C, seguido por agitación a 0°C durante 1.5 horas, bajo una atmósfera de nitrógeno. Después de remover el material sólido blanco por filtración en Celite, se le agregó una solución acuosa saturada de carbonato ácido de

sodio (100 mL) y se extrajo con cloruro de metileno (400 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 3%-5%), para producir el compuesto deseado como un sólido blanco amarillento (1.95 g, rendimiento de 46%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 3.24 (3H, s), 7.67 (1H, ddd, J = 9.9, 6.9, 1.9 Hz), 8.16 (1H, dd, J = 8.6, 4.3 Hz), 8.59 (1H, d, J = 2.7 Hz).

(65c) 5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[5-(1,3-tiazol-2-il)-1H-pirrol-2-il]fenoxi}-2-(metilsulfonil)piridina

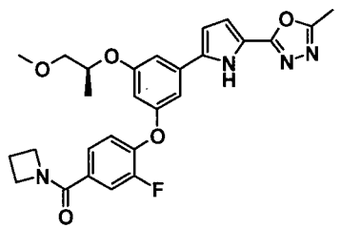
El 2-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-5-(1,3-tiazol-2-il)-1H-pirrol-1-carboxilato de t-butilo (70.0 mg, 0.16 mmol) sintetizado en el ejemplo (38d), y la 5-fluoro-2-(metilsulfonil)piridina (35.0 mg, 0.20 mmol) sintetizada en el ejemplo (65b), se disolvieron en N,N-dimetilformamida (5 mL) y la mezcla se agitó a 90°C durante 3 días bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó agua (15 mL), seguido por extracción con acetato de etilo (30 mL) y lavado con salmuera saturada (30 mL), seguido por secado sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-40%), para producir el compuesto deseado como un sólido amarillo pálido (28 mg, rendimiento de 35%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.24 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 10.4, 4.1 Hz), 3.59 (1H, dd, J = 10.2, 6.3 Hz), 4.58 (1H, dd, J = 10.4, 6.1 Hz), 6.54-6.56 (2H, m), 6.73 (1H, dd, J = 3.7, 2.5 Hz), 6.86 (1H, t, J = 1.8 Hz), 7.04 (1H, t, J = 2.0 Hz), 7.18 (1H, d, J = 3.5 Hz), 7.43 (1H, dd, J = 8.6, 2.7 Hz), 7.68 (1H, d, J = 3.1 Hz), 8.05 (1H, d, J = 9.0 Hz), 8.49 (1H, d, J = 2.7 Hz), 9.62 (1H, br s).

MS (ESI) m/z: 486.11507 $(M+H)^+$.

EJEMPLO 66

2-(5-{3-[4-(Azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-5-metil-1,3,4-oxadiazol



(66a) 2,5-Dibromo-1H-pirrol-1-carboxilato de t-butilo

Se disolvió 1-pirrolcarboxilato de t-butilo (46.68 g, 279 mmol), disponible comercialmente, en tetrahidrofurano (500 mL), y se enfrió a -78°C. A esto se le agregó N-bromosuccinimida (100.48 g, 565 mmol) en pequeñas porciones durante 1 hora. La temperatura de la solución de reacción se elevó naturalmente y la solución se agitó a temperatura ambiente durante 18 horas. La solución de reacción se enfrió a 0°C, seguido por la adición de sulfito de sodio (36.43 g) y agitación durante 30 minutos; subsiguientemente se le

agregó hexano (200 mL) para producir un precipitado que se removió por filtración en Celite. El disolvente del filtrado se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 1%-5%), para producir el compuesto deseado como un aceite incoloro (52.69 g, rendimiento de 58%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.65 (9H, s), 6.25 (2H, s).

MS (EI) m/z: 323 (M^+).

(66b) 5-Bromo-1H-pirrol-1,2-dicarboxilato de 2-bencilo-1-t-butilo

El 2,5-dibromo-1H-pirrol-1-carboxilato de t-butilo (10.98 g, 33.8 mmol) sintetizado en el ejemplo (66a) se disolvió en éter dietílico (135 mL), y se enfrió a -78°C. Se le agregó lentamente, gota a gota, n-butil-litio (solución en hexano 2.77M, 12.8 mL, 35.5 mmol), y se agitó durante 1 hora. A la solución de reacción se le agregó lentamente, gota a gota, cloroformiato de bencilo (6.25 mL, 44.0 mmol), y se agitó durante 30 minutos. Con la temperatura de la solución de reacción elevándose gradualmente a temperatura ambiente, se agitó durante 1 hora. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (200 mL) y éter dietílico (300 mL) y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 5%-45%), para producir el compuesto

deseado como un aceite pardo rojizo (8.80 g, rendimiento de 68%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.56 (9H, s), 5.26 (2H, s), 6.21 (1H, d, J = 3.9 Hz), 6.85 (1H, d, J = 3.9 Hz), 7.28-7.39 (5H, m).

MS (FAB) m/z: 380 $(M+H)^+$.

(66c) 5-{3-Hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-1,2-dicarboxilato de 2-bencilo-1-t-butilo

El 5-bromo-1H-pirrol-1,2-dicarboxilato de 2-bencilo-1-t-butilo (8.75 g, 23.0 mmol) sintetizado en el ejemplo (66b), y el 3-[(1S)-2-metoxi-1-metiletoxi]-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenol (7.11 g, 23.1 mmol) sintetizado en el ejemplo (38c), se disolvieron en un disolvente mixto de 1,4-dioxano (92 mL) y agua (23 mL), y se les agregó complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano (570 mg, 0.698 mmol) y carbonato de potasio (7.95 g, 57.5 mmol), seguido por agitación a 55°C durante 3 horas bajo una atmósfera de nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente, se le agregó agua (200 mL) y se extrajo con acetato de etilo (200 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 15%-35%), para producir el compuesto deseado como un aceite pardo (8.32 g, rendimiento de 75%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.29 (3H, d, J = 6.3 Hz), 1.41 (9H, s), 3.40 (3H, s), 3.47 (1H, dd, J = 10.3, 4.4 Hz), 3.57 (1H, dd, J = 10.3, 5.9 Hz),

4.48-4.54 (1H, m), 5.20 (1H, s), 5.30 (2H, s), 6.17 (1H, d, J = 3.4 Hz), 6.44 (1H, s), 6.48 (1H, s), 6.57 (1H, s), 6.94 (1H, d, J = 3.4 Hz), 7.42-7.31 (5H, m).

MS (FAB) m/z: 481 (M^+).

(66d) 5-{3-(2-Fluoro-4-formilfenoxi)-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-carboxilato de bencilo

El 5-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-1,2-dicarboxilato de 2-bencilo-1-t-butilo (8.30 g, 17.2 mmol) sintetizado en el ejemplo (66c) se disolvió en N,N-dimetilformamida (86 mL), y se le agregó 3,4-difluorobenzaldehído (2.85 mL, 25.9 mmol) y carbonato de potasio (11.96 g, 86.5 mmol), seguido por agitación a 90°C durante 24 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (100 mL) y se extrajo con éter dietílico (300 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro.

El disolvente se removió por destilación bajo presión reducida para producir un residuo, que se disolvió en diclorometano (20 mL) y se le agregó ácido trifluoroacético (10 mL), seguido por agitación a temperatura ambiente durante 1 hora. El disolvente se removió por destilación bajo presión reducida para producir un residuo, que se disolvió en acetato de etilo (200 mL) y se lavó con una solución acuosa saturada de carbonato ácido de sodio (200 mL). Después de lavar con salmuera saturada, se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida para producir un residuo, que se purificó por cromatografía

en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 15%-35%), para producir el compuesto deseado como un sólido blanco (6.34 g, rendimiento de 73%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 3.40 (3H, s), 3.50 (1H, dd, J = 10.2, 3.9 Hz), 3.58 (1H, dd, J = 10.4, 6.1 Hz), 4.53-4.60 (1H, m), 5.32 (2H, s), 6.50 (1H, t, J = 3.3 Hz), 6.59 (1H, s), 6.83 (1H, s), 6.96-6.98 (2H, m), 7.12 (1H, t, J = 8.0 Hz), 7.32-7.44(5H, m), 7.62 (1H, d, J = 8.2 Hz), 7.72 (1H, dd, J = 10.4, 1.8 Hz), 9.29 (1H, s), 9.92 (1H, d, J = 2.0 Hz).

MS (FAB) m/z: 503 (M^+).

(66e) Acido 4-(3-{5-[(benciloxi)carbonil]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)-3-fluorobenzoico

El 5-{3-(2-fluoro-4-formilfenoxi)-5-[(1S)-2-metoxi-1-metiletoxi]-fenil}-1H-pirrol-2-carboxilato de bencilo (6.33 g, 12.6 mmol) sintetizado en el ejemplo (66d) se suspendió en un disolvente mixto de t-butanol (120 mL) y agua (40 mL), y se le agregó fosfato diácido de sodio dihidratado (8.86 g, 56.8 mmol) y 2-metil-2-buteno (12.05 mL, 113 mmol). Bajo enfriamiento con hielo se le agregó lentamente clorito de sodio (80%, 2.93 g, 25.9 mmol) y se agitó a temperatura ambiente durante 2 horas. Se le agregó salmuera saturada (200 mL), seguido por extracción con diclorometano (200 mL), y se secó sobre sulfato de magnesio anhidro para producir el compuesto deseado como un aceite amarillo pálido (7.17 g, rendimiento de ~100%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.36 (3H, d, J = 6.3 Hz), 3.43 (3H, s), 3.53 (1H, dd, J = 10.2, 3.9 Hz), 3.62 (1H, dd, J = 10.2, 5.9 Hz), 4.58-4.65

(1H, m), 5.34 (2H, s), 6.55 (1H, dd, J = 3.9, 2.7 Hz), 6.69 (1H, t, J = 2.0 Hz), 7.02-7.06 (3H, m), 7.11 (1H, s), 7.34-7.44(5H, m), 7.66 (1H, d, J = 8.6 Hz), 7.77 (1H, dd, J = 10.9, 2.0 Hz), 10.68 (1H, br s).

MS (FAB) m/z: 519 (M^+).

(66f) 5-{3-[4-(Azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-carboxilato de bencilo

El ácido 4-(3-{5-[(benciloxi)carbonil]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)-3-fluorobenzoico (7.14 g, 13.7 mmol) sintetizado en el ejemplo (66e) se disolvió en diclorometano (120 mL). Bajo enfriamiento con hielo, se le agregó clorhidrato de azetidina (1.772 g, 18.9 mmol), WSCI·HCl (3.62 g, 18.9 mmol), trietilamina (2.65 mL, 19.1 mmol) y 4-dimetilaminopiridina (464 mg, 3.80 mmol), y se agitó a temperatura ambiente durante 6 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó ácido clorhídrico 0.5N (300 mL) y se extrajo con diclorometano (300 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 60%-85%), para producir el compuesto deseado como un sólido blanco (4.12 g, rendimiento de 59%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J = 6.3 Hz), 2.34-2.41 (2H, m), 3.40 (3H, s), 3.49 (1H, dd, J = 10.4,4.1 Hz), 3.57 (1H, dd, J = 10.4, 6.1 Hz), 4.21-4.27 (2H, br m), 4.33-4.39 (2H, br m), 4.51-4.57 (1H, m), 5.33

(2H, s), 6.48 (1H, dd, J = 3.9, 2.7 Hz), 6.53 (1H, t, J = 2.2 Hz), 6.78 (1H, t, J = 1.8 Hz), 6.89 (1H, t, J = 1.8 Hz), 6.97 (1H, dd, J = 3.9, 2.3 Hz), 7.06 (1H, t, J = 8.0 Hz), 7.34-7.44 (6H, m), 7.52 (1H, dd, J = 10.9, 2.0 Hz), 9.19 (1H, br s).

MS (FAB) m/z: 558 (M^+).

(66g) Acido 5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-carboxílico

El 5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-carboxilato de bencilo (4.25 g, 7.61 mmol) sintetizado en el ejemplo (66f) se disolvió en etanol (150 mL), y se le agregó un catalizador de paladio al 10% en carbón (804 mg), seguido por agitación durante 2 horas bajo una atmósfera de hidrógeno. El catalizador de paladio en carbón se removió por filtración en Celite y el disolvente se removió por destilación bajo presión reducida, para producir el compuesto deseado como un sólido blanco (3.45 g, rendimiento de 97%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J = 6.3 Hz), 2.32-2.40 (2H, m), 3.44 (3H, s), 3.52 (1H, dd, J = 10.0, 4.1 Hz), 3.64 (1H, dd, J = 10.0, 6.3 Hz), 4.20-4.26 (2H, br m), 4.31-4.38 (2H, br m), 4.66-4.72 (1H, m), 6.48-6.50 (2H, m), 6.86 (1H, s), 7.00 (1H, s), 7.05 (1H, t, J = 7.6 Hz), 7.16 (1H, s), 7.38 (1H, d, J = 7.8 Hz), 7.50 (1H, d, J = 11.3 Hz), 10.17 (1H, br s).

MS (ESI) m/z: 469.17889 $(M+H)^+$.

(66h) N'-Acetil-5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-carbohidrazida

El ácido 5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-

metoxi-1-metiletoxi]fenil}-1H-pirrol-2-carboxílico (126 mg, 0.27 mmol) sintetizado en el ejemplo (66g) y acetohidrazida (40 mg, 0.54 mmol) se disolvieron en diclorometano (5 mL), y se les agregó HATU (153 mg, 0.40 mmol) y N,N-diisopropiletilamina (70 μL, 0.40 mmol) a temperatura ambiente, seguido por agitación durante 1 hora bajo una atmósfera de nitrógeno. La solución de reacción se diluyó con diclorometano (60 mL), se lavó con ácido clorhídrico 1N, solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/diclorometano = 5%), para producir el producto deseado como un sólido blanco (87 mg, rendimiento de 62%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.26 (3H, d, J = 6.3 Hz), 1.91 (3H, s), 2.30-3.38 (2H, m), 3.37 (3H, s), 3.46 (1H, dd, J = 3.8, 10.1 Hz) 3.58 (1H, dd, J = 6.2, 10.1 Hz), 4.18-4.24 (2H, brm), 4.30-4.36 (2H, brm), 4.55-4.59 (1H, m), 6.43 (1H, dd, J = 2.7, 4.0 Hz), 6.46 (1H, t, J = 2.1 Hz), 6.81 (1H, dd, J = 2.4,4.1 Hz), 6.87 (1H, s), 7.01 (1H, t, J = 8.2 Hz), 7.07 (1H, s), 7.35 (1H, d, J = 8.6 Hz), 7.46 (1H, dd, J = 2.0, 10.9 Hz), 9.10 (1H, brs), 9.36 (1H, brs), 10.62 (1H, brs).

(66i) 2-(5-{3-[4-(Azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-5-metil-1,3,4-oxadiazol

La N'-acetil-5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-carbohidrazida (86 mg, 0.16 mmol)

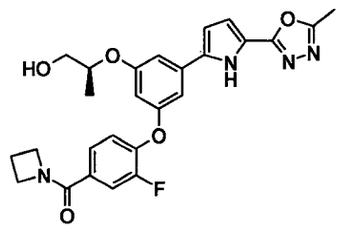
sintetizada en el ejemplo (66h), se disolvió en diclorometano (5 mL) y se le agregó trietilamina (0.1 mL, 0.72 mmol) y cloruro de ácido p-toluenosulfónico (69 mg, 0.36 mmol), seguido por agitación a temperatura ambiente durante la noche. La solución de reacción se diluyó con diclorometano (60 mL), se lavó con ácido clorhídrico 1N, solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-100%), para producir el producto deseado como un sólido blanco (57 mg, rendimiento de 69%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 2.34-3.42 (2H, m), 2.58 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 3.9, 10.4 Hz) 3.59 (1H, dd, J = 6.1, 10.3 Hz), 4.22-4.27 (2H, brm), 4.35-4.40 (2H, brm), 4.54-4.59 (1H, m), 6.54 (1H, t, J = 2.2 Hz), 6.55 (1H, dd, J = 2.2, 2.7 Hz), 6.80 (1H, t, J = 1.7 Hz), 6.85 (1H, dd, J = 1.9, 2.4 Hz), 6.93 (1H, dd, J = 1.2, 1.6 Hz), 7.08 (1H, t, J = 8.2 Hz), 7.41 (1H, d, J = 8.5 Hz), 7.52 (1H, dd, J = 2.0, 11.1 Hz), 9.49 (1H, brs).

MS (ESI) m/z: 507.20129 $(M+H)^+$.

EJEMPLO 67

(2S)-2-{3-[4-(Azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]fenoxi}propan-1-ol



El 2-(5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-5-metil-1,3,4-oxadiazol (379.2 mg, 0.748 mmol) sintetizado en el ejemplo (66i) se disolvió en diclorometano (15 mL), y se le agregó una solución de tribromuro de boro/diclorometano (1M, 750 μL, 0.75 mmol) a -78°C, bajo una atmósfera de nitrógeno, seguido por agitación a 0°C durante 3 horas. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/diclorometano = 2%-8%), para producir el compuesto deseado como un sólido amarillo pálido (76.9 mg, rendimiento de 21%).

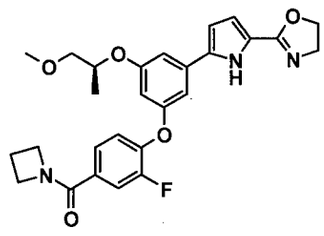
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.29 (3H, d, J = 6.3 Hz), 2.34-2.42 (2H, m), 2.58 (3H, s), 2.80 (1H, t, J = 6.1 Hz), 3.76-3.79 (2H, m), 4.22-4.26 (2H, br m), 4.35-4.39 (2H, br m), 4.52-4.59 (1H, m), 6.45 (1H, t, J = 2.2 Hz),

6.53 (1H, dd, J = 3.9, 2.7 Hz), 6.79 (1H, t, J = 1.8 Hz), 6.84 (1H, dd, J = 3.9, 2.3 Hz), 6.91 (1H, t, J = 1.8 Hz), 7.05 (1H, t, J = 8.2 Hz), 7.38-7.41 (1H, m), 7.51 (1H, dd, J = 10.9, 2.0 Hz), 9.92 (1H, br s).

MS (ESI) m/z: 493.18999 $(M+H)^+$.

EJEMPLO 68

2-(5-{3-[4-(Azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol



(68a) 5-{3-[4-(Azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-N-(2-cloroetil)-1H-pirrol-2-carboxamida

El ácido 5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-carboxílico (66 mg, 0.15 mmol) sintetizado en el ejemplo (66g), clorhidrato de 2-cloroetilamina (34 mg, 0.30 mmol) y 4-dimetilaminopiridina (18 mg, 0.15 mmol), se disolvieron en diclorometano (10 mL), y se les agregó WSCI·HCl (31 mg, 0.16 mmol) a temperatura ambiente, seguido por agitación durante 1 hora bajo una atmósfera de nitrógeno. La solución de reacción se diluyó con diclorometano (60 mL), se lavó con ácido clorhídrico 1N, solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, y subsiguientemente se secó

sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-60%), para producir el producto deseado como un sólido blanco (56 mg, rendimiento de 79%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 2.35-3.49 (2H, m), 3.41 (3H, s), 3.50 (1H, dd, J = 4.1,10.7 Hz) 3.58 (1H, dd, J = 6.1,10.3 Hz), 3.71 (2H, t, J = 5.4 Hz), 3.77 (2H, t, J = 5.6 Hz), 4.22-4.27 (2H, brm), 4.35-4.40 (2H, brm), 4.53-4.57 (1H, m), 6.24-6.28 (1H, m), 6.47 (1H, t, J = 3.0 Hz), 6.52 (1H, t, J = 2.1 Hz), 6.62 (1H, dd, J = 2.5, 4.1 Hz), 6.78 (1H, t, J = 1.6 Hz), 6.90 (1H, t, J = 1.6 Hz), 7.06 (1H, t, J = 8.0 Hz), 7.40 (1H, d, J = 8.5 Hz), 7.52 (1H, dd, J = 2.0, 11.0 Hz), 9.43 (1H, brs).

(68b) 2-(5-{3-[4-(Azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-4,5-dihidro-1,3-oxazol

La 5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-N-(2-cloroetil)-1H-pirrol-2-carboxamida (85 mg, 0.16 mmol) sintetizada en el ejemplo (68a) se disolvió en tetrahidrofurano (3 mL), y se le agregó hidruro de sodio (37 mg, 0.82 mmol) a 0°C, seguido por agitación a temperatura ambiente durante 20 horas. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con acetato de etilo (50 mL). Después de lavar con salmuera saturada, se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por

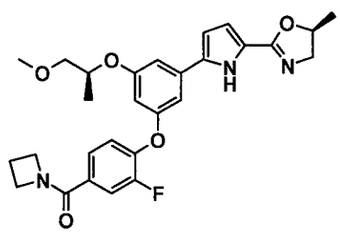
cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo 100%-metanol/cloroformo = 2%), para producir el producto deseado como un sólido amarillo pálido (33 mg, rendimiento de 41%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 2.34-3.41 (2H, m), 3.41 (3H, s), 3.49 (1H, dd, J = 3.9, 10.5 Hz) 3.58 (1H, dd, J = 5.9, 10.2 Hz), 4.00 (2H, t, J = 9.3 Hz), 4.22-4.26 (2H, brm), 4.35-4.39 (2H, brm), 4.40 (2H, t, J = 9.3 Hz), 4.53-4.57 (1H, m), 6.48 (1H, d, J = 3.8 Hz), 6.51 (1H, t, J = 2.0 Hz), 6.75 (1H, d, J = 3.8 Hz), 6.78 (1H, t, J = 1.6 Hz), 6.91 (1H, s), 7.06 (1H, t, J = 8.1 Hz), 7.40 (1H, d, J = 8.5 Hz), 7.52 (1H, dd, J = 2.0, 11.0 Hz).

MS (ESI) m/z: 494.20834 $(M+H)^+$.

EJEMPLO 69

(5S)-2-(5-{3-[4-(Azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol



(69a) 5-{3-[4-(Azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-N-[(2R)-2-hidroxipropil]-1H-pirrol-2-carboxamida

El ácido 5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-carboxílico (580 mg, 1.24 mmol) sintetizado en el ejemplo (66g) se disolvió en diclorometano (15 mL), y se le

agregó (R)-(-)-1-amino-2-propanol (196 μL, 2.48 mmol), WSCI·HCl (366 mg, 1.91 mmol) y 4-dimetilaminopiridina (228 mg, 1.87 mmol), seguido por agitación a temperatura ambiente durante 18 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó ácido clorhídrico 0.25 N (100 mL) y se extrajo con acetato de etilo (100 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/diclorometano = 3%-9%), para producir el compuesto deseado como un sólido blanco (486 mg, rendimiento de 75%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.22 (3H, d, J = 6.3 Hz), 1.30 (3H, d, J = 6.3 Hz), 2.33-2.41 (2H, m), 2.77 (1H, d, J = 3.9 Hz), 3.22-3.29 (1H, m), 3.41 (3H, s), 3.50 (1H, dd, J = 10.2, 3.9 Hz), 3.55-3.62 (2H, m), 3.94-4.01 (1H, br m), 4.20-4.26 (2H, br m), 4.33-4.39 (2H, br m), 4.51-4.59 (1H, m), 6.43-6.46 (2H, m), 6.51 (1H, t, J = 2.2 Hz), 6.62 (1H, dd, J = 3.9, 2.3 Hz), 6.80 (1H, t, J = 1.8 Hz), 6.91 (1H, t, J = 1.8 Hz), 7.04 (1H, t, J = 8.2 Hz), 7.37 (1H, d, J = 8.6 Hz), 7.50 (1H, dd, J = 11.3,2.0 Hz), 9.80 (1H, br s).

MS (FAB) m/z: 526 $(M+H)^+$.

(69b) (5S)-2-(5-{3-[4-(Azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol

La 5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-N-[(2R)-2-hidroxipropil]-1H-pirrol-2-carboxamida (464 mg, 0.883 mmol) sintetizada en el ejemplo (69a) se disolvió en tetrahidrofurano (17

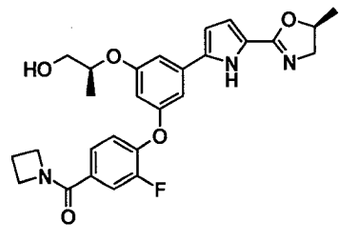
mL), y se le agregó ácido metanosulfónico anhidro (558 mg, 3.20 mmol) y trietilamina (860 μL, 6.20 mmol), seguido por agitación a temperatura ambiente durante 3 días bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/diclorometano = 3%-9%), para producir el compuesto deseado como un sólido blanco (228 mg, rendimiento de 51%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J = 6.3 Hz), 1.43 (3H, d, J = 6.3 Hz), 2.34-2.41 (2H, m), 3.41 (3H, s), 3.50 (1H, dd, J = 10.2, 3.9 Hz), 3.52-3.59 (2H, m), 4.08 (1H, dd, J = 13.9, 9.2 Hz), 4.22-4.26 (2H, br m), 4.35-4.38 (2H, br m), 4.53-4.60 (1H, m), 4.80-4.89 (1H, m), 6.48 (1H, d, J = 3.9 Hz), 6.51 (1H, t, J = 2.2 Hz), 6.77 (1H, d, J = 3.9 Hz), 6.79 (1H, t, J = 1.8 Hz), 6.93 (1H, s), 7.05 (1H, t, J = 8.2 Hz), 7.37-7.40 (1H, m), 7.51 (1H, dd, J = 10.9, 2.0 Hz).

MS (ESI) m/z: 508.22382 $(M+H)^+$.

EJEMPLO 70

(2S)-2-(3-[4-(Azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)propan-1-ol



El (5S)-2-(5-{3-[4-(azetidin-1-ilcarbonil)-2-fluorofenoxi]-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol (337.8 mg, 0.666 mmol) sintetizado en el ejemplo (69b) se disolvió en diclorometano (10 mL), y se le agregó una solución de tribromuro de boro/diclorometano (1M, 1 mL, 1 mmol) a -78°C y bajo una atmósfera de nitrógeno, seguido por agitación a temperatura ambiente durante 1 hora. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/diclorometano = 2%-8%), para producir el compuesto deseado como un sólido amarillo pálido (93.7 mg, rendimiento de 29%).

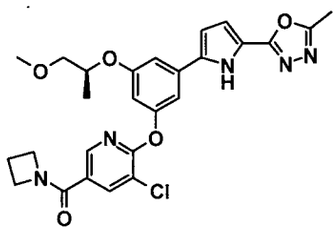
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.26 (3H, d, J = 6.3 Hz), 1.43 (3H, d, J = 6.3 Hz), 2.33-2.41 (2H, m), 3.55 (1H, dd, J = 13.7, 7.4 Hz), 3.73-3.81 (2H, m), 4.08 (1H, dd, J = 13.7, 9.4 Hz), 4.22-4.26 (2H, br m), 4.33-4.37 (2H,

br m), 4.56-4.64 (1H, m), 4.81-4.90 (1H, m), 6.30 (1H, t, J = 2.2 Hz), 6.44 (1H, d, J = 3.9 Hz), 6.74-6.76 (2H, m), 6.86 (1H, s), 7.00 (1H, t, J = 8.2 Hz), 7.34-7.37 (1H, m), 7.49 (1H, dd, J = 10.9, 2.0 Hz).

MS (ESI) m/z: 494.20864 $(M+H)^+$.

EJEMPLO 71

5-(Azetidin-1-ilcarbonil)-3-cloro-2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]fenoxi}piridina



(71a) Acido 5-(3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(1S)-2-metoxi-1-metiletoxi]fenil)-1H-pirrol-2-carboxílico

El 5-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-1,2-dicarboxilato de 2-bencilo-1-t-butilo (5.21 g, 10.82 mmol) sintetizado en el ejemplo (66c), y la 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina (2.55 g, 11.04 mmol) sintetizada en el ejemplo (60a), se disolvieron en acetonitrilo (100 mL) y se les agregó carbonato de potasio (4.30 g, 31.11 mmol), seguido por agitación durante 1 día con calentamiento a reflujo bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (200 mL) y se extrajo con acetato de etilo (200 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre

sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 75%-90%).

El compuesto resultante se disolvió en ácido trifluoroacético (15 mL) y se agitó a temperatura ambiente durante 1.5 horas bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 75%-90%).

El compuesto resultante se disolvió en tetrahidrofurano (20 mL) y se le agregó paladio carbón (800mg), seguido por agitación a temperatura ambiente durante 4 horas bajo una atmósfera de hidrógeno. Después de filtración en Celite, el disolvente se removió por destilación. Al residuo resultante se le agregó una solución acuosa saturada de carbonato ácido de sodio (30 mL) y se extrajo con éter dietílico. A la capa acuosa resultante se le agregó ácido clorhídrico 2N (50 mL) y se extrajo con acetato de etilo. La capa orgánica resultante se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida para producir el compuesto deseado como un sólido blanco (3.52 g, rendimiento de 67%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.35 (3H, d, J = 6.3 Hz), 2.35-2.42 (2H, m), 3.45 (3H, s), 3.54 (1H, dd, J = 10.0, 4.1 Hz), 3.65 (1H, dd, J = 10.4, 6.1 Hz), 4.24 (2H, t, J = 7.6 Hz), 4.35 (2H, t, J = 6.3 Hz), 4.65-4.71 (1H, m),

6.53 (1H, dd, J = 3.5, 2.7 Hz), 6.70 (1H, t, J = 2.2 Hz), 7.01-7.02 (2H, br m), 7.21 (1H, s), 8.16 (1H, d, J = 2.3 Hz), 8.27 (1H, d, J = 2.0 Hz), 9.97 (1H, br s).

(71b) 5-(Azetidin-1-ilcarbonil)-3-cloro-2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]fenoxi}piridina

El ácido 5-(3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(1S)-2-metoxi-1-metiletoxi]fenil)-1H-pirrol-2-carboxílico (600 mg, 1.23 mmol) sintetizado en el ejemplo (71a) se disolvió en diclorometano (15 mL), y se le agregó acetohidrazida (200 mg, 2.70 mmol), WSCI·HCl (510 mg, 2.66 mmol) y 4-dimetilaminopiridina (300 mg, 2.46 mmol), seguido por agitación a temperatura ambiente durante 1 día bajo una atmósfera de nitrógeno. Se le agregó una solución acuosa saturada de cloruro de amonio (100 mL) y se extrajo con diclorometano (100 mL). La capa orgánica se lavó con salmuera saturada; subsiguientemente se secó sobre sulfato de magnesio anhidro y el disolvente se removió por destilación bajo presión reducida.

Este residuo se disolvió en diclorometano (15 mL) y se le agregó cloruro de p-toluenosulfonilo (500 mg, 2.62 mmol) y trietilamina (1.0 mL, 7.17 mmol), seguido por agitación a temperatura ambiente durante 5 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo con diclorometano (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución:

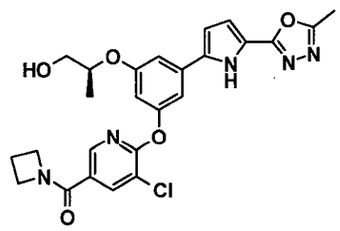
acetato de etilo), para producir el compuesto deseado como un sólido blanco (520 mg, rendimiento de 81%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.35 (3H, d, J = 6.3 Hz), 2.35-2.43 (1H, m), 2.59 (3H, s), 3.42 (3H, s), 3.52 (1H, dd, J = 10.2, 4.3 Hz), 3.61 (1H, dd, J = 10.2, 5.9 Hz), 4.24 (2H, t, J = 7.4 Hz), 4.37 (2H, t, J = 7.6 Hz), 4.56-4.62 (1H, m), 6.58 (1H, dd, J = 3.9, 2.7 Hz), 6.70 (1H, t, J = 2.2 Hz), 6.85 (1H, dd, J = 3.9, 2.3 Hz), 6.96 (1H, t, J = 1.6 Hz), 7.05 (1H, t, J = 2.0 Hz), 8.17 (1H, d, J = 2.0 Hz), 8.27 (1H, d, J = 2.0 Hz), 9.57 (1H, br s).

MS (ESI) m/z: 524.17210 $(M+H)^+$.

EJEMPLO 72

(2S)-2-(3-{[5-(Azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]fenoxi)propan-1-ol



La 5-(azetidin-1-ilcarbonil)-3-cloro-2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]fenoxi}piridina (370 mg, 0.706 mmol) sintetizada en el ejemplo (71b) se disolvió en diclorometano (10 mL), y se le agregó a gotas a -78°C tribromuro de boro (solución en diclorometano 1.0 mol/L, 1.10 mL, 1.10 mmol), seguido por agitación a temperatura ambiente durante 1 hora bajo una atmósfera de nitrógeno. A esta

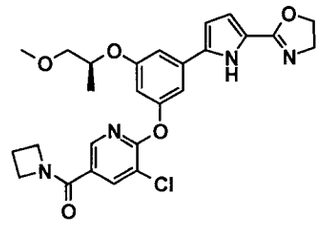
solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (20 mL) y se extrajo con diclorometano (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/diclorometano = 1%-3%), para producir el compuesto deseado como un sólido blanco (205 mg, rendimiento de 57%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.30 (3H, d, J = 6.3 Hz), 1.78 (1H, d, J = 7.8 Hz), 2.34-2.42 (2H, m), 2.57 (3H, s), 2.71-2.87 (1H, m), 3.73-3.80 (2H, m), 4.23 (2H, t, J = 7.6 Hz), 4.35 (2H, t, J = 7.4 Hz), 4.52-4.58 (1H, m), 6.56 (1H, t, J = 2.9 Hz), 6.64 (1H, d, J = 1.6 Hz), 6.84 (1H, dd, J = 3.9, 2.3 Hz), 6.96 (1H, t, J = 1.8 Hz), 7.01 (1H, t, J = 1.8 Hz), 8.16 (1H, d, J = 2.0 Hz), 8.26 (1H, d, J = 2.3 Hz), 9.92 (1H, s).

MS (ESI) m/z: 510.15468 $(M+H)^+$.

EJEMPLO 73

5-(Azetidin-1-ilcarbonil)-3-cloro-2-{3-[5-(4,5-dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi}piridina



(73a) 5-(3-{[5-(Azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(1S)-2-metoxi-1-metiletoxi]fenil)-N-(2-cloroetil)-1H-pirrol-2-carboxamida

El ácido 5-(3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(1S)-2-metoxi-1-metiletoxi]fenil)-1H-pirrol-2-carboxílico (800 mg, 1.65 mmol) sintetizado en el ejemplo (71a) se disolvió en diclorometano (10.0 mL), y se le agregó clorhidrato de 2-cloroetilamina (300 mg, 2.59 mmol), WSCI·HCl (630 mg, 3.29 mmol) y 4-dimetilaminopiridina (400 mg, 3.27 mmol), seguido por agitación a temperatura ambiente bajo una atmósfera de nitrógeno durante 2.5 días. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo con diclorometano (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo), para producir el compuesto deseado como un sólido blanco (210 mg, rendimiento de 23%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 2.35-2.42

1729

(2H, m), 3.42 (3H, s), 3.51 (1H, dd, J = 10.6, 4.7 Hz), 3.60 (1H, dd, J = 10.2, 5.9 Hz), 3.68-3.73 (2H, m), 3.75-3.80 (2H, m), 4.24 (2H, t, J = 7.8 Hz), 4.36 (2H, t, J = 7.0 Hz), 4.55-4.60 (1H, m), 6.27 (1H, t, J = 5.7 Hz), 6.50 (1H, dd, J = 3.9, 2.7 Hz), 6.63 (1H, dd, J = 3.7, 2.5 Hz), 6.68 (1H, t, J = 2.2 Hz), 6.95 (1H, t, J = 1.8 Hz), 7.03 (1H, t, J = 1.8 Hz), 8.16 (1H, d, J = 2.3 Hz), 8.26 (1H, d, J = 2.0 Hz), 9.55 (1H, br s).

(73b) 5-(Azetidin-1-ilcarbonil)-3-cloro-2-{3-[5-(4,5-dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi}piridina

La 5-(3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(1S)-2-metoxi-1-metiletoxi]fenil)-N-(2-cloroetil)-1H-pirrol-2-carboxamida (210 mg, 0.384 mmol) sintetizada en el ejemplo (73a) se disolvió en tetrahidrofurano (10.0 mL), y se le agregó hidruro de sodio (60%, 80 mg, 2.00 mmol), seguido por agitación a temperatura ambiente durante 7.5 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo con diclorometano (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo), para producir el compuesto deseado como un sólido blanco (120 mg, rendimiento de 62%).

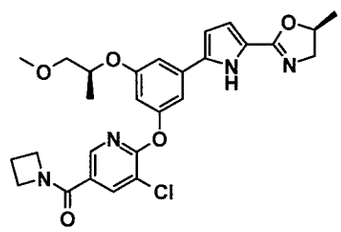
^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 2.35-2.42 (2H, m), 3.41 (3H, s), 3.50 (1H, dd, J = 10.3, 4.4 Hz), 3.60 (1H, dd, J = 10.3,

5.9 Hz), 4.00 (2H, t, J = 9.3 Hz), 4.24 (2H, t, J = 6.8 Hz), 4.36 (2H, t, J = 6.3 Hz), 4.40 (2H, t, J = 9.3 Hz), 4.55-4.61 (1H, m), 6.50 (1H, d, J = 3.9 Hz), 6.66 (1H, t, J = 2.0 Hz), 6.75 (1H, d, J = 3.9 Hz), 6.94 (1H, s), 7.04 (1H, t, J = 5.1 Hz), 8.15 (1H, d, J = 2.0 Hz), 8.26 (1H, d, J = 2.0 Hz).

MS (ESI) m/z: 511.17658 $(M+H)^+$.

EJEMPLO 74

5-(Azetidin-1-ilcarbonil)-3-cloro-2-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)piridina



El ácido 5-(3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(1S)-2-metoxi-1-metiletoxi]fenil)-1H-pirrol-2-carboxílico (800 mg, 1.65 mmol) sintetizado en el ejemplo (71a) se disolvió en diclorometano (15 mL), y se le agregó (R)-(-)-1-amino-2-propanol (0.35 mL, 4.45 mmol), WSCI·HCl (630 mg, 3.29 mmol) y 4-dimetilaminopiridina (800 mg, 6.55 mmol), seguido por agitación a temperatura ambiente durante 8 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo con diclorometano (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por

destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice para producir un sólido amarillo (disolvente de elución: metanol/diclorometano = 3%-8%).

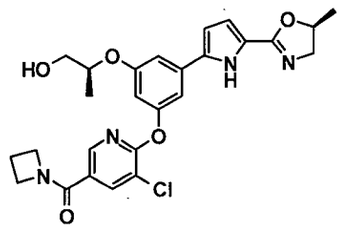
Este se disolvió en tetrahidrofurano (15 mL) y se le agregó ácido metanosulfónico anhidro (500 mg, 2.87 mmol) y trietilamina (0.80 mL, 5.74 mmol), seguido por agitación a temperatura ambiente durante la noche bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo con diclorometano (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo), para producir el compuesto deseado como un sólido amarillo (520 mg, rendimiento de 60%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 1.43 (3H, d, J = 6.3 Hz), 2.35-2.42 (2H, m), 3.41 (3H, s), 3.45-3.64 (3H, m), 4.08-4.12 (1H, m), 4.23 (2H, t, J = 7.0 Hz), 4.36 (2H, t, J = 8.4 Hz), 4.54-4.62 (1H, m), 4.84-4.87 (1H, m), 6.51 (1H, d, J = 3.5 Hz), 6.66 (1H, t, J = 2.2 Hz), 6.75-6.78 (1H, m), 6.94 (1H, s), 7.02-7.09 (1H, m), 8.16 (1H, d, J = 2.0 Hz), 8.26 (1H, d, J = 2.0 Hz).

MS (ESI) m/z: 525.19126 $(M+H)^+$.

EJEMPLO 75

(2S)-2-(3-{[5-(Azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)propan-1-ol



La 5-(azetidin-1-ilcarbonil)-3-cloro-2-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-piridina (320 mg, 0.610 mmol) sintetizada en el ejemplo 74 se disolvió en diclorometano (10 mL), y se le agregó a gotas a -78°C tribromuro de boro (solución en diclorometano 1.0 mol/L, 0.92 mL, 0.92 mmol), seguido por agitación a temperatura ambiente durante 1 hora bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (20 mL) y se extrajo con diclorometano (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/diclorometano = 1%-3%), para producir el compuesto deseado como un sólido amarillo (165 mg, rendimiento de 53%).

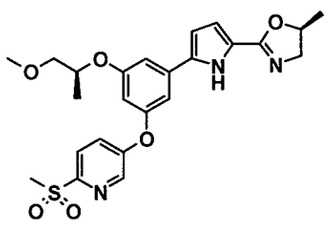
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.28 (3H, d, J = 6.3 Hz), 1.40 (3H, d, J = 5.9 Hz), 2.34-2.42 (2H, m), 3.52 (1H, dd, J = 13.7, 7.4 Hz), 3.76 (2H, d, J

= 5.5 Hz), 4.06 (1H, dd, J = 13.9, 9.2 Hz), 4.23 (2H, t, J = 7.8 Hz), 4.34 (2H, t, J = 7.4 Hz), 4.51-4.60 (1H, m), 4.76-4.86 (1H, m), 6.44 (1H, d, J = 3.1 Hz), 6.53 (1H, s), 6.72 (1H, d, J = 3.5 Hz), 6.87-6.92 (2H, m), 8.15 (1H, d, J = 2.0 Hz), 8.23 (1H, d, J = 1.2 Hz), 10.05 (1H, br s).

MS (ESI) m/z: 511.17339 $(M+H)^+$.

EJEMPLO 76

5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-2-(metilsulfonil)piridina



(76a) 5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxilato de bencilo

El 5-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-1,2-dicarboxilato de 2-bencilo-1-t-butilo (5.05 g, 10.49 mmol) sintetizado en el ejemplo (66c), y la 5-fluoro-2-(metilsulfonil)piridina (2.05 g, 11.70 mmol) sintetizada en el ejemplo (65b), se disolvieron en N,N-dimetilformamida (30 mL), y se les agregó carbonato de potasio (4.50 g, 32.56 mmol), seguido por agitación a 80°C durante 3 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (150 mL) y se extrajo con éter dietílico (150 mL). La capa orgánica se lavó

con salmuera saturada; subsiguientemente se secó sobre sulfato de magnesio anhidro y el disolvente se removió por destilación bajo presión reducida.

El compuesto resultante se disolvió en ácido trifluoroacético (10 mL) y se agitó a temperatura ambiente durante 1 hora bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 35%-50%), para producir el compuesto deseado como un aceite blanco (5.08 g, rendimiento de 90%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.51 (1H, dd, J = 10.3, 3.9 Hz), 3.58 (1H, dd, J = 10.3, 6.3 Hz), 4.54-4.61 (1H, m), 5.33 (2H, s), 6.51 (1H, t, J = 3.2 Hz), 6.59 (1H, s), 6.86 (1H, s), 6.99 (1H, t, J = 2.9 Hz), 7.02 (1H, s), 7.32-7.45 (7H, m), 8.04 (1H, d, J = 8.8 Hz), 8.48 (1H, s), 9.36 (1H, br s).

(76b) Acido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxílico

El 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxilato de bencilo (5.08 g, 9.47 mmol) sintetizado en el ejemplo (76a) se disolvió en acetato de etilo (30 mL), y se le agregó un catalizador de paladio al 10% en carbón (1.10 g), seguido por agitación a temperatura ambiente durante 3 horas bajo una atmósfera de hidrógeno. Después de filtración en Celite, el disolvente se removió por destilación bajo presión reducida para producir el compuesto deseado como un sólido blanco (4.30 g, rendimiento de ~100%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 5.9 Hz), 3.23 (3H, s), 3.47 (3H, s), 3.57 (1H, dd, J = 9.8, 3.9 Hz), 3.67 (1H, dd, J = 10.0, 6.6 Hz), 4.72-4.80 (1H, m), 6.52 (1H, s), 6.59 (1H, s), 6.92 (1H, s), 7.03 (1H, s), 7.32 (1H, s), 7.45 (1H, dd, J = 8.5, 1.7 Hz), 8.05 (1H, d, J = 8.8 Hz), 8.49 (1H, d, J = 2.4 Hz), 10.31 (1H, br s).

(76c) 5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-2-(metilsulfonil)piridina

El ácido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxílico (1000 mg, 2.24 mmol) sintetizado en el ejemplo (76b) se disolvió en metanol (20 mL), y se le agregó (R)-(-)-1-amino-2-propanol (0.40 mL, 5.08 mmol) y cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio n-hidratado (1000 mg, 3.61 mmol), seguido por agitación a temperatura ambiente durante la noche bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 1%-3%), para producir un sólido amarillo.

Este se disolvió en tetrahidrofurano (20 mL) y se le agregó ácido metanosulfónico anhidro (600 mg, 3.44 mmol) y trietilamina (0.70 mL, 5.02 mmol), seguido por agitación a temperatura ambiente durante la noche bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con cloruro de metileno (50 mL). La capa orgánica se lavó con salmuera saturada

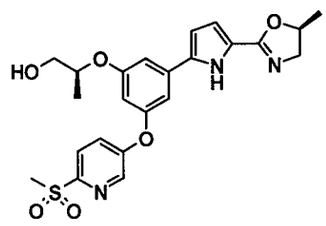
y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 1%-3%), para producir el compuesto deseado como un sólido blanco (450 mg, rendimiento de 41%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 1.43 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.42 (3H, s), 3.49-3.61 (4H, m), 4.09 (1H, dd, J = 13.9, 8.8 Hz), 4.53-4.63 (1H, m), 4.79-4.88 (1H, m), 6.51 (1H, d, J = 3.9 Hz), 6.57 (1H, d, J = 1.6 Hz), 6.76 (1H, d, J = 3.9 Hz), 6.83 (1H, s), 7.02 (1H, s), 7.44 (1H, dd, J = 8.6, 2.3 Hz), 8.05 (1H, d, J = 8.6 Hz), 8.49 (1H, s).

MS (ESI) m/z: 486.17067 $(M+H)^+$.

EJEMPLO 77

(2S)-2-(3-{5-[(5S)-5-Metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol



La 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-2-(metilsulfonil)piridina (310 mg, 0.638 mmol) sintetizada en el ejemplo (76c) se disolvió en cloruro de metileno (7.0 mL), y se le agregó a gotas a -78°C tribromuro de boro (solución en

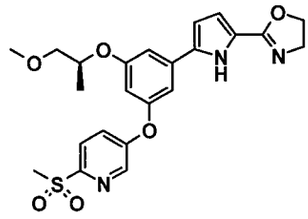
diclorometano 1.0 mol/L, 1.00 mL, 1.0 mmol), seguido por agitación a temperatura ambiente durante 1 hora bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (20 mL) y se extrajo con cloruro de metileno (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 1%-3%), para producir el compuesto deseado como un sólido blanco (245 mg, rendimiento de 81%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.29 (3H, d, J = 6.3 Hz), 1.43 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.55 (1H, dd, J = 13.9, 7.2 Hz), 3.79 (2H, d, J = 5.1 Hz), 4.09 (1H, dd, J = 14.1,9.4 Hz), 4.56-4.63 (1H, m), 4.81-4.88 (1H, m), 6.38 (1H, br s), 6.48 (1H, t, J = 3.3 Hz), 6.75 (1H, d, J = 3.5 Hz), 6.80 (1H, br s), 6.96 (1H, br s), 7.39 (1H, br s), 8.03 (1H, d, J = 8.2 Hz), 8.45 (1H, s).

MS (ESI) m/z: 472.15208 $(M+H)^+$.

EJEMPLO 78

5-{3-[5-(4,5-Dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi}-2-(metilsulfonil)piridina



(78a) 3-Bromo-5-metoxifenol

Se disolvió 1-bromo-3,5-dimetoxibenceno (18.74 g, 86.3 mmol), disponible comercialmente, en 1-metil-2-pirrolidona (100 mL), y se le agregó tiometóxido de sodio (6.74 g, 96.2 mmol), seguido por agitación a 100°C durante 3 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó ácido clorhídrico 1N (200 mL) y se extrajo con éter dietílico (500 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-25%), para producir el compuesto deseado como un sólido blanco (15.03 g, rendimiento de 86%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 3.77 (3H, s), 4.82 (1H, s), 6.33 (1H, t, J = 2.4 Hz), 6.61 (1H, t, J = 2.0 Hz), 6.66 (1H, t, J = 2.0 Hz).

(78b) 1-Bromo-3-metoxi-5-[(1S)-2-metoxi-1-metiletoxi]benceno

El 3-bromo-5-metoxifenol (7.60 g, 37.4 mmol) sintetizado en el

ejemplo (78a) se disolvió en tolueno (100 mL), y se le agregó R-(-)-1-metoxi-2-propanol (4.40 mL, 44.9 mmol) y trifenilfosfina (13.8 g, 52.6 mmol), seguido por la adición de azodicarboxilato de dietilo (solución en tolueno 2.2 mol/l, 24 mL, 52.8 mmol), gota a gota a 0°C, y agitación a temperatura ambiente durante 1.5 horas bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida, se le agregó éter dietílico (100 mL) y el depósito se filtró para removerlo. El licor madre se destiló bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-20%), para producir el compuesto deseado como un líquido incoloro (9.22 g, rendimiento de 89%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.30 (3H, d, J = 6.3 Hz), 3.40 (3H, s), 3.47 (1H, dd, J = 10.6, 4.3 Hz), 3.55 (1H, dd, J = 10.4, 6.1 Hz), 3.76 (3H, s), 4.46-4.52 (1H, m), 6.42 (1H, t, J = 2.2 Hz), 6.65 (1H, dd, J = 2.3, 1.6 Hz), 6.69 (1H, t, J = 2.0 Hz).

MS (EI) m/z: 274 $(M)^+$.

(78c) 3-Bromo-5-[(1S)-2-metoxi-1-metiletoxi]fenol

El 1-bromo-3-metoxi-5-[(1S)-2-metoxi-1-metiletoxi]benceno (9.21 g, 33.5 mmol) sintetizado en el ejemplo (78b) se disolvió en 1-metil-2-pirrolidona (100 mL), y se le agregó tiometóxido de sodio (2.75 g, 37.3 mmol), seguido por agitación a 130°C durante 3 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó ácido clorhídrico 2N (500 mL) y se extrajo con éter dietílico (300 mL).

La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-25%), para producir el compuesto deseado como un líquido incoloro (8.30 g, rendimiento de 95%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.29 (3H, d, J = 6.3 Hz), 3.41 (3H, s), 3.46 (1H, dd, J = 10.2, 4.3 Hz), 3.55 (1H, dd, J = 10.6, 5.9 Hz), 4.45-4.51 (1H, m), 4.96 (1H, br s), 6.36 (1H, t, J = 2.0 Hz), 6.59 (1H, t, J = 2.0 Hz), 6.68 (1H, t, J = 2.0 Hz).

MS (EI) m/z: 260 $(M)^+$.

(78d) 3-[(1S)-2-Metoxi-1-metiletoxi]-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenol

El 3-bromo-5-[(1S)-2-metoxi-1-metiletoxi]fenol (8.30 g, 31.8 mmol) sintetizado en el ejemplo (78c) se disolvió en N,N-dimetilformamida (100 mL), y se le agregó bis(pinacolato)diboro (10.50 g, 41.3 mmol), complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano (810 mg, 0.992 mmol) y acetato de potasio (15.50 g, 158 mmol), seguido por agitación a 90°C durante 3 horas bajo una atmósfera de nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente, se le agregó agua (500 mL) y se extrajo con éter dietílico (300 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión

reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-30%), para producir el compuesto deseado como un aceite pardo (8.75 g, rendimiento de 89%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.26 (3H, d, J = 4.1 Hz), 1.33 (12H, s), 3.41 (1H, s), 3.47 (1H, dd, J = 10.2, 4.7 Hz), 3.57 (1H, dd, J = 10.6, 5.9 Hz), 4.52-4.58 (1H, m), 4.80 (1H, brs), 6.55 (1H, t, J = 2.4 Hz), 6.83 (1H, d, J = 2.4 Hz), 6.95 (1H, d, J = 2.4 Hz).

MS (FAB) m/z: 309 $(M+H)^+$.

(78e) 2,5-Dibromo-1H-pirrol-1-carboxilato de t-butilo

Se disolvió 1-pirrolcarboxilato de t-butilo (46.68 g, 279 mmol), disponible comercialmente, en tetrahidrofurano (500 mL), y se enfrió a -78°C. A esto se le agregó N-bromosuccinimida (100.48 g, 565 mmol) en pequeñas porciones durante 1 hora. La temperatura de la solución de reacción se elevó naturalmente, y la solución se agitó a temperatura ambiente durante 18 horas. La solución de reacción se enfrió a 0°C, se le agregó sulfito de sodio (36.43g), seguido por agitación durante 30 minutos, y subsiguientemente se le agregó hexano (200 mL) para producir un precipitado, que se removió por filtración en Celite. El disolvente del filtrado se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 1%-5%), para producir el compuesto deseado como un aceite incoloro (52.69 g, rendimiento de 58%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.65 (9H, s), 6.25 (2H, s).

MS (EI) m/z: 323 (M^+).

(78f) 5-Bromo-1H-pirrol-1,2-dicarboxilato de 2-bencilo-1-t-butilo

El 2,5-dibromo-1H-pirrol-1-carboxilato de t-butilo (10.98 g, 33.8 mmol) sintetizado en el ejemplo (78e) se disolvió en éter dietílico (135 mL) y se enfrió a -78°C. Lentamente se le agregó n-butil-litio (solución en hexano 2.77 mol/L, 12.8 mL, 35.5 mmol), gota a gota, y se agitó durante 1 hora. A la solución de reacción se le agregó lentamente, gota a gota, cloroformiato de bencilo (6.25 mL, 44.0 mmol), y se agitó durante 30 minutos. Con la temperatura de la solución de reacción elevándose gradualmente a la temperatura ambiente, se agitó durante 1 hora. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (200 mL) y éter dietílico (300 mL), y la solución se separó. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 5%-45%), para producir el compuesto deseado como un aceite pardo rojizo (8.80 g, rendimiento de 68%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.56 (9H, s), 5.26 (2H, s), 6.21 (1H, d, J = 3.9 Hz), 6.85 (1H, d, J = 3.9 Hz), 7.28-7.39 (5H, m).

MS (FAB) m/z: 380 $(M+H)^+$.

(78g) 5-{3-Hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-1,2-dicarboxilato de 2-bencilo-1-t-butilo

El 5-bromo-1H-pirrol-1,2-dicarboxilato de 2-bencilo-1-t-butilo (8.75 g, 23.0 mmol) sintetizado en el ejemplo (78f), y el 3-[(1S)-2-metoxi-1-metiletoxi]-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenol (7.11 g, 23.1 mmol) sintetizado en el ejemplo (78d), se disolvieron en un disolvente mixto de 1,4-dioxano (92 mL) y agua (23 mL), y se les agregó complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano (570 mg, 0.698 mmol) y carbonato de potasio (7.95 g, 57.5 mmol), seguido por agitación a 55°C durante 3 horas bajo una atmósfera de nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente, se le agregó agua (200 mL) y se extrajo con acetato de etilo (200 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 15%-35%), para producir el compuesto deseado como un aceite pardo (8.32 g, rendimiento de 75%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.29 (3H, d, J = 6.3 Hz), 1.41 (9H, s), 3.40 (3H, s), 3.47 (1H, dd, J = 10.3, 4.4 Hz), 3.57 (1H, dd, J = 10.3, 5.9 Hz), 4.48-4.54 (1H, m), 5.20 (1H, s), 5.30 (2H, s), 6.17 (1H, d, J = 3.4 Hz), 6.44 (1H, s), 6.48 (1H, s), 6.57 (1H, s), 6.94 (1H, d, J = 3.4 Hz), 7.42-7.31 (5H, m).

MS (FAB) m/z: 481 (M^+).

(78h) 5-Bromo-2-(metiltio)piridina

Se disolvió 2,5-dibromo-piridina (6.01 g, 25.4 mmol), disponible comercialmente, en N,N-dimetilformamida (50 mL), y se le agregó tiometóxido de sodio (2.20 g, 31.4 mmol), seguido por agitación a 0°C durante 3.5 horas bajo una atmósfera de nitrógeno. La solución de reacción se llevó de vuelta a la temperatura ambiente, se le agregó agua (250 mL) y se extrajo con éter dietílico (250 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 3%-5%), para producir el compuesto deseado como un sólido blanco (4.90 g, rendimiento de 94%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.54 (3H, s), 7.08 (1H, d, J = 8.2 Hz), 7.58 (1H, dd, J = 8.6, 2.3 Hz), 8.49 (1H, d, J = 2.0 Hz).

(78i) 5-Fluoro-2-(metilsulfonil)piridina

La 5-bromo-2-(metiltio)piridina (4.90 g, 24.0 mmol) sintetizada en el ejemplo (78h) se disolvió en tetrahidrofurano (100 mL), y se le agregó a gotas a -78°C n-butil-litio (solución en hexano 1.57 mol/L, 17.0 mL, 26.7 mmol), seguido por agitación a -78°C durante 1 hora, bajo una atmósfera de nitrógeno. Se disolvió N-fluorobencenosulfonimida (11.0 g, 34.9 mmol) en tetrahidrofurano (25 mL), seguido por su adición a gotas a la solución de reacción a -78°C, y se agitó a -78°C durante 2 horas bajo una atmósfera de nitrógeno. La solución de reacción se llevó de vuelta a la temperatura

ambiente y se agitó durante 1.5 horas. Se le agregó una solución acuosa saturada de cloruro de amonio (200 mL) y se extrajo con éter dietílico (300 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión ligeramente reducida.

El residuo resultante se disolvió en cloruro de metileno (150 mL), y se le agregó lentamente ácido m-cloroperbenzoico (65%, 16.5 g, 62.1 mmol) a 0°C, seguido por agitación a 0°C durante 1.5 horas bajo una atmósfera de nitrógeno. Después de que el material sólido blanco se removió por filtración en Celite, se le agregó una solución acuosa saturada de carbonato ácido de sodio (100 mL) y se extrajo con cloruro de metileno (400 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 3%-5%), para producir el compuesto deseado como un sólido blanco amarillento (1.95 g, rendimiento de 46%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 3.24 (3H, s), 7.67 (1H, ddd, J = 9.9, 6.9, 1.9 Hz), 8.16 (1H, dd, J = 8.6, 4.3 Hz), 8.59 (1H, d, J = 2.7 Hz).

(78j) 5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxilato de bencilo

El 5-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-1,2-dicarboxilato de 2-bencilo-1-t-butilo (5.05 g, 10.49 mmol) sintetizado en el

ejemplo (78g), y la 5-fluoro-2-(metilsulfonil)piridina (2.05 g, 11.70 mmol) sintetizada en el ejemplo (78i), se disolvieron en N,N-dimetilformamida (30 mL), y se les agregó carbonato de potasio (4.50 g, 32.56 mmol), seguido por agitación a 80°C durante 3 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (150 mL) y se extrajo con éter dietílico (150 mL). La capa orgánica se lavó con salmuera saturada, subsiguientemente se secó sobre sulfato de magnesio anhidro, y el disolvente se removió por destilación bajo presión reducida.

El compuesto resultante se disolvió en ácido trifluoroacético (10 mL) y se agitó a temperatura ambiente durante 1 hora bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 35%-50%), para producir el compuesto deseado como un aceite blanco (5.08 g, rendimiento de 90%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.51 (1H, dd, J = 10.3, 3.9 Hz), 3.58 (1H, dd, J = 10.3, 6.3 Hz), 4.54-4.61 (1H, m), 5.33 (2H, s), 6.51 (1H, t, J = 3.2 Hz), 6.59 (1H, s), 6.86 (1H, s), 6.99 (1H, t, J = 2.9 Hz), 7.02 (1H, s), 7.32-7.45 (7H, m), 8.04 (1H, d, J = 8.8 Hz), 8.48 (1H, s), 9.36 (1H, br s).

(78k) Acido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxílico

El 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxilato de bencilo (5.08 g, 9.47 mmol) sintetizado

en el ejemplo (78j) se disolvió en acetato de etilo (30 mL), y se le agregó un catalizador de paladio al 10% en carbón (1.10 g), seguido por agitación a temperatura ambiente durante 3 horas bajo una atmósfera de hidrógeno. Después de filtración en Celite, el disolvente se removió por destilación bajo presión reducida para producir el compuesto deseado como un sólido blanco (4.30 g, rendimiento de ~100%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 5.9 Hz), 3.23 (3H, s), 3.47 (3H, s), 3.57 (1H, dd, J = 9.8, 3.9 Hz), 3.67 (1H, dd, J = 10.0, 6.6 Hz), 4.72-4.80 (1H, m), 6.52 (1H, s), 6.59 (1H, s), 6.92 (1H, s), 7.03 (1H, s), 7.32 (1H, s), 7.45 (1H, dd, J = 8.5, 1.7 Hz), 8.05 (1H, d, J = 8.8 Hz), 8.49 (1H, d, J = 2.4 Hz), 10.31 (1H, br s).

(78l) 5-{3-[5-(4,5-Dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi}-2-(metilsulfonil)piridina

El ácido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxílico (1.00 g, 2.24 mmol) sintetizado en el ejemplo (78k) se disolvió en metanol (20 mL), y se le agregó etanolamina (0.30 mL, 4.97 mmol) y cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio n-hidratado (1.00 g, 3.61 mmol), seguido por agitación a temperatura ambiente durante 1 día bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 1%-3%), para producir un compuesto como un sólido blanco.

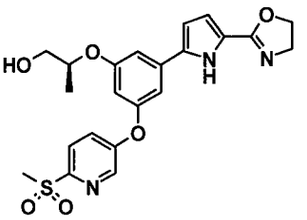
Este se disolvió en tetrahidrofurano (20 mL) y se le agregó ácido metanosulfónico anhidro (700 mg, 4.02 mmol) y trietilamina (0.85 mL, 6.10 mmol), seguido por agitación a 50°C durante 5 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo con cloruro de metileno (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 1%-3%), para producir el compuesto deseado como un sólido blanco (410 mg, rendimiento de 39%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 10.2, 3.9 Hz), 3.59 (1H, dd, J = 10.6, 6.3 Hz), 4.00 (2H, t, J = 9.2 Hz), 4.43 (2H, t, J = 9.4 Hz), 4.55-4.61 (1H, m), 6.51 (1H, d, J = 3.5 Hz), 6.57 (1H, t, J = 2.2 Hz), 6.77 (1H, d, J = 3.9 Hz), 6.84 (1H, t, J = 1.8 Hz), 7.03 (1H, t, J = 1.6 Hz), 7.44 (1H, dd, J = 8.6, 2.7 Hz), 8.05 (1H, d, J = 8.6 Hz), 8.49 (1H, d, J = 2.7 Hz).

MS (ESI) m/z: 472.15408 $(M+H)^+$.

EJEMPLO 79

(2S)-2-(3-[5-(4,5-Dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol



La 5-{3-[5-(4,5-dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi}-2-(metilsulfonil)piridina (230 mg, 0.49 mmol) sintetizada en el ejemplo (78l) se disolvió en cloruro de metileno (10 mL), y se le agregó a gotas a -78°C tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 0.75 mL, 0.75 mmol), seguido por agitación a temperatura ambiente durante 1.5 horas bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (20 mL) y se extrajo con cloruro de metileno (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 2%-4%), para producir el compuesto deseado como un sólido blanco (170 mg, rendimiento de 76%).

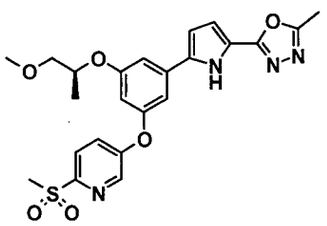
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.30 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.79 (2H, d, J = 5.9 Hz), 4.01 (2H, t, J = 9.4 Hz), 4.43 (2H, t, J = 9.4 Hz),

4.55-4.61 (1H, m), 6.44 (1H, t, J = 2.2 Hz), 6.49 (1H, d, J = 3.9 Hz), 6.76 (1H, d, J = 3.5 Hz), 6.81 (1H, t, J = 2.0 Hz), 6.96 (1H, s), 7.40 (1H, dd, J = 8.6, 2.3 Hz), 8.04 (1H, d, J = 8.6 Hz), 8.46 (1H, d, J = 2.3 Hz).

MS (ESI) m/z: 458.13852 $(M+H)^+$.

EJEMPLO 80

5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]fenoxi}-2-(metilsulfonil)piridina



El ácido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxílico (600 mg, 1.34 mmol) sintetizado en el ejemplo (78k) se disolvió en cloruro de metileno (20 mL), y se le agregó acetohidrazida (220 mg, 2.97 mmol), WSCI·HCl (580 mg, 3.03 mmol) y 4-dimetilaminopiridina (150 mg, 1.23 mmol), seguido por agitación a temperatura ambiente durante la noche bajo una atmósfera de nitrógeno. Se le agregó una solución acuosa saturada de cloruro de amonio (100 mL) y se extrajo con cloruro de metileno (100 mL). La capa orgánica se lavó con salmuera saturada, subsiguientemente se secó sobre sulfato de magnesio anhidro y el disolvente se removió por destilación bajo presión reducida.

Este residuo se disolvió en cloruro de metileno (20 mL) y se le

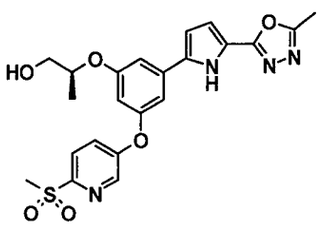
agregó cloruro de p-toluenosulfonilo (510 mg, 2.68 mmol) y trietilamina (0.75 mL, 5.38 mmol), seguido por agitación a temperatura ambiente durante 4 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con cloruro de metileno (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 60-80%), para producir el compuesto deseado como un sólido blanco (450 mg, rendimiento de 69%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.35 (3H, d, J = 6.3 Hz), 2.59 (3H, s), 3.24 (3H, s), 3.42 (3H, s), 3.52 (1H, dd, J = 10.6, 3.5 Hz), 3.61 (1H, dd, J = 11.3, 5.5 Hz), 4.51-4.72 (1H, m), 6.59-6.61 (2H, br m), 6.87-6.90 (2H, br m), 7.06 (1H, br s), 7.46 (1H, d, J = 8.6 Hz), 8.06 (1H, d, J = 8.6 Hz), 8.50 (1H, d, J = 1.6 Hz), 9.66 (1H, br s).

MS (ESI) m/z: 485.14739 $(M+H)^+$.

EJEMPLO 81

(2S)-2-(3-[5-(5-Metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol



La 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]fenoxi}-2-(metilsulfonil)piridina (320 mg, 0.660 mmol) sintetizada en el ejemplo 80 se disolvió en cloruro de metileno (10 mL), y se le agregó a gotas a -78°C tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 1.00 mL, 1.00 mmol), y se agitó a temperatura ambiente durante 1 hora bajo una atmósfera de nitrógeno. A esta solución de reacción, se le agregó una solución acuosa saturada de cloruro de amonio (20 mL) y se extrajo con cloruro de metileno (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 1%-3%), para producir el compuesto deseado como un sólido amarillo (190 mg, rendimiento de 61%).

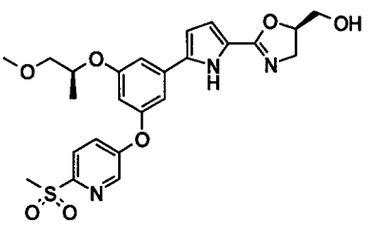
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.29 (3H, d, J = 6.3 Hz), 2.34 (1H, br s), 2.55 (3H, s), 3.21 (3H, s), 3.76 (2H, br s), 4.49-4.58 (1H, m), 6.52 (1H, s), 6.55 (1H, dd, J = 3.9, 2.7 Hz), 6.81-6.84 (2H, m), 7.00 (1H, t, J = 2.0 Hz),

7.42 (1H, dd, J = 8.6, 2.7 Hz), 8.03 (1H, d, J = 8.6 Hz), 8.45 (1H, d, J = 2.7 Hz), 9.76 (1H, br s).

MS (ESI) m/z: 471.13599 $(M+H)^+$.

EJEMPLO 82

{(5R)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol



(82a) 5-(3-{[(2S)-1-Metoxipropan-2-il]oxi}-5-{5-[(5R)-5-{[(tripropan-2-ilsilil)oxi]metil}-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-2-(metilsulfonil)piridina

El ácido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxílico (1.70 g, 3.81 mmol) sintetizado en el ejemplo (78k) se disolvió en metanol (30 mL), y se le agregó (S)-(-)-3-amino-1,2-propanodiol (0.80 g, 8.78 mmol) y cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio n-hidratado (1.70 g, 6.14 mmol), seguido por agitación a temperatura ambiente durante 3 días bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 7%-10%), para producir

un sólido amarillo.

Este se disolvió en cloruro de metileno (40 mL) y se le agregó triisopropilclorosilano (1.32 mL, 6.17 mmol), 4-dimetilaminopiridina (0.75 g, 6.14 mmol) y trietilamina (2.87 mL, 20.59 mmol), seguido por agitación a temperatura ambiente durante 1 día, bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con cloruro de metileno (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice para producir un sólido amarillo (disolvente de elución: metanol/cloruro de metileno = 1%).

Este se disolvió en tetrahidrofurano (30 mL) y se le agregó ácido metanosulfónico anhidro (1.05 g, 6.03 mmol) y trietilamina (1.70 mL, 12.20 mmol), seguido por agitación a 50°C durante 4.5 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con cloruro de metileno (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-70%), para producir el compuesto deseado como un sólido amarillo pálido (1.18 g, rendimiento de 47%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 0.99-1.16 (21H, m), 1.32 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.40 (3H, s), 3.50 (1H, dd, J = 10.3, 3.9 Hz), 3.58 (1H, dd, J = 10.3, 5.9 Hz), 3.81-3.90 (2H, m), 3.92-4.01 (2H, m), 4.51-4.62 (1H, br s), 4.70-4.78 (1H, br s), 6.49 (1H, d, J = 3.9 Hz), 6.56 (1H, s), 6.72 (1H, t, J = 2.0 Hz), 6.83 (1H, s), 7.01 (1H, s), 7.43 (1H, dd, J = 7.6, 1.7 Hz), 8.04 (1H, d, J = 8.3 Hz), 8.48 (1H, d, J = 2.4 Hz).

(82b) {(5R)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}-metanol

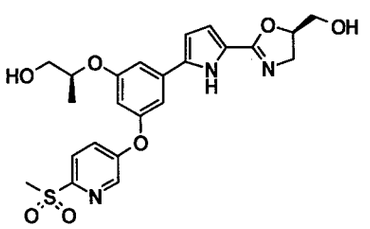
La 5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{5-[(5R)-5-{[(tripropan-2-ilsilil)oxi]metil}-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-2-(metilsulfonil)-piridina (1.18 g, 1.79 mmol) sintetizada en el ejemplo (82a) se disolvió en tetrahidrofurano (10 mL), y se le agregó fluoruro de tetrabutilamonio (solución en tetrahidrofurano 1.0 mol/L, 2.00 mL, 2.00 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante 30 minutos bajo una atmósfera de nitrógeno. A esta solución de reacción, se le agregó una solución acuosa saturada de cloruro de amonio (20 mL) y se extrajo con cloruro de metileno (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 2%-3%), para producir el compuesto deseado como un sólido blanco (680 mg, rendimiento de 76%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.27 (3H, d, J = 6.3 Hz), 3.21 (3H, s), 3.40 (3H, s), 3.48 (1H, dd, J = 10.2, 3.9 Hz), 3.56 (1H, dd, J = 10.2, 6.3 Hz), 3.68 (1H, dd, J = 12.1, 5.1 Hz), 3.75 (1H, dd, J = 14.5, 7.4 Hz), 3.85 (1H, d, J = 9.4 Hz), 4.00 (1H, dd, J = 14.1, 9.8 Hz), 4.53 (1H, br s), 4.78 (1H, br s), 6.46 (1H, d, J = 3.9 Hz), 6.55 (1H, t, J = 2.2 Hz), 6.72 (1H, d, J = 3.9 Hz), 6.81 (1H, d, J = 2.0 Hz), 6.97 (1H, s), 7.42 (1H, dd, J = 8.6, 2.7 Hz), 8.03 (1H, d, J = 8.6 Hz), 8.46 (1H, d, J = 2.7 Hz).

MS (ESI) m/z: 502.16243 $(M+H)^+$.

EJEMPLO 83

(2S)-2-(3-{5-[(5R)-5-(Hidroximetil)-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol



El {(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol (520 mg, 1.04 mmol) sintetizado en el ejemplo (82b) se disolvió en cloruro de metileno (10 mL), y se le agregó a gotas a -78°C tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 2.00 mL, 2.00 mmol), seguido por agitación a temperatura ambiente durante 4 horas bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa de hidróxido de

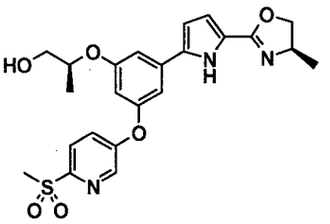
sodio 1N (20 mL) y se extrajo con cloruro de metileno (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 3%-5%), para producir el compuesto deseado como un sólido blanco (148 mg, rendimiento de 29%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.30 (3H, d, J = 5.9 Hz), 3.23 (3H, s), 3.70-3.82 (3H, m), 3.90-3.99 (2H, m), 4.07 (1H, t, J = 11.5 Hz), 4.62 (1H, br s), 4.95 (1H, br s), 6.47 (2H, d, J = 3.9 Hz), 6.86 (2H, d, J = 3.9 Hz), 7.15 (1H, s), 7.40 (1H, dd, J = 8.8, 2.4 Hz), 8.03 (1H, d, J = 8.8 Hz), 8.45 (1H, d, J = 2.4 Hz), 11.26 (1H, br s).

MS (ESI) m/z: 488.14896 $(M+H)^+$.

EJEMPLO 84

(2S)-2-(3-{5-[(4R)-4-Metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol



(84a) N-[(1R)-2-Hidroxi-1-metiletil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxamida

El ácido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxílico (2.00 g, 4.48 mmol) sintetizado en el ejemplo (78k), D-alaninol (0.52 mL, 6.72 mmol), HOBT·H_2O (0.73 g, 5.38 mmol) y N-metilmorfolina (0.99 mL, 8.96 mmol), se disolvieron en cloruro de metileno (40 mL), y se les agregó WSCI·HCl (0.94 g, 4.93 mmol) a temperatura ambiente, seguido por agitación durante 30 horas bajo una atmósfera de nitrógeno. La solución de reacción se diluyó con cloruro de metileno (100 mL), se lavó con ácido clorhídrico 1N, solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-90%), para producir el compuesto deseado como un sólido blanco (1.94 g, 86%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.27 (3H, d, J = 6.8 Hz), 1.33 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.51 (1H, dd, J = 3.9, 10.3 Hz), 3.57-3.64 (2H, m), 3.76 (1H, dd, J = 3.5, 11.0 Hz), 4.21-4.27 (1H, brm), 4.55-4.60 (1H, m), 6.06 (1H, d, J = 7.3 Hz), 6.48 (1H, dd, J = 2.7, 4.0 Hz), 6.57 (1H, t, J = 2.1 Hz), 6.60 (1H, dd, J = 2.0, 2.3 Hz), 6.84 (1H, t, J = 1.7 Hz), 7.01 (1H, t, J = 1.7 Hz), 7.44 (1H, dd, J = 2.7, 8.7 Hz), 8.04 (1H, d, J = 8.7 Hz), 8.47 (1H, d, J = 2.7 Hz), 9.71 (1H, brs).

(84b) 5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-2-(metilsulfonil)piridina

La N-[(1R)-2-hidroxi-1-metiletil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxamida (1.94 g, 3.85 mmol) sintetizada en el ejemplo (84a) se disolvió en tetrahidrofurano (35 mL), y se le agregó ácido metanosulfónico anhidro (1.38 g, 7.70 mmol) y trietilamina (2.15 mL, 15.41 mmol), seguido por agitación a 50°C durante 1.5 horas, bajo una atmósfera de nitrógeno. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (30 mL) y la solución se separó con acetato de etilo (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-75%), para producir el compuesto deseado como un sólido blanco (1.59 g, rendimiento de 85%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (6H, d, J = 6.3 Hz), 3.23 (3H,

s), 3.41 (3H, s), 3.50 (1H, dd, J = 3.9, 10.2 Hz), 3.59 (1H, dd, J = 6.1,10.4 Hz), 3.93 (1H, t, J = 7.8 Hz), 4.30-4.36 (1H, m), 4.50 (1H, dd, J = 8.2, 9.2 Hz), 4.56-4.60 (1H, m), 6.51 (1H, d, J = 3.9 Hz), 6.57 (1H, t, J = 2.2 Hz), 6.75 (1H, d, J = 3.8 Hz), 6.84 (1H, t, J = 1.8 Hz), 7.04 (1H, t, J = 1.8 Hz), 7.44 (1H, dd, J = 2.8, 8.7 Hz), 8.05 (1H, d, J = 8.8 Hz), 8.45 (1H, d, J = 2.7 Hz).

(84c) (2S)-2-(3-{5-[(4R)-4-Metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol

La 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-2-(metilsulfonil)piridina (1.20 g, 2.47 mmol) sintetizada en el ejemplo (84b) se disolvió en cloruro de metileno (25 mL), seguido por enfriamiento a -78°C, y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 2.72 mL, 2.72 mmol) bajo una atmósfera de nitrógeno. Después de que la temperatura se elevó naturalmente y se agitó a temperatura ambiente durante 30 minutos, se le agregó una solución acuosa saturada de carbonato ácido de sodio para neutralizar la solución de reacción, seguido por extracción con cloruro de metileno (80 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 70%-100%), para producir el compuesto deseado como un sólido blanco (895 mg, 77%).

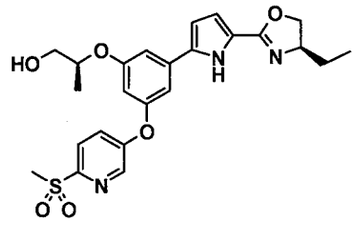
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.29 (3H, d, J = 6.2 Hz), 1.34 (1H,

d, J = 6.6 Hz), 3.23 (3H, s), 3.79-3.81 (2H, m), 3.95 (1H, t, J = 7.9 Hz), 4.32-4.38 (1H, m), 4.52 (1H, dd, J = 8.1, 9.3 Hz), 4.61-4.65 (1H, m), 6.35 (1H, t, J = 2.2 Hz), 6.47 (1H, d, J = 3.9 Hz), 6.75 (1H, d, J = 3.8 Hz), 6.80 (1H, dd, J = 1.4, 2.4 Hz), 6.97 (1H, t, J = 1.8 Hz), 7.37 (1H, dd, J = 2.7, 8.8 Hz), 8.02 (1H, d, J = 8.8 Hz), 8.43 (1H, d, J = 2.7 Hz).

MS (ESI) m/z: 472.15382 $(M+H)^+$.

EJEMPLO 85

(2S)-2-(3-{5-[(4R)-4-Etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol



(85a) N-[(1R)-1-(Hidroximetil)propil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxamida

El ácido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxílico (1.20 g, 2.69 mmol) sintetizado en el ejemplo (78k), (R)-(-)-2-amino-1-butanol (0.38 mL, 4.03 mmol), HOBT·H_2O (0.44 g, 3.23 mmol) y N-metilmorfolina (0.59 mL, 5.38 mmol), se disolvieron en cloruro de metileno (30 mL) y se les agregó WSCI·HCl (0.62 g, 3.23 mmol) a temperatura ambiente, seguido por agitación durante 6 horas bajo una atmósfera de nitrógeno. La solución de reacción se diluyó con cloruro de

metileno (50 mL), se lavó con ácido clorhídrico 1N, solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-90%), para producir el compuesto deseado como un sólido blanco (1.18 g, 85%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.01 (3H, t, J = 7.4 Hz), 1.33 (3H, d, J = 6.3 Hz), 1.67-1.74 (2H, m), 3.23 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 3.9, 10.4 Hz), 3.59 (1H, dd, J = 6.2, 10.4 Hz), 3.69 (1H, dd, J = 5.7, 10.9 Hz), 3.79 (1H, dd, 3.4, 11.0 Hz), 4.01-4.06 (1H, brm), 4.56-4.60 (1H, m), 6.02 (1H, d, J = 8.3 Hz), 6.49 (1H, dd, J = 2.9, 3.9 Hz), 6.58 (1H, t, J = 2.3 Hz), 6.61 (1H, dd, J = 2.5, 4.1 Hz), 6.84 (1H, t, J = 1.8 Hz), 7.02 (1H, t, J = 1.8 Hz), 7.45 (1H, dd, J = 2.8, 8.7 Hz), 8.05 (1H, d, J = 8.7 Hz), 8.45 (1H, dd, J = 0.8, 2.8 Hz), 9.60 (1H, brs).

(85b) 5-(3-{5-[(4R)-4-Etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)-2-(metilsulfonil)piridina

La N-[(1R)-1-(hidroximetil)propil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxamida (1.18 g, 2.28 mmol) sintetizada en el ejemplo (85a) se disolvió en tetrahidrofurano (20 mL), y se le agregó ácido metanosulfónico anhidro (0.82 g, 4.56 mmol) y trietilamina (1.27 mL, 9.12 mmol), seguido por agitación a 50°C durante 1.5 horas, bajo una atmósfera de nitrógeno. Se le agregó una

solución acuosa saturada de carbonato ácido de sodio (30 mL) y la solución se separó con acetato de etilo (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 40%-70%), para producir el compuesto deseado como un sólido blanco (1.06 g, rendimiento de 93%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 0.99 (3H, t, J = 7.4 Hz), 1.34 (3H, d, J = 6.4 Hz), 1.56-1.65 (1H, m), 1.66-1.74 (1H, m), 3.23 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 4.0, 10.2 Hz), 3.60 (1H, dd, J = 6.1,10.3 Hz), 4.02 (1H, t, J = 7.8 Hz), 4.16-4.20 (1H, m), 4.46 (1H, t, J = 8.7 Hz), 4.56-4.60 (1H, m), 6.51 (1H, d, J = 3.9 Hz), 6.56 (1H, t, J = 2.2 Hz), 6.74 (1H, d, J = 3.8 Hz), 6.85 (1H, t, J = 1.7 Hz), 7.05 (1H, t, J = 1.7 Hz), 7.44 (1H, dd, J = 2.7, 8.7 Hz), 8.05 (1H, dd, J = 0.8, 8.5 Hz), 8.45 (1H, dd, J = 0.8, 2.7 Hz).

(85c) (2S)-2-(3-{5-[(4R)-4-Etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol

La 5-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)-2-(metilsulfonil)piridina (1.06 g, 2.12 mmol) sintetizada en el ejemplo (85b) se disolvió en cloruro de metileno (20 mL), seguido por enfriamiento a -78°C, y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 2.33 mL, 2.33 mmol) bajo una atmósfera de nitrógeno. Después de que la temperatura se elevó naturalmente y se agitó a temperatura ambiente durante 30 minutos, se le agregó una solución acuosa

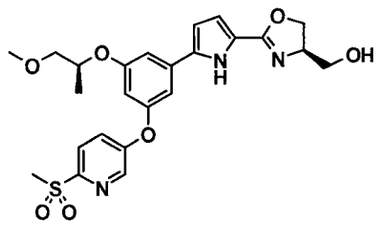
saturada de carbonato ácido de sodio para neutralizar la solución de reacción, seguido por extracción con cloruro de metileno (80 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 70%-100%), para producir el compuesto deseado como un sólido blanco (738 mg, 71%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.02 (3H, t, J = 7.4 Hz), 1.28 (3H, d, J = 6.2 Hz), 1.58-1.66 (1H, m), 1.67-1.74 (1H, m), 3.22 (3H, s), 3.80-3.82 (2H, m), 4.03 (1H, t, J = 8.0 Hz), 4.16-4.23 (1H, m), 4.49 (1H, t, J = 8.7 Hz), 4.62-4.68 (1H, m), 6.29 (1H, d, J = 2.2 Hz), 6.45 (1H, t, J = 3.7 Hz), 6.74 (1H, d, J = 3.9 Hz), 6.79 (1H, t, J = 1.8 Hz), 6.95 (1H, t, J = 1.7 Hz), 7.35 (1H, dd, J = 2.7, 8.7 Hz), 8.01 (1H, d, 8.7 Hz), 8.42 (1H, d, J = 2.7 Hz).

MS (ESI) m/z: 486.16955 $(M+H)^+$.

EJEMPLO 86

{(4R)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}metanol



(86a) N-{[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]carbonil}-L-serinato de metilo

El ácido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxílico (1.60 g, 3.58 mmol) sintetizado en el ejemplo (78k), clorhidrato del éster metílico de L-serina (0.61 g, 3.94 mmol), HOBT·H_2O (0.53 g, 3.94 mmol) y N-metilmorfolina (0.79 mL, 7.17 mmol), se disolvieron en un disolvente mixto de cloruro de metileno (30 mL) y N,N-dimetilformamida (7 mL), y se le agregó WSCI·HCl (0.82 g, 4.30 mmol) a temperatura ambiente, seguido por agitación durante 15 horas bajo una atmósfera de nitrógeno. La solución de reacción se diluyó con cloruro de metileno (100 mL), se lavó con ácido clorhídrico 1N, solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-80%), para producir el compuesto deseado como un

sólido blanco (1.91 g, 97%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.33 (3H, d, J = 6.4 Hz), 3.22 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 3.8, 10.3 Hz), 3.58 (1H, dd, J = 6.3, 10.3 Hz), 3.78 (3H, s), 3.98 (1H, dd, J = 3.4, 11.3 Hz), 4.04 (1H, dd, J = 3.9, 11.3 Hz), 4.56-4.59 (1H, brm), 4.80-4.83 (1H, m), 6.48 (1H, dd, J = 2.7, 3.8 Hz), 6.56 (1H, t, J = 2.0 Hz), 6.74 (1H, dd, J = 2.0, 2.4 Hz), 6.88 (1H, t, J = 1.7 Hz), 6.97 (1H, d, J = 7.5 Hz), 7.04 (1H, t, J = 1.9 Hz), 7.43 (1H, dd, J = 2.8, 8.8 Hz), 8.03 (1H, d, J = 8.8 Hz), 8.46 (1H, d, J = 2.8 Hz), 10.5 (1H, brs).

(86b) (4S)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-carboxilato de metilo

El N-{[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]carbonil}-L-serinato de metilo (1.91 g, 3.57 mmol) sintetizado en el ejemplo (86a) se disolvió en cloruro de metileno (40 mL), y se le agregó a gotas a -78°C trifluoruro de bis(2-metoxietil)aminoazufre (0.85 mL, 4.64 mmol). Después de agitar durante 30 minutos bajo una atmósfera de nitrógeno, se le agregó carbonato de potasio (0.74 g, 5.35 mmol) y se agitó a 0°C durante 10 minutos, seguido por agitación a temperatura ambiente durante 3 horas. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (30 mL), seguido por extracción con cloruro de metileno (100 mL), y la capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de

gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-70%), para producir el compuesto deseado como un polvo blanco (1.76 g, 93%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.34 (3H, d, J = 6.2 Hz), 3.23 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 4.1,10.3 Hz), 3.59 (1H, dd, J = 6.3, 10.3 Hz), 3.82 (1H, s), 4.56-4.60 (2H, m), 4.67 (1H, t, J = 8.2 Hz), 4.90 (1H, dd, J = 5.2, 7.8 Hz), 6.50 (1H, d, J = 3.8 Hz), 6.59 (1H, t, J = 2.2 Hz), 6.81 (1H, d, J = 3.9 Hz), 6.84 (1H, t, J = 1.7 Hz), 7.03 (1H, s), 7.45 (1H, dd, J = 2.7, 8.6 Hz), 8.06 (1H, d, J = 8.7 Hz), 8.48 (1H, d, J = 2.7 Hz).

(86c) {(4R)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-metanol

El (4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-carboxilato de metilo (1.76 g, 3.32 mmol) sintetizado en el ejemplo (86b) se disolvió en tetrahidrofurano (30 mL), y se le agregó hidruro de litio y aluminio (0.25 g, 6.65 mmol) a 0°C. Después de agitar 30 minutos bajo una atmósfera de nitrógeno, se le agregó agua (0.25 mL), una solución acuosa de hidróxido de sodio 5N (0.25 mL) y agua (0.75 mL), en este orden, y se agitó durante 10 minutos. Se le agregó acetato de etilo (100 mL), seguido por agitación durante 5 minutos, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado

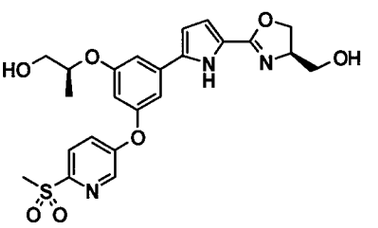
como un polvo blanco (1.15 g, 69%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.51 (1H, dd, J = 4.1, 10.4 Hz), 3.58-3.62 (2H, m), 3.97 (1H, d, J = 12.2 Hz), 4.10-4.15 (2H, m), 4.31-4.39 (2H, m), 4.56-4.60 (1H, m), 6.37 (1H, d, J = 3.8 Hz), 6.47 (1H, d, J = 3, 9 Hz), 6.57 (1H, t, J = 2.2 Hz), 6.87 (1H, dd, J = 1.2, 1.4 Hz), 7.05 (1H, t, J = 1.8 Hz), 7.46 (1H, dd, J = 2.8, 8.8 Hz), 8.05 (1H, dd, J = 0.7, 8.8 Hz), 8.50 (1H, dd, J = 0.7, 2.8 Hz).

MS (ESI) m/z: 502.16431 $(M+H)^+$.

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(2S)-2-(3-{5-[(4R)-4-(Hidroximetil)-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol



El {(4R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}metanol (200 mg, 0.40 mmol) sintetizado en el ejemplo (86c) se disolvió en cloruro de metileno (5 mL), seguido por enfriamiento a -78°C, y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 0.80 mL, 0.80 mmol), bajo una atmósfera de nitrógeno. Después de que la temperatura se elevó naturalmente y se agitó a temperatura ambiente durante 30 minutos, se le

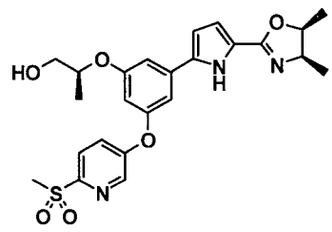
agregó una solución acuosa saturada de carbonato ácido de sodio para neutralizar la solución de reacción, seguido por extracción con cloruro de metileno (80 mL). La capa orgánica se lavó con una solución acuosa de hidróxido de sodio 1N y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-4%), para producir el compuesto deseado como un sólido blanco (143 mg, 74%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.65 (1H, dd, J = 3.5, 12.1 Hz), 3.74-3.80 (2H, m), 3.95 (1H, dd, J = 2.7, 12.2 Hz), 4.20 (1H, t, J = 6.8 Hz), 4.34-4.41 (1H, m), 4.41 (1H, t, J = 9.8 Hz), 4.57-4.61 (1H, m), 6.37 (1H, d, J = 3.9 Hz), 6.48 (1H, t, J = 2.2 Hz), 6.53 (1H, d, J = 3.9 Hz), 6.85 (1H, t, J = 1.8 Hz), 7.01 (1H, t, J = 1.8 Hz), 7.42 (1H, dd, J = 2.7, 8.8 Hz), 8.04 (1H, d, J = 8.8 Hz), 8.47 (1H, d, J = 2.7 Hz)

MS (ESI) m/z: 488.14910 $(M+H)^+$.

EJEMPLO 88

(2S)-2-(3-{5-[(4R,5S)-4,5-Dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol



(88a) (2R,3R)-3-Aminobutan-2-ol

El (2R,3R)-3-(dibencilamino)butan-2-ol ($[\alpha]^{23}_D$ -82°, c: 1.60, solución en cloroformo) (2.70 g, 10.0 mmol), sintetizado de acuerdo con un método conocido (*J. Org. Chem.*, 2006, 71, 6420), se disolvió en metanol (20 mL), y se le agregó hidróxido de paladio en carbón (0.85 g), seguido por agitación a 0.41368 MPa y a temperatura ambiente durante 4 horas bajo una atmósfera de hidrógeno. Después de filtración en Celite, el disolvente se removió por destilación bajo presión reducida para producir el compuesto deseado como un líquido incoloro (0.73 g, rendimiento de 82%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.10 (3H, d, J = 6.6 Hz), 1.17 (3H, d, J = 6.3 Hz), 2.60-2.67 (1H, m), 3.31-3.37 (1H, m).

(88b) N-[(1R,2R)-2-Hidroxi-1-metilpropil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxamida

El ácido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxílico (2.00 g, 4.48 mmol) sintetizado en el ejemplo (78k), y el (2R,3R)-3-aminobutan-2-ol (0.94 g, 8.96 mmol)

sintetizado en el ejemplo (88a), se disolvieron en metanol (30 mL), y se les agregó cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio n-hidratado (2.84 g, 8.96 mmol) a temperatura ambiente, seguido por agitación durante 3 días bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida, se le agregó agua (30 mL) y la solución se separó con acetato de etilo (70 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-90%), para producir el compuesto deseado como un sólido blanco (1.33 g, 57%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.23 (3H, t, J = 6.3 Hz), 1.27 (3H, d, J = 6.6 Hz), 1.33 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.52 (1H, dd, J = 3.9, 10.3 Hz), 3.59 (1H, dd, J = 6.2, 10.3 Hz), 3.82-3.86 (1H, m), 4.05-4.09 (1H, m), 4.58-4.62 (1H, m), 6.17 (1H, d, J = 8.7 Hz), 6.49 (1H, dd, J = 2.9, 3.9 Hz), 6.57 (1H, t, J = 2.2 Hz), 6.63 (1H, dd, J = 2.3, 3.9 Hz), 6.86 (1H, t, J = 1.8 Hz), 7.05 (1H, t, J = 1.8 Hz), 7.44 (1H, dd, J = 2.8, 8.7 Hz), 8.04 (1H, d, J = 8.7 Hz), 8.48 (1H, d, J = 2.8 Hz), 9.83 (1H, brs).

(88c) 5-(3-{5-[(4R,5S)-4,5-Dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)-2-(metilsulfonil)piridina

La N-[(1R,2R)-2-hidroxi-1-metilpropil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxamida (1.33 g, 2.57 mmol) sintetizada en el ejemplo (88b) se disolvió en

tetrahidrofurano (25 mL), y se le agregó ácido metanosulfónico anhidro (0.92 g, 5.14 mmol) y trietilamina (1.43 mL, 10.28 mmol), seguido por agitación a 50°C durante 5 horas bajo una atmósfera de nitrógeno. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (40 mL) y la solución se separó con acetato de etilo (80 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 40%-70%), para producir el compuesto deseado como un sólido blanco (0.95 g, rendimiento de 74%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.20 (3H, t, J = 6.9 Hz), 1.33 (3H, d, J = 6.3 Hz), 1.33 (3H, d, J = 6.6 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 4.0, 10.4 Hz), 3.58 (1H, dd, J = 6.1,10.4 Hz), 4.24-4.29 (1H, m), 4.55-4.58 (1H, m), 4.79-4.84 (1H, m), 6.50 (1H, d, J = 3.8 Hz), 6.56 (1H, t, J = 2.2 Hz), 6.74 (1H, d, J = 3.8 Hz), 6.83 (1H, t, J = 1.8 Hz), 7.01 (1H, t, J = 1.8 Hz), 7.43 (1H, dd, J = 2.8, 8.6 Hz), 8.05 (1H, d, J = 8.6 Hz), 8.48 (1H, d, J = 2.8 Hz).

(88d) (2S)-2-(3-{5-[(4R,5S)-4,5-Dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol

La 5-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)-2-(metilsulfonil)piridina (0.95 g, 1.96 mmol) sintetizada en el ejemplo (88c) se disolvió en cloruro de metileno (20 mL), se enfrió a -78°C y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 2.15 mL, 2.15 mmol), bajo una atmósfera de

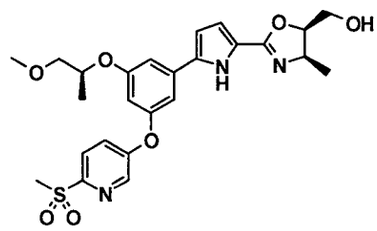
nitrógeno. Después de que la temperatura se elevó naturalmente y la solución se agitó a temperatura ambiente durante 30 minutos, se le agregó una solución acuosa saturada de carbonato ácido de sodio para neutralizar la solución de reacción, seguido por extracción con cloruro de metileno (80 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 70%-100%), para producir el compuesto deseado como un sólido blanco (617 mg, 67%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.23 (3H, t, J = 7.0 Hz), 1.27 (3H, d, J = 6.2 Hz), 1.34 (3H, d, J = 6.6 Hz), 3.23 (3H, s), 3.81-3.83 (2H, m), 4.27-4.35 (1H, m), 4.65-4.70 (1H, m), 4.81-4.89 (1H, m), 6.24 (1H, t, J = 2.2 Hz), 6.44 (1H, d, J = 3.8 Hz), 6.73 (1H, d, J = 3.8 Hz), 6.76 (1H, dd, J = 1.2, 2.2 Hz), 6.92 (1H, t, J = 1.7 Hz), 7.32 (1H, dd, J = 2.8, 8.8 Hz), 8.00 (1H, d, J = 8.8 Hz), 8.41 (1H, d, J = 2.8 Hz).

MS (ESI) m/z: 486.17002 $(M+H)^+$.

EJEMPLO 89

{(4R,5R)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4-metil-4,5-dihidro-1,3-oxazol-5-il}metanol



(89a) (2R,3R)-3-[(Difenilmetil)amino]-1-[(tripropan-2-ilsilil)oxi]-butan-2-ol

A cloruro de metileno (200 mL) deshidratado se le agregaron tamices moleculares de 4A (10 g). A este sistema se le agregó tetraisopropóxido de titanio (8.8 mL, 30 mmol) y ácido dietil L-(+)-tartárico (6.2 mL, 36 mmol) a -20°C, y se agitó a la misma temperatura durante 15 minutos. Se le agregó a gotas a -20°C (2E)-2-buten-1-ol (25 mL, 295 mmol) disuelto en cloruro de metileno deshidratado (50 mL), agitando a la misma temperatura durante 15 minutos. Subsiguientemente se agregó al sistema, a -20°C, hidroperóxido de t-butilo (se le agregó cloruro de metileno para separar la solución, seguido por la adición de tamices moleculares de 4A (5g) y agitación durante 20 minutos) (solución en decano 5-6 mol/L, 100 mL, 0.5-0.6 mmol)), y se agitó a -20°C durante 8.5 horas bajo una atmósfera de nitrógeno; la solución se dejó en reposo durante la noche a -30°C.

A este sistema se le agregó n-tributilfosfina (75 mL, 300 mmol),

tetraisopropóxido de titanio (135 mL, 460 mmol) y 1,1-difenilmetanamina (75 mL, 440 mmol) a temperatura ambiente, y se agitó a la misma temperatura durante 1 semana. A la solución de reacción se le agregó agua (30 mL) y el depósito se filtró. Al licor madre se le agregó agua (400 mL) y se extrajo con cloruro de metileno (1L). El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 15%-40%), para producir un líquido pardo oscuro.

Este líquido se disolvió en cloruro de metileno (300 mL) y se le agregó trietilamina (85 mL, 610 mmol) y cloruro de triisopropilsililo (50 mL, 234 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante 1.5 días. Se le agregó una solución acuosa saturada de cloruro de amonio (500 mL), y se extrajo con cloruro de metileno (500 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-5%), para producir el compuesto deseado como un sólido blanco (80.5 g, rendimiento de 64%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 0.96-1.07 (21H, m), 1.10 (3H, d, J = 6.3 Hz), 2.72-2.81 (1H, m), 3.28 (1H, br s), 3.56-3.63 (1H, m), 3.72 (1H, dd, J = 10.2, 5.9 Hz), 3.80 (1H, dd, J = 10.2, 3.9 Hz), 4.98 (1H, s), 7.15-7.20 (2H, m), 7.23-7.29 (4H, m), 7.34-7.40 (4H, m).

(89b) {(2R,3R)-3-Hidroxi-4-[(tripropan-2-ilsilil)oxi]butan-2-il}carbamato de bencilo

El (2R,3R)-3-[(difenilmetil)amino]-1-[(triisopropan-2-ilsilil)oxi]-butan-2-ol (10.3 g, 24.1 mmol) sintetizado en el ejemplo (89a) se disolvió en etanol (40 mL), y se le agregó paladio en carbón (3.20g), seguido por agitación a temperatura ambiente durante 6 horas bajo una atmósfera de hidrógeno. Después de filtración en Celite, el disolvente se removió por destilación bajo presión reducida para producir un compuesto como un líquido incoloro.

Este se disolvió en agua (40 mL) calentada a 50°C, y se le agregó carbonato ácido de sodio (4.50 g, 53.6 mmol) y cloroformiato de bencilo (3.50 mL, 24.5 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante 5 horas. Se le agregó cloruro de metileno (100 mL) y se extrajo. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-15%), para producir el compuesto deseado como un líquido incoloro (7.00 g, rendimiento de 73%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.04-1.09 (21H, m), 1.18 (3H, d, J = 6.8 Hz), 2.67 (1H, br s), 3.65-3.73 (2H, m), 3.77 (1H, dd, J = 10.0, 3.7 Hz), 3.86 (1H, br s), 5.10 (2H, s), 5.27 (1H, br s), 7.30-7.38 (5H, m).

(89c) 4-Nitrobenzoato de (5R,6S)-5,10-dimetil-3-oxo-1-fenil-9,9-di(propan-2-il)-2,8-dioxa-4-aza-9-silaundecan-6-ilo

El {(2R,3R)-3-hidroxi-4-[(tripropan-2-ilsilil)oxi]butan-2-il}-carbamato de bencilo (7.00 g, 17.7 mmol) sintetizado en el ejemplo (89b) se disolvió en tolueno (80 mL), y se le agregó ácido 4-nitro-benzoico (6.10 g, 36.5 mmol) y trifenilfosfina (11.85g, 45.2 mmol), seguido por enfriamiento a 0°C. Bajo una atmósfera de nitrógeno, se le agregó a gotas durante 10 minutos azodicarboxilato de dietilo (solución en tolueno al 40%, 20.3 mL, 44.7 mmol), y se agitó a temperatura ambiente durante 4 horas. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-15%), para producir el compuesto deseado como un líquido amarillo (7.90 g, rendimiento de 82%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 0.96-1.09 (21H, m), 1.29 (3H, d, J = 7.0 Hz), 3.90-4.01 (1H, m), 4.25-4.32 (1H, m), 4.95-5.10 (3H, m), 5.13-5.20 (1H, m), 7.24-7.39 (5H, m), 8.14-8.21 (2H, m), 8.23-8.30 (2H, m).

(89d) {(2R,3S)-3-Hidroxi-4-[(tripropan-2-ilsilil)oxi]butan-2-il}-carbamato de bencilo

El 4-nitrobenzoato de (5R,6S)-5,10-dimetil-3-oxo-1-fenil-9,9-di(propan-2-il)-2,8-dioxa-4-aza-9-silaundecan-6-ilo (7.90 g, 14.5 mmol) sintetizado en el ejemplo (89c) se disolvió en cloruro de metileno (150 mL), y se le agregó hidruro de diisobutilaluminio (solución en hexano 1.0 mol/L, 30.0 mL, 30.0 mmol), seguido por agitación a -40°C durante 8 horas, bajo una

atmósfera de nitrógeno. La solución de reacción se llevó a 0°C y se le agregó metanol (5.0 mL), seguido por la adición de una solución acuosa de hidróxido de sodio 5N (150 mL), y se extrajo con cloruro de metileno (200 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-15%), para producir el compuesto deseado como un líquido incoloro (3.70 g, rendimiento de 65%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.01-1.13 (21H, m), 1.26 (3H, d, J = 6.6 Hz), 2.72 (1H, br s), 3.55-3.67 (2H, m), 3.73 (2H, br s), 5.10 (2H, s), 5.13 (1H, br s), 7.31-7.36 (5H, m).

(89e) (2S,3R)-3-Amino-1-[(tripropan-2-ilsilil)oxi]butan-2-ol

El {(2R,3S)-3-hidroxi-4-[(tripropan-2-ilsilil)oxi]butan-2-il}-carbamato de bencilo (3.70 g, 9.35 mmol) sintetizado en el ejemplo (89d) se disolvió en etanol (30 mL), y se le agregó paladio en carbón (1.00g), seguido por agitación a temperatura ambiente durante 8 horas bajo una atmósfera de hidrógeno. Después de filtración en Celite, el disolvente se removió por destilación bajo presión reducida para producir el compuesto deseado como un líquido amarillo pálido (2.65 g, rendimiento de ~100%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.04-1.14 (24H, m), 2.95-3.02 (1H, m), 3.30-3.35 (1H, m), 3.66 (1H, dd, J = 9.8, 6.3 Hz), 3.76 (1H, dd, J = 9.8, 4.3 Hz).

(89f) N-{(1R,2S)-2-Hidroxi-1-metil-3-[(triisopropilsilil)oxi]propil}-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxamida

El ácido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxílico (1.20 g, 2.69 mmol) sintetizado en el ejemplo (78k), el (2S,3R)-3-amino-1-[(tripropan-2-ilsilil)oxi]butan-2-ol (1.08 g, 4.11 mmol) sintetizado en el ejemplo (89e), HOBT·H_2O (0.44 g, 3.23 mmol) y N-metilmorfolina (0.59 mL, 5.38 mmol), se disolvieron en N,N-dimetilformamida (20 mL), y se les agregó WSCI·HCl (0.62 g, 3.23 mmol) a temperatura ambiente, seguido por agitación durante 18 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó salmuera saturada (30 mL) y se extrajo con acetato de etilo (60 mL). Después de lavar con ácido clorhídrico 1N, solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-50%), para producir el compuesto deseado como un polvo blanco (1.69 g, 91%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.03-1.13 (21H, m), 1.34 (3H, d, J = 6.3 Hz), 1.35 (3H, d, J = 6.8 Hz), 3.23 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 4.0, 10.3 Hz), 3.54-3.61 (2H, m), 3.73-3.78 (2H, m), 4.14-4.18 (1H, m), 4.56-4.60 (1H, m), 6.31 (1H, brm), 6.49 (1H, dd, J = 2.9, 3.9 Hz), 6.57-6.60 (2H, m), 6.84 (1H, dd, J = 1.5, 2.3 Hz), 7.02 (1H, t, J = 1.8 Hz), 7.45 (1H, dd, J = 2.8,

8.8 Hz), 8.09 (1H, d, J = 8.7 Hz), 8.49 (1H, d, J = 2.7 Hz), 9.52 (1H, brs).

(89g) 5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(4R,5R)-4-metil-5-{[(triisopropilsilil)oxi]metil}-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-2-(metilsulfonil)piridina

La N-[(1R,2S)-2-hidroxi-1-metil-3-[(triisopropilsilil)oxi]propil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxamida (1.69 g, 2.45 mmol) sintetizada en el ejemplo (89f) se disolvió en tetrahidrofurano (25 mL), y se le agregó ácido metanosulfónico anhidro (0.88 g, 4.90 mmol) y trietilamina (1.37 mL, 9.80 mmol), seguido por agitación a 50°C durante 5 horas bajo una atmósfera de nitrógeno. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (40 mL) y la solución se separó con acetato de etilo (60 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-50%), para producir el compuesto deseado como un sólido blanco (1.23 g, rendimiento de 75%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.04-1.14 (21H, m), 1.34 (6H, d, J = 6.3 Hz), 3.23 (3H, s), 3.42 (3H, s), 3.50 (1H, dd, J = 4.0, 10.3 Hz), 3.59 (1H, dd, J = 6.1,10.3 Hz), 3.94 (2H, d, J = 5.3 Hz), 4.37-4.41 (1H, m), 4.56-4.60 (1H, m), 4.65-4.69 (1H, m), 6.49 (1H, d, J = 3.9 Hz), 6.56 (1H, t, J = 2.1 Hz), 6.74 (1H, d, J = 3.8 Hz), 6.85 (1H, s), 7.04 (1H, s), 7.44 (1H, dd, J = 2.8, 8.6 Hz), 8.05 (1H, d, J = 8.6 Hz), 8.48 (1H, d, J = 2.8 Hz).

(89h) {(4R,5R)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4-metil-4,5-dihidro-1,3-oxazol-5-il}metanol

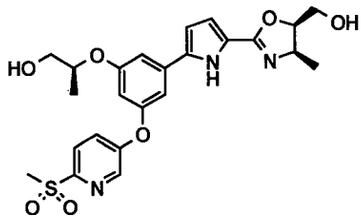
La 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(4R,5R)-4-metil-5-{[(triisopropilsilil)oxi]metil}-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-2-(metilsulfonil)piridina (1.23 g, 1.83 mmol) sintetizada en el ejemplo (89g) se disolvió en tetrahidrofurano (20 mL), y se le agregó fluoruro de tetrabutilamonio (solución en tetrahidrofurano 1.0 mol/L, 2.11 mL, 2.11 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante 1 hora bajo una atmósfera de nitrógeno. Se le agregó agua (20 mL) y se extrajo con acetato de etilo (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 90%-100%), para producir el compuesto deseado como un sólido blanco (715 mg, rendimiento de 76%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.26 (3H, d, J = 7.1 Hz), 1.31 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.42 (3H, s), 3.50 (1H, dd, J = 3.9, 10.3 Hz), 3.59 (1H, dd, J = 6.3, 10.3 Hz), 3.85 (2H, d, J = 5.4 Hz), 4.36-4.42 (1H, m), 4.53-4.48 (1H, m), 4.70-4.76 (1H, m), 6.50 (1H, d, J = 3.8 Hz), 6.57 (1H, t, J = 2.1 Hz), 6.77 (1H, d, J = 3.8 Hz), 6.84 (1H, t, 1.8 Hz), 7.00 (1H, t, 1.8 Hz), 7.43 (1H, dd, J = 2.8, 8.8 Hz), 8.04 (1H, d, J = 8.8 Hz), 8.48 (1H, d, J = 2.8 Hz).

MS (ESI) m/z: 516.17829 $(M+H)^+$.

EJEMPLO 90

(2S)-2-(3-{5-[(4R,5R)-5-(Hidroximetil)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol



El {(4R,5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4-metil-4,5-dihidro-1,3-oxazol-2-il}metanol (200 mg, 0.39 mmol) sintetizado en el ejemplo (89h) se disolvió en cloruro de metileno (5 mL), y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 0.78 mL, 0.78 mmol) a -78°C y bajo una atmósfera de nitrógeno; subsiguientemente la temperatura se regresó a la temperatura ambiente y se agitó durante 45 minutos. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con cloruro de metileno. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-4%), para producir el compuesto deseado como un sólido blanco (87 mg, rendimiento de 45%).

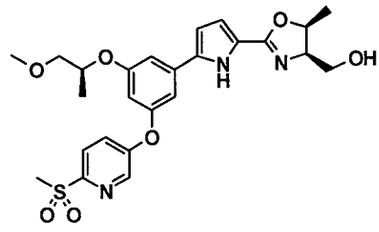
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.29 (6H, t, J = 5.9 Hz), 3.23 (3H, s), 3.79 (2H, d, J = 4.9 Hz), 3.85 (2H, d, J = 6.3 Hz), 4.41 (1H, dt, J = 16.3, 7.1

Hz), 4.59 (1H, dd, J = 11.5, 5.6 Hz), 4.73-4.77 (1H, m), 6.38 (1H, s), 6.46 (1H, d, J = 3.4 Hz), 6.77 (1H, d, J = 3.9 Hz), 6.81 (1H, s), 6.98 (1H, s), 7.35 (1H, d, J = 8.8 Hz), 8.01 (1H, d, J = 8.8 Hz), 8.44 (1H, s).

MS (ESI) m/z: 502.16510 $(M+H)^+$.

EJEMPLO 91

{(4R,5S)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol



(91a) N-[(1R,2R)-2-Hidroxi-1-(hidroximetil)propil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxamida

El ácido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxílico (1.20 g, 2.69 mmol) sintetizado en el ejemplo (78k), y L-treoninol (0.57 g, 5.38 mmol), disponible comercialmente, se disolvieron en metanol (25 mL) y se les agregó cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio n-hidratado (1.70 g, 5.38 mmol) a temperatura ambiente, seguido por agitación durante 3.5 horas bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se diluyó con acetato de etilo (100 mL).

Después de lavar con ácido clorhídrico 1N, solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio anhidro; el disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-6%), para producir el compuesto deseado como un sólido blanco (883 mg, 62%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.23 (3H, d, J = 6.4 Hz), 1.30 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 3.9, 10.2 Hz), 3.58 (1H, dd, J = 6.4, 10.4 Hz), 3.87 (2H, d, J = 4.0 Hz), 3.97-4.03 (1H, brm), 4.22-4.26 (1H, m), 4.55-4.58 (1H, m), 6.49 (1H, dd, J = 2.8, 3.9 Hz), 6.57 (1H, t, J = 2.2 Hz), 6.68-6.71 (2H, m), 6.86 (1H, t, J = 1.7 Hz), 7.02 (1H, t, J = 1.8 Hz), 7.44 (1H, dd, J = 2.7, 8.7 Hz), 8.04 (1H, d, J = 8.8 Hz), 8.47 (1H, d, J = 2.7 Hz), 10.05 (1H, brs).

(91b) N-[(1R,2R)-2-Hidroxi-1-{[(triisopropilsilil)oxi]metil}propil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxamida

La N-[(1R,2R)-2-hidroxi-1-(hidroximetil)propil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxamida (883 mg, 1.65 mmol) sintetizada en el ejemplo (91a), trietilamina (1.15 mL, 8.27 mmol) y 4-dimetilaminopiridina (404 mg, 3.31 mmol), se disolvieron en cloruro de metileno (20 mL) y se les agregó cloruro de triisopropilsililo (0.60 mL, 2.81 mmol) a temperatura ambiente, seguido por agitación durante 20 horas bajo una atmósfera de nitrógeno. El disolvente se

removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-60%), para producir el compuesto deseado como un sólido blanco (1.03 g, 90%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.05-1.08 (18H, m), 1.09-1.16 (3H, m), 1.23 (3H, d, J = 6.4 Hz), 1.34 (3H, d, J = 6.3 Hz), 3.24 (3H, s), 3.42 (3H, s), 3.52 (1H, dd, J = 4.0, 10.2 Hz), 3.60 (1H, dd, J = 6.2, 10.4 Hz), 3.99-4.04 (1H, m), 4.03-4.06 (2H, m), 4.30-4.35 (1H, m), 4.56-4.61 (1H, m), 6.51 (1H, t, J = 3.4 Hz), 6.59 (1H, t, J = 2.2 Hz), 6.62-6.66 (2H, m), 6.85 (1H, t, J = 1.8 Hz), 7.03 (1H, t, J = 1.7 Hz), 7.46 (1H, dd, J = 2.7, 8.8 Hz), 8.06 (1H, d, J = 8.8 Hz), 8.49 (1H, d, J = 2.7 Hz), 9.49 (1H, brs).

(91c) 5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(4R,5S)-5-metil-4-{[(triisopropilsilil)oxi]metil}-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-2-(metilsulfonil)piridina

La N-[(1R,2R)-2-hidroxi-1-{[(triisopropilsilil)oxi]metil}propil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxamida (1.03 g, 1.49 mmol) sintetizada en el ejemplo (91b) se disolvió en tetrahidrofurano (20 mL), y se le agregó ácido metanosulfónico anhidro (0.54 g, 2.99 mmol) y trietilamina (0.83 mL, 5.97 mmol), seguido por agitación a 50°C durante 4.5 horas bajo una atmósfera de nitrógeno. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (30 mL) y la solución se separó con acetato de etilo (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio

anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-50%), para producir el compuesto deseado como un sólido blanco (901 mg, rendimiento de 90%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.03-1.13 (21H, m), 1.33 (3H, d, J = 6.3 Hz), 1.52 (3H, d, J = 6.6 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 3.9, 10.4 Hz), 3.58 (1H, dd, J = 6.2, 10.5 Hz), 3.81 (1H, t, J = 9.5 Hz), 3.95 (1H, dd, J = 3.9, 10.4 Hz), 4.21-4.25 (2H, m), 4.56-4.59 (1H, m), 4.89-4.93 (1H, m), 6.50 (1H, d, J = 3.9 Hz), 6.56 (1H, t, J = 2.2 Hz), 6.76 (1H, d, J = 3.9 Hz), 6.84 (1H, s), 7.02 (1H, s), 7.44 (1H, dd, J = 2.7, 8.8 Hz), 8.05 (1H, d, J = 8.8 Hz), 8.48 (1H, d, J = 2.7 Hz).

(91d) {(4R,5S)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol

La 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(4R,5S)-5-metil-4-{[(triisopropilsilil)oxi]metil}-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-2-(metilsulfonil)piridina (901 mg, 1.34 mmol) sintetizada en el ejemplo (91c) se disolvió en tetrahidrofurano (15 mL), y se le agregó fluoruro de tetrabutilamonio (solución en tetrahidrofurano 1 mol/L, 1.54 mL, 1.54 mmol) a 0°C, seguido por agitación a temperatura ambiente durante 1 hora bajo una atmósfera de nitrógeno. Se le agregó agua (20 mL) y se extrajo con acetato de etilo (40 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente

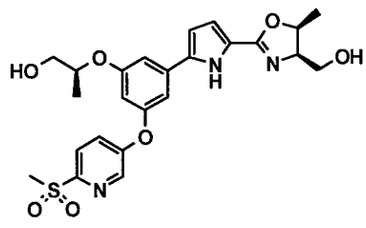
se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 80%-100%), para producir el compuesto deseado como un sólido blanco (578 mg, rendimiento de 84%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 1.39 (3H, d, J = 6.8 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 4.1, 10.4 Hz), 3.59 (1H, dd, J = 6.1, 10.4 Hz), 3.77 (1H, dd, J = 6.2, 11.2 Hz), 3.84 (1H, dd, J = 3.7, 11.8 Hz), 4.22-4.27 (1H, m), 4.54-4.61 (1H, m), 4.83-4.90 (1H, m), 6.45 (1H, d, J = 3.8 Hz), 6.55 (1H, t, J = 2.2 Hz), 6.68 (1H, d, J = 3.9 Hz), 6.90 (1H, t, 1.8 Hz), 7.07 (1H, t, 1.8 Hz), 7.43 (1H, dd, J = 2.8, 8.7 Hz), 8.04 (1H, d, J = 8.7 Hz), 8.49 (1H, d, J = 2.8 Hz).

MS (ESI) m/z: 516.17933 $(M+H)^+$.

EJEMPLO 92

(2S)-2-(3-{5-[(4R,5S)-4-(Hidroximetil)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol



El {(4R,5S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol (178 mg, 0.35 mmol) sintetizado en el ejemplo (91d) se disolvió

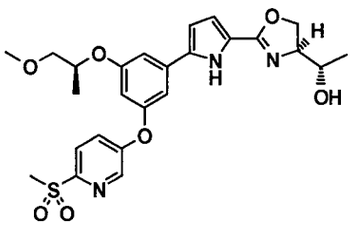
en cloruro de metileno (5 mL), y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 0.70 mL, 0.70 mmol) a -78°C, y subsiguientemente la temperatura se regresó a la temperatura ambiente y se agitó durante 45 minutos. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con cloruro de metileno. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-4%), para producir el compuesto deseado como un sólido blanco (142 mg, rendimiento de 82%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.30 (3H, d, J = 6.3 Hz), 1.43 (3H, d, J = 6.6 Hz), 3.23 (3H, s), 3.76-3.87 (4H, m), 4.22-4.27 (1H, m), 4.53-4.60 (1H, m), 4.92-4.84 (1H, m), 6.45 (1H, d, J = 3.9 Hz), 6.48 (1H, s), 6.69 (1H, d, J = 3.9 Hz), 6.87 (1H, t, J = 1.8 Hz), 7.02 (1H, s), 7.41 (1H, dd, J = 8.6, 2.7 Hz), 8.03 (1H, d, J = 8.6 Hz), 8.47 (1H, d, J = 2.7 Hz).

MS (ESI) m/z: 502.16583 $(M+H)^+$.

EJEMPLO 93

(1S)-1-{(4S)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol



(93a) N-[(1S,2S)-2-Hidroxi-1-(hidroximetil)propil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxamida

El ácido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxílico (1.20 g, 2.69 mmol) sintetizado en el ejemplo (78k), D-treoninol (0.34 g, 3.23 mmol), disponible comercialmente, HOBT·H_2O (0.40 g, 3.23 mmol) y N-metilmorfolina (0.59 mL, 5.38 mmol), se disolvieron en N,N-dimetilformamida (20 mL) y se les agregó WSCI·HCl (0.62 g, 3.23 mmol) a temperatura ambiente, seguido por agitación durante 20 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó salmuera saturada (30 mL) y se extrajo con acetato de etilo (60 mL). Después de lavar con ácido clorhídrico 1N, solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-7%), para producir el

compuesto deseado como un sólido blanco (1.24 g, 86%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.25 (3H, d, J = 6.3 Hz), 1.33 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 3.9, 10.3 Hz), 3.59 (1H, dd, J = 6.3, 10.4 Hz), 3.90-3.91 (2H, m), 3.98-4.03 (1H, brm), 4.23-4.29 (1H, m), 4.56-4.60 (1H, m), 6.50 (1H, t, J = 3.2 Hz), 6.58 (1H, t, J = 2.2 Hz), 6.66 (1H, brm), 6.69-6.70 (1H, m), 6.85 (1H, t, J = 1.7 Hz), 7.03 (1H, t, J = 1.7 Hz), 7.44 (1H, dd, J = 2.7, 8.7 Hz), 8.04 (1H, d, J = 8.7 Hz), 8.48 (1H, d, J = 2.7 Hz), 9.77 (1H, brs).

(93b) (1S)-1-{(4S)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol

La N-[(1S,2S)-2-hidroxi-1-(hidroximetil)propil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxamida (1.24 g, 2.32 mmol) sintetizada en el ejemplo (93a) se disolvió en tetrahidrofurano (20 mL), y se le agregó ácido metanosulfónico anhidro (0.63 g, 3.49 mmol) y trietilamina (0.97 mL, 6.97 mmol) a 0°C, seguido por agitación durante 1 hora bajo una atmósfera de nitrógeno. La temperatura se elevó naturalmente, y la solución se agitó a temperatura ambiente durante 2 horas, seguido por agitación a 50°C durante 2 horas. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (30 mL) y la solución se separó con acetato de etilo (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo

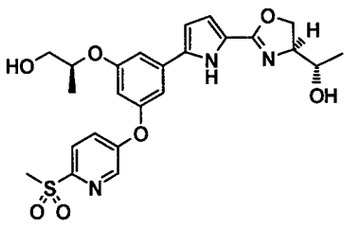
resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 60%-100%), para producir el compuesto deseado como un sólido blanco (800 mg, rendimiento de 67%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.24 (3H, d, J = 6.3 Hz), 1.33 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.40 (3H, s), 3.50 (1H, dd, J = 4.0, 10.3 Hz), 3.58 (1H, dd, J = 6.3, 10.3 Hz), 3.71 (1H, t, J = 6.2 Hz), 4.08-4.14 (2H, m), 4.41-4.44 (1H, m), 4.54-4.59 (1H, m), 6.50 (1H, d, J = 3.9 Hz), 6.56 (1H, t, J = 2.1 Hz), 6.74 (1H, d, J = 3.9 Hz), 6.86 (1H, t, 2.0 Hz), 7.05 (1H, t, 1.9 Hz), 7.42 (1H, dd, J = 2.7, 8.8 Hz), 8.03 (1H, d, J = 8.8 Hz), 8.47 (1H, d, J = 2.8 Hz).

MS (ESI) m/z: 516.17981 $(M+H)^+$.

EJEMPLO 94

(2S)-2-[3-(5-{(4S)-4-[(1S)-1-Hidroxietil]-4,5-dihidro-1,3-oxazol-2-il}-1H-pirrol-2-il)-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi]propan-1-ol



El (1S)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol (187 mg, 0.36 mmol) sintetizado en el ejemplo (93b) se disolvió en cloruro de metileno (5 mL) y subsiguientemente se enfrió a -78°C; se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 0.73 mL,

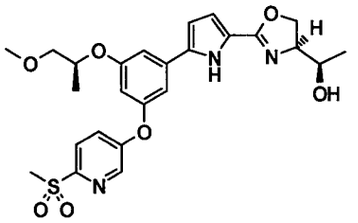
0.73 mmol) bajo una atmósfera de nitrógeno. La temperatura se elevó naturalmente, seguido por agitación a temperatura ambiente durante 30 minutos; subsiguientemente se le agregó una solución acuosa saturada de carbonato ácido de sodio para neutralizar la solución de reacción, seguido por extracción con cloruro de metileno (70 mL). La capa orgánica se lavó con una solución acuosa de hidróxido de sodio 1N y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-4%), para producir el compuesto deseado como un sólido blanco (134 mg, 74%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.28 (6H, d, J = 6.6 Hz), 3.22 (3H, s), 3.72-3.81 (3H, m), 4.13-4.19 (2H, m), 4.42-4.45 (1H, m), 4.59-4.65 (1H, m), 6.41 (1H, t, J = 2.2 Hz), 6.45 (1H, d, J = 3.9 Hz), 6.72 (1H, d, J = 3.9 Hz), 6.83 (1H, s), 6.99 (1H, s), 7.37 (1H, dd, J = 2.7, 8.8 Hz), 8.02 (1H, d, J = 8.8 Hz), 8.44 (1H, d, J = 2.7 Hz).

MS (ESI) m/z: 502.16521 $(M+H)^+$.

EJEMPLO 95

(1R)-1-{(4S)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol



(95a) N-[(1S,2R)-2-Hidroxi-1-(hidroximetil)propil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxamida

El ácido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxílico (1.47 g, 3.29 mmol) sintetizado en el ejemplo (78k), D-alo-treoninol (0.52 g, 4.94 mmol), disponible comercialmente, HOBT·H_2O (0.49 g, 3.62 mmol) y N-metilmorfolina (0.72 mL, 6.58 mmol), se disolvieron en N,N-dimetilformamida (10 mL), y se les agregó WSCI·HCl (0.76 g, 3.95 mmol) a temperatura ambiente, seguido por agitación durante 5.5 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó salmuera saturada (40 mL) y se extrajo con acetato de etilo (70 mL). Después de lavar con salmuera saturada, se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-6%), para producir el compuesto deseado como un sólido blanco (1.42 g, 81%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.31 (3H, d, J = 6.2 Hz), 1.32 (3H, d, J = 6.6 Hz), 2.84-2.86 (1H, m), 2.89 (1H, d, J = 6.2 Hz), 3.23 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 3.9, 10.3 Hz), 3.59 (1H, dd, J = 6.3, 10.3 Hz), 3.80-3.84 (1H, brm), 3.92-3.96 (1H, m), 4.07-4.11 (2H, brm), 4.54-4.59 (1H, m), 6.49 (1H, dd, J = 2.9, 3.9 Hz), 6.57 (1H, t, J = 2.2 Hz), 6.67 (1H, dd, J = 2.3, 3.9 Hz), 6.80 (1H, d, J = 8.0 Hz), 6.86 (1H, t, J = 1.8 Hz), 7.01 (1H, t, J = 1.8 Hz), 7.43 (1H, dd, J = 2.8, 8.7 Hz), 8.03 (1H, d, J = 8.7 Hz), 8.47 (1H, d, J = 2.8 Hz), 9.94 (1H, brs).

(95b) (1R)-1-{(4S)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol

La N-[(1S,2R)-2-hidroxi-1-(hidroximetil)propil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-carboxamida (1.42 g, 2.66 mmol) sintetizada en el ejemplo (95a) se disolvió en tetrahidrofurano (25 mL), y se le agregó ácido metanosulfónico anhidro (0.72 g, 3.99 mmol) y trietilamina (1.11 mL, 7.98 mmol) a 0°C, seguido por agitación durante 1 hora bajo una atmósfera de nitrógeno. La temperatura se elevó naturalmente, y la solución se agitó a temperatura ambiente durante 1 hora, seguido por agitación a 50°C durante 2 horas. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (30 mL) y la solución se separó con acetato de etilo (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo

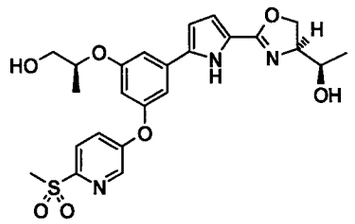
resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-100%), para producir el compuesto deseado como un sólido blanco (758 mg, rendimiento de 55%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.15 (3H, d, J = 6.3 Hz), 1.35 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.51 (1H, dd, J = 4.0, 10.4 Hz), 3.59 (1H, dd, J = 6.2, 10.4 Hz), 4.20-4.27 (4H, m), 4.56-4.62 (1H, m), 6.36 (1H, d, J = 3.8 Hz), 6.41 (1H, d, J = 3.8 Hz), 6.57 (1H, t, J = 2.1 Hz), 6.90 (1H, t, 1.8 Hz), 7.07 (1H, t, 1.8 Hz), 7.45 (1H, dd, J = 2.8, 8.7 Hz), 8.05 (1H, d, J = 8.7 Hz), 8.50 (1H, d, J = 2.8 Hz).

MS (ESI) m/z: 516.17893 $(M+H)^+$.

EJEMPLO 96

(2S)-2-[3-(5-{(4S)-4-[(1R)-1-Hidroxietil]-4,5-dihidro-1,3-oxazol-2-il}-1H-pirrol-2-il)-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi]propan-1-ol



El (1R)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol (178 mg, 0.35 mmol) sintetizado en el ejemplo (95b) se disolvió en cloruro de metileno (5 mL), y subsiguientemente se enfrió a -78°C y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 0.69 mL,

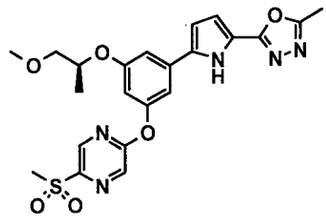
0.69 mmol) bajo una atmósfera de nitrógeno. La temperatura se elevó naturalmente, seguido por agitación a temperatura ambiente durante 30 minutos; subsiguientemente se le agregó una solución acuosa saturada de carbonato ácido de sodio para neutralizar la solución de reacción, seguido por extracción con cloruro de metileno (70 mL). La capa orgánica se lavó con una solución acuosa de hidróxido de sodio 1N y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-4%), para producir el compuesto deseado como un sólido blanco (132 mg, 76%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.19 (3H, d, 6.3 Hz), 1.31 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.73-3.81 (2H, m), 4.17-4.25 (2H, m), 4.32 (1H, s), 4.34 (1H, d, J = 1.5 Hz), 4.57-4.61 (1H, m), 6.39 (1H, d, J = 3.9 Hz), 6.49 (1H, d, J = 2.1 Hz), 6.54 (1H, d, J = 3.9 Hz), 6.87 (1H, t, J = 1.8 Hz), 7.02 (1H, t, J = 1.8 Hz), 7.42 (1H, dd, J = 2.8, 8.6 Hz), 8.04 (1H, d, J = 8.6 Hz), 8.47 (1H, d, J = 2.8 Hz).

MS (ESI) m/z: 502.16427 $(M+H)^+$.

EJEMPLO 97

2-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]fenoxi}-5-(metilsulfonil)pirazina



(97a) 5-(Metilsulfanil)pirazin-2-amina

Se disolvió 2-aminopirazina (50.8 g, 0.53 mol) en cloruro de metileno (1.0 L) y se le agregó N-bromosuccinimida (97.9 g, 0.55 mol) a 0°C durante 30 minutos, seguido por agitación a 0°C durante 2.5 horas, bajo una atmósfera de nitrógeno. La solución de reacción se llevó de vuelta a la temperatura ambiente y el depósito se filtró. El depósito que se filtró se lavó con acetato de etilo. El licor madre se recogió y el disolvente se removió por destilación bajo presión reducida. Esta operación se repitió dos veces para producir un licor madre, del cual se removió el disolvente por destilación bajo presión reducida para producir un compuesto como un sólido amarillo.

Este se disolvió en N,N-dimetilformamida (300 mL) y se le agregó tiometóxido de sodio (75.0 g, 1.07 mol), seguido por agitación a 100°C durante 3 horas bajo una atmósfera de nitrógeno. La solución de reacción se llevó a temperatura ambiente y se le agregó agua (1.5L), seguido por extracción con acetato de etilo (1.0 L). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El

disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 20%-30%), para producir el compuesto deseado como un sólido anaranjado (42.5 g, rendimiento de 56%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.52 (3H, s), 4.41 (2H, br s), 7.92 (1H, d, J = 1.6 Hz), 7.98 (1H, d, J = 1.6 Hz).

(97b) 2-Cloro-5-(metilsulfanil)pirazina

Se disolvió nitrito de sodio (50.9 g, 0.74 mol) en agua (150 mL), seguido por su adición a gotas a una solución acuosa de ácido clorhídrico 5N (1.0 L) a 0°C durante 1 hora. Subsiguientemente se le agregó la 5-(metilsulfanil)pirazin-2-amina (40.4 g, 0.28 mol) sintetizada en el ejemplo (97a) a 0°C durante 40 minutos, y se agitó a 0°C durante 1 hora. La solución de reacción se llevó de vuelta a la temperatura ambiente y se le agregó agua (500 mL), seguido por extracción con acetato de etilo (1.0 L). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-20%), para producir el compuesto deseado como un sólido blanco (11.9 g, rendimiento de 26%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.57 (3H, s), 8.24 (1H, d, J = 1.2 Hz), 8.39 (1H, d, J = 1.2 Hz).

(97c) 2-Cloro-5-(metilsulfonil)pirazina

La 2-cloro-5-(metilsulfanil)pirazina (10.82 g, 67.4 mmol) sintetizada en el ejemplo (97b) se disolvió en cloruro de metileno (200 mL), y se le agregó lentamente ácido m-cloroperbenzoico (aproximadamente 65%, 37.4 g, aproximadamente 140 mmol) a 0°C, seguido por agitación a 0°C durante 1.5 horas bajo una atmósfera de nitrógeno. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (300 mL) y se extrajo con cloruro de metileno (400 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-50%), para producir el compuesto deseado como un sólido blanco (10.1 g, rendimiento de 78%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 3.27 (3H, s), 8.70 (1H, d, J = 1.2 Hz), 9.09 (1H, d, J = 1.2 Hz).

(97d) 5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-carboxilato de bencilo

El 5-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-1,2-dicarboxilato de 2-bencilo-1-t-butilo (3.40 g, 7.06 mmol) sintetizado en el ejemplo (78g), y la 2-cloro-5-(metilsulfonil)pirazina (1.92 g, 7.06 mmol) sintetizada en el ejemplo (97c), se disolvieron en acetonitrilo (35 mL), y se les agregó carbonato de potasio (2.93 g, 21.2 mmol), seguido por calentamiento a reflujo durante 11 horas bajo una atmósfera de nitrógeno. La solución de

reacción se enfrió a temperatura ambiente y se le agregó agua (100 mL), seguido por extracción dos veces con acetato de etilo (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-50%).

El sólido pardo resultante (3.85g) se disolvió en cloruro de metileno (5 mL) y se le agregó ácido trifluoroacético (5 mL), seguido por agitación a temperatura ambiente durante 1 hora. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio (50 mL) y se extrajo dos veces con acetato de etilo (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-60%), para producir el compuesto deseado como un sólido blanco (3.58 g, rendimiento de 88%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.35 (3H, d, J = 6.3 Hz), 3.24 (3H, s), 3.42 (3H, s), 3.52 (1H, dd, J = 10.3, 3.9 Hz), 3.60 (1H, dd, J = 10.3, 5.9 Hz), 4.57-4.61 (1H, m), 5.34 (2H, s), 6.53 (1H, dd, J = 3.9, 2.9 Hz), 6.70 (1H, t, J = 2.2 Hz), 6.93 (1H, t, J = 1.5 Hz), 6.99 (1H, dd, J = 3.9, 2.4 Hz), 7.06 (1H, t, J = 1.7 Hz), 7.34-7.45 (5H, m), 8.50 (1H, d, J = 1.5 Hz), 8.81 (1H, d, J = 1.5 Hz),

9.18 (1H, s).

(97e) Acido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-carboxílico

El 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-carboxilato de bencilo (3.58 g, 6.66 mmol) sintetizado en el ejemplo (97d) se disolvió en metanol (100 mL), y se le agregó un catalizador de paladio al 10% en carbón (2.00 g), seguido por agitación a temperatura ambiente durante 3 horas bajo una atmósfera de hidrógeno. El catalizador de paladio en carbón se removió por filtración en Celite, seguido por lavado con tetrahidrofurano. El disolvente se removió por destilación bajo presión reducida para producir el compuesto deseado como un sólido blanco (2.56 g, 86%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 3.22 (3H, s), 3.45 (3H, s), 3.55 (1H, dd, J = 10.2, 3.9 Hz), 3.66 (1H, dd, J = 9.4, 5.9 Hz), 4.72 (1H, s), 6.49 (1H, s), 6.66 (1H, s), 6.99 (2H, s), 7.29 (1H, s), 8.47 (1H, s), 8.79 (1H, s), 10.23 (1H, br s).

(97f) 2-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]fenoxi}-5-(metilsulfonil)pirazina

El ácido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-carboxílico (700 mg, 1.56 mmol) sintetizado en el ejemplo (97e) y 4-dimetilaminopiridina (172 mg, 1.41 mmol), se disolvieron en cloruro de metileno (15 mL), y se les agregó WSCI·HCl (689 mg, 3.60 mmol) y acetohidrazida (255 mg, 3.44 mmol) a temperatura ambiente, seguido

por agitación durante 14 horas bajo una atmósfera de nitrógeno. La solución de reacción se diluyó con cloruro de metileno (50 mL) y se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, seguido por secado sobre sulfato de magnesio anhidro; subsiguientemente el disolvente se removió por destilación bajo presión reducida.

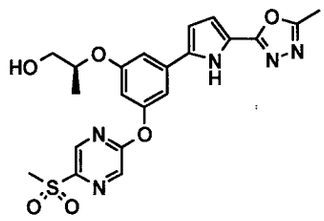
El sólido amarillo resultante (788 mg) se disolvió en cloruro de metileno (10 mL) y se le agregó cloruro de p-toluenosulfonilo (597 mg, 3.13 mmol) y trietilamina (0.87 mL, 6.26 mmol), seguido por agitación a temperatura ambiente durante 6 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio (30 mL) y se extrajo dos veces con cloruro de metileno (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido amarillo pálido (456 mg, rendimiento de 60%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.36 (3H, d, J = 6.3 Hz), 2.59 (3H, s), 3.24 (3H, s), 3.42 (3H, s), 3.53 (1H, dd, J = 10.4, 4.1 Hz), 3.61 (1H, dd, J = 10.2, 5.9 Hz), 4.56-4.63 (1H, m), 6.59 (1H, t, J = 3.1 Hz), 6.69 (1H, t, J = 2.0 Hz), 6.86 (1H, dd, J = 3.7, 2.5 Hz), 6.95 (1H, t, J = 1.6 Hz), 7.08 (1H, t, J = 1.8 Hz), 8.51 (1H, d, J = 1.2 Hz), 8.81 (1H, d, J = 1.2 Hz), 9.43 (1H, s).

MS (ESI) m/z: 486.14274 $(M+H)^+$.

EJEMPLO 98

(2S)-2-(3-[5-(5-Metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenoxi)propan-1-ol



La 2-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[5-(5-metil-1,3,4-oxadiazol-2-il)-1H-pirrol-2-il]fenoxi}-5-(metilsulfonil)pirazina (382 mg, 0.79 mmol) sintetizada en el ejemplo (97f) se disolvió en cloruro de metileno (10 mL), y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 1.58 mL, 1.58 mmol) a -78°C y bajo una atmósfera de nitrógeno. Subsiguientemente la temperatura se regresó a la temperatura ambiente, seguido por agitación durante 1.5 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido blanco (219 mg, rendimiento de 59%).

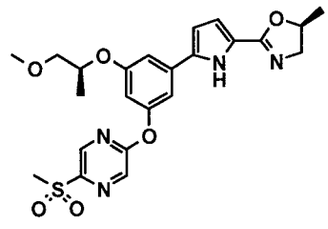
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 2.59 (3H, s), 2.70 (1H, br s), 3.25 (3H, s), 3.79-3.82 (2H, m), 4.54-4.61 (1H, m), 6.57

(1H, t, J = 3.1 Hz), 6.63 (1H, t, J = 2.0 Hz), 6.86 (1H, dd, J = 3.7, 2.5 Hz), 6.96 (1H, t, J = 1.8 Hz), 7.07 (1H, t, J = 1.8 Hz), 8.50 (1H, d, J = 1.6 Hz), 8.80 (1H, d, J = 1.2 Hz), 9.84 (1H, br s).

MS (ESI) m/z: 472.12965 $(M+H)^+$.

EJEMPLO 99

2-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-5-(metilsulfonil)pirazina



El ácido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-carboxílico (700 mg, 1.56 mmol) sintetizado en el ejemplo (97e), y 4-dimetilaminopiridina (96 mg, 0.78 mmol), se disolvieron en cloruro de metileno (20 mL) y se les agregó WSCI·HCl (480 mg, 2.50 mmol) y (R)-1-amino-2-propanol (283 μL, 3.60 mmol) a temperatura ambiente, seguido por agitación durante 14 horas bajo una atmósfera de nitrógeno. La solución de reacción se diluyó con cloruro de metileno (60 mL), se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente

de elución: metanol/cloruro de metileno = 0%-8%).

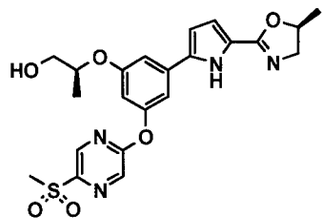
El sólido blanco resultante (546 mg) se disolvió en tetrahidrofurano (15 mL) y se le agregó ácido metanosulfónico anhidro (377 mg, 2.16 mmol) y trietilamina (0.45 mL, 3.25 mmol), seguido por agitación a 50°C durante 4 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio (30 mL) y se extrajo dos veces con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido amarillo pálido (509 mg, rendimiento de 67%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 1.42 (3H, d, J = 6.3 Hz), 3.24 (3H, s), 3.42 (3H, s), 3.49-3.62 (3H, m), 4.07 (1H, dd, J = 13.5, 8.8 Hz), 4.53-4.61 (1H, m), 4.79-4.87 (1H, m), 6.51 (1H, d, J = 3.9 Hz), 6.65 (1H, t, J = 2.0 Hz), 6.75 (1H, d, J = 3.9 Hz), 6.91 (1H, t, J = 1.6 Hz), 7.06 (1H, t, J = 1.8 Hz), 8.49 (1H, s), 8.81 (1H, s).

MS (ESI) m/z: 487.16506 $(M+H)^+$.

EJEMPLO 100

(2S)-2-(3-{5-[(5S)-5-Metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol



La 2-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-5-(metilsulfonil)pirazina (426 mg, 0.88 mmol) sintetizada en el ejemplo 99 se disolvió en cloruro de metileno (10 mL), y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 1.76 mL, 1.76 mmol) a -78°C y bajo una atmósfera de nitrógeno. Subsiguientemente, la temperatura se regresó a la temperatura ambiente, seguido por agitación durante 1.5 horas. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con cloruro de metileno. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido blanco (243 mg, rendimiento de 59%).

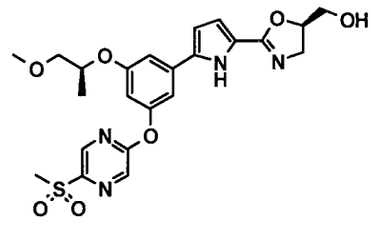
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J = 6.3 Hz), 1.44 (3H, d, J = 6.3 Hz), 3.25 (3H, s), 3.56 (1H, dd, J = 13.9, 7.2 Hz), 3.80 (2H, d, J = 5.5

Hz), 4.10 (1H, dd, J = 14.1, 9.4 Hz), 4.61 (1H, q, J = 5.6 Hz), 4.86 (1H, dt, J = 11.6, 4.5 Hz), 6.47 (1H, d, J = 3.5 Hz), 6.50 (1H, s), 6.75 (1H, d, J = 3.5 Hz), 6.89 (1H, s), 6.99 (1H, s), 8.47 (1H, d, J = 1.2 Hz), 8.80 (1H, d, J = 1.2 Hz).

MS (ESI) m/z: 473.14774 $(M+H)^+$.

EJEMPLO 101

{(5R)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol



(101a) N-[(2S)-2,3-Dihidroxipropil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-carboxamida

El ácido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-carboxílico (1.07 g, 2.39 mmol) sintetizado en el ejemplo (97e) se disolvió en cloruro de metileno (20 mL), y se le agregó WSCI·HCl (732 mg, 3.82 mmol), (S)-(-)-3-amino-1,2-propanodiol (500 mg, 5.49 mmol) y 4-dimetilaminopiridina (146 mg, 1.19 mmol) a temperatura ambiente, seguido por agitación durante 25 horas bajo una atmósfera de nitrógeno. La solución de reacción se diluyó con acetato de etilo (50 mL), se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio

anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el producto deseado como un sólido blanco (666 mg, 54%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.35 (4H, d, J = 6.1 Hz), 3.24 (4H, s), 3.42 (3H, s), 3.53 (1H, dd, J = 10.3, 3.9 Hz), 3.59-3.63 (5H, m), 3.84-3.87 (1H, m), 4.58 (1H, dt, J = 11.7, 5.2 Hz), 6.41 (1H, s), 6.50 (1H, t, J = 3.2 Hz), 6.64 (1H, dd, J = 3.7, 2.7 Hz), 6.68 (1H, d, J = 2.0 Hz), 6.95 (1H, s), 7.08 (1H, s), 8.50 (1H, s), 8.81 (1H, s), 9.79 (1H, s).

(101b) N-{(2S)-2-Hidroxi-3-[(triisopropilsilil)oxi]propil}-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-carboxamida

La N-[(2S)-2,3-dihidroxipropil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-carboxamida (666 mg, 1.28 mmol) sintetizada en el ejemplo (101a) se disolvió en cloruro de metileno (20 mL), y se le agregó trietilamina (0.89 mL, 6.40 mmol), cloruro de triisopropilsililo (410 μL, 1.92 mmol) y 4-dimetilaminopiridina (234 mg, 1.92 mmol), seguido por agitación durante 14 horas bajo una atmósfera de nitrógeno. La solución de reacción se diluyó con cloruro de metileno (50 mL), se lavó con agua y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano =

10%-60%), para producir el producto deseado como un sólido blanco (558 mg, 64%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.06-1.15 (21H, m), 1.35 (3H, d, J = 6.3 Hz), 3.13 (1H, d, J = 3.9 Hz), 3.24 (3H, s), 3.42 (3H, s), 3.52 (1H, dd, J = 10.3, 3.9 Hz), 3.60 (1H, dd, J = 10.3, 6.8 Hz), 3.68 (1H, dd, J = 10.0, 6.1 Hz), 3.73 (1H, td, J = 7.0, 3.1 Hz), 3.77 (1H, dd, J = 10.0, 4.6 Hz), 3.87 (1H, s), 4.58 (1H, dd, J = 10.3, 6.3 Hz), 6.33 (1H, t, J = 5.6 Hz), 6.50 (1H, t, J = 3.2 Hz), 6.60 (1H, t, J = 3.2 Hz), 6.67 (1H, s), 6.92 (1H, s), 7.06 (1H, s), 8.50 (1H, d, J = 1.0 Hz), 8.81 (1H, d, J = 1.0 Hz), 9.44 (1H, s).

(101c) 2-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5R)-5-{[(triisopropilsilil)oxi]metil}-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-5-(metilsulfonil)pirazina

La N-{(2S)-2-hidroxi-3-[(triisopropilsilil)oxi]propil}-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-carboxamida (558 mg, 0.82 mmol) sintetizada en el ejemplo (101b) se disolvió en tetrahidrofurano (20 mL), y se le agregó ácido metanosulfónico anhidro (287 mg, 1.65 mmol) y trietilamina (0.34 mL, 2.47 mmol), seguido por agitación a 50°C durante 6 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó agua (40 mL) y se extrajo dos veces con cloruro de metileno (40 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente

de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido blanco (496 mg, rendimiento de 94%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.00-1.13 (21H, m), 1.34 (3H, d, J = 6.3 Hz), 3.24 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 10.6, 3.9 Hz), 3.60 (1H, dd, J = 10.4, 6.1 Hz), 3.83-4.04 (4H, m), 4.57 (1H, td, J = 6.3, 4.3 Hz), 4.72-4.79 (1H, m), 6.50 (1H, d, J = 3.9 Hz), 6.65 (1H, t, J = 2.0 Hz), 6.73 (1H, d, J = 3.9 Hz), 6.90 (1H, t, J = 1.8 Hz), 7.05 (1H, t, J = 1.8 Hz), 8.49 (1H, d, J = 1.2 Hz), 8.81 (1H, d, J = 1.2 Hz).

(101d) {(5R)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}-metanol

La 2-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5R)-5-{[(triisopropilsilil)-oxi]metil}-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-5-(metilsulfonil)-pirazina (496 mg, 0.82 mmol) sintetizada en el ejemplo (101c) se disolvió en tetrahidrofurano (20 mL), y se le agregó fluoruro de tetrabutilamonio (solución en tetrahidrofurano 1.0 mol/L, 0.82 mL, 0.82 mmol), seguido por agitación durante 2 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó agua (40 mL) y se extrajo dos veces con acetato de etilo (40 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido blanco (133 mg,

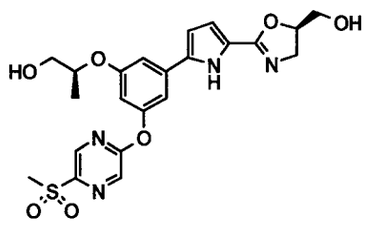
rendimiento de 35%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 3.24 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 10.4, 4.1 Hz), 3.60 (1H, dd, J = 10.2, 5.9 Hz), 3.71 (1H, dd, J = 12.5, 5.5 Hz), 3.79 (1H, dd, J = 14.3, 7.6 Hz), 3.88 (1H, dd, J = 12.5, 3.1 Hz), 4.04 (1H, dd, J = 14.3, 10.0 Hz), 4.57 (1H, dd, J = 10.0, 5.7 Hz), 4.85-4.78 (1H, m), 6.50 (1H, d, J = 3.9 Hz), 6.66 (1H, t, J = 2.2 Hz), 6.77 (1H, d, J = 3.9 Hz), 6.93 (1H, s), 7.06 (1H, s), 8.49 (1H, d, J = 1.2 Hz), 8.81 (1H, d, J = 1.6 Hz).

MS (ESI) m/z: 503.15918 $(M+H)^+$.

EJEMPLO 102

(2S)-2-(3-{5-[(5R)-5-(Hidroximetil)-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol



El {(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol (105 mg, 0.21 mmol) sintetizado en el ejemplo (101d) se disolvió en cloruro de metileno (10 mL), y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 315 μL, 0.315 mmol) a -78°C y bajo una atmósfera de nitrógeno; subsiguientemente la temperatura se regresó a la temperatura ambiente,

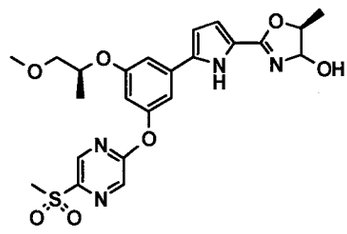
seguido por agitación durante 1 hora. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con cloruro de metileno. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-7.5%), para producir el compuesto deseado como un sólido blanco (67 mg, rendimiento de 66%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.29 (3H, d, J = 6.3 Hz), 3.24 (3H, s), 3.70-3.91 (5H, m), 4.03 (1H, dd, J = 14.1, 9.8 Hz), 4.55 (1H, dd, J = 10.6, 5.9 Hz), 4.85-4.78 (1H, m), 6.47 (1H, d, J = 3.9 Hz), 6.58 (1H, t, J = 2.0 Hz), 6.75 (1H, d, J = 3.5 Hz), 6.92 (1H, t, J = 1.8 Hz), 7.01 (1H, t, J = 1.6 Hz), 8.48 (1H, d, J = 1.2 Hz), 8.80 (1H, d, J = 1.2 Hz).

MS (ESI) m/z: 489.14448 $(M+H)^+$.

EJEMPLO 103

(5S)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)pirazin-2-il]-oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-ol



(103a) L-Treoninato de bencilo

Se disolvió L-treonina 21.2g (178 mmol) en tolueno (100 mL) y se le agregó alcohol bencílico (100 mL, 966 mmol) y ácido p-toluenosulfónico monohidrato (35.0 g, 194 mmol), seguido por calentamiento a reflujo durante 17 horas bajo una atmósfera de nitrógeno. Después de enfriar a temperatura ambiente se le agregó agua (200 mL), seguido por lavado tres veces con acetato de etilo (100 mL). A la capa acuosa se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo tres veces con acetato de etilo (100 mL). Después de que la capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-15%), para producir el producto deseado como un sólido blanco (10.6 g, rendimiento de 28%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.22 (3H, d, J = 6.3 Hz), 3.30 (1H, d, J = 6.3 Hz), 3.49 (1H, brs), 5.19 (2H, s), 7.34-7.39 (5H, m).

(103b) N-{[5-(3-[(1S)-2-Metoxi-1-metoxietoxi]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]carbonil}-L-treoninato de bencilo

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-[5-(metilsulfonil)-pirazin-2-il]oxi)fenil}-1H-pirrol-2-carboxílico (9.49 g, 21.2 mmol) sintetizado en el ejemplo (97e) se disolvió en N,N-dimetilformamida (200 mL), y se le agregó L-treoninato de bencilo (4.44 g, 21.2 mmol) sintetizado en el ejemplo (103a), WSCI·HCl (4.88 g, 25.5 mmol), HOBT·H_2O (3.15 g, 23.3 mmol) y N-metilmorfolina (4.66 mL, 42.4 mmol), seguido por agitación a temperatura ambiente durante 1.5 horas bajo una atmósfera de nitrógeno. Se le agregó agua (200 mL) y se extrajo dos veces con acetato de etilo (200 ml). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 70%-100%), para producir el producto deseado como un aceite amarillo pálido (13.5 g, rendimiento de ~100%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.27 (3H, d, J = 6.3 Hz), 1.35 (3H, d, J = 6.3 Hz), 3.24 (3H, s), 3.42 (3H, s), 3.52 (1H, dd, J = 4.3, 10.2 Hz), 3.61 (1H, dd, J = 5.9, 10.2 Hz), 4.44 (1H, m), 4.59 (1H, m), 4.81 (1H, dd, J = 2.7, 8.6 Hz), 5.21 (1H, d, J = 12.5 Hz), 5.25 (1H, d, J = 12.5 Hz), 6.52 (1H, t, J = 3.9 Hz), 6.67 (1H, t, J = 2.0 Hz), 6.71 (1H, brd, J = 8.6 Hz), 6.75 (1H, dd, J = 2.4, 3.9 Hz), 6.94 (1H, t, J = 1.9 Hz), 7.08 (1H, t, J = 1.9 Hz), 7.33-7.38 (5H, m), 8.49 (2H, m), 8.81 (2H, m), 9.63 (1H, brs).

(103c) (4S,5S)-2-[5-(3-[(1S)-2-Metoxi-1-metoxietoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-carboxilato de bencilo

El N-{[5-(3-[(1S)-2-metoxi-1-metoxietoxi]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]carbonil}-L-treoninato de bencilo (13.5 g, 21.2 mmol) sintetizado en el ejemplo (103b) se disolvió en cloruro de metileno (150 mL) y se enfrió a -78°C. Se le agregó a gotas trifluoruro de bis(2-metoxietil)aminoazufre (5.47 mL, 29.7 mmol) y se agitó a -78°C durante 40 minutos. Se le agregó carbonato de potasio (5.86 g, 42.4 mmol) y se agitó durante 1.5 horas, aumentando la temperatura gradualmente a la temperatura ambiente. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (100 mL) a 0°C y se extrajo dos veces con cloruro de metileno (100 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 40%-70%), para producir el producto deseado como un sólido blanco (9.68 g, rendimiento de 74%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.29 (3H, d, J = 6.3 Hz), 1.35 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.51 (1H, dd, J = 3.9, 10.2 Hz), 3.60 (1H, dd, J = 5.9, 10.2 Hz), 4.58 (1H, m), 4.94 (1H, d, J = 9.8 Hz), 5.02 (1H, m), 5.19 (1H, d, J = 12.1 Hz), 5.24 (1H, d, J = 12.1 Hz), 6.51 (1H, t, J = 3.9 Hz), 6.66 (1H, t, J = 2.4 Hz), 6.78 (1H, t, J = 3.9 Hz), 6.94 (1H, t, J = 2.0 Hz), 7.08

(1H, t, J = 2.4 Hz), 7.35-7.39 (5H, m), 8.48 (2H, d, J = 1.2 Hz), 8.81 (2H, d, J = 1.2 Hz).

(103d) (5S)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-ol

El (4S,5S)-2-[5-(3-[(1S)-2-metoxi-1-metoxietoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-carboxilato de bencilo (1.53 g, 2.47 mmol) sintetizado en el ejemplo (103c) se disolvió en tetrahidrofurano (50 mL), y se le agregó un catalizador de paladio al 10% en carbón (600 mg), seguido por agitación a temperatura ambiente durante 2.5 horas bajo una atmósfera de hidrógeno. El catalizador de paladio en carbón se removió por filtración en Celite, seguido por lavado con acetato de etilo. El disolvente se removió por destilación bajo presión reducida.

El residuo resultante se disolvió en acetonitrilo (60 mL) y se le agregó una solución de diamonio nitrato de cerio (IV) (2.03 g, 3.70 mmol) en agua (30 mL), gota a gota a 0°C. Después de agitar a temperatura ambiente durante 17 horas bajo una atmósfera de nitrógeno, se le agregó una solución acuosa saturada de carbonato ácido de sodio (30 mL) y se extrajo dos veces con acetato de etilo (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente

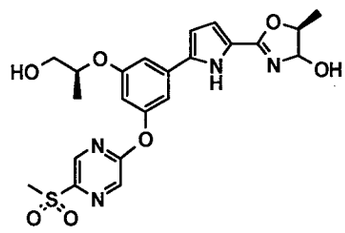
de elución: acetato de etilo/hexano = 70%-100%), para producir el producto deseado como un sólido blanco (645 mg, rendimiento de 52%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 1.37 (6/3H, d, J = 6.7 Hz), 1.47 (3/3H, d, J = 6.7 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 4.3, 10.2 Hz), 3.60 (1H, dd, J = 5.9, 10.2 Hz), 4.50-4.66 (2H, m), 5.39 (2/3H, d, J = 3.1 Hz), 5.66 (1/3H, d, J = 6.7 Hz), 6.50 (1H, brd, J = 3.9 Hz), 6.65 (1H, t, J = 2.4 Hz), 6.82 (1H, brd, J = 3.9 Hz), 6.94 (1H, t, J = 2.0 Hz), 7.08 (1H, t, J = 2.0 Hz), 8.48 (2H, d, J = 1.2 Hz), 8.80 (2H, d, J = 1.2 Hz).

MS (ESI) m/z: 503.16004 $(M+H)^+$.

EJEMPLO 104

(5S)-2-[5-(3-[(1S)-2-Hidroxi-1-metiletoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-ol



El (5S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-ol (410 mg, 0.816 mmol) sintetizado en el ejemplo (103d) se disolvió en cloruro de metileno (20 mL) y se enfrió a -78°C. Se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 2.04 mL, 2.04 mmol) y se agitó durante 2 horas, aumentando la temperatura gradualmente a la temperatura

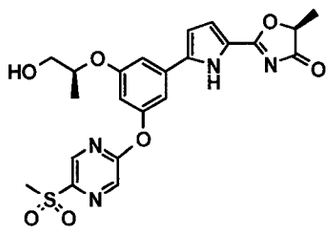
ambiente. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (20 mL) y se extrajo dos veces con cloruro de metileno (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 2%-10%), para producir el producto deseado como un sólido blanco (362 mg, rendimiento de 91%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.30 (3H, d, J = 6.3 Hz), 1.38 (6/3H, d, J = 6.7 Hz), 1.49 (3/3H, d, J = 6.7 Hz), 3.23 (3H, s), 3.76 (2H, brd, J = 5.5 Hz), 4.51-4.57 (2H, m), 5.39 (2/3H, d, J = 3.5 Hz), 5.66 (1/3H, d, J = 6.7 Hz), 6.49 (1H, d, J = 3.9 Hz), 6.61 (1H, t, J = 2.4 Hz), 6.81 (1H, d, J = 3.9 Hz), 6.94 (1H, t, J = 2.0 Hz), 7.06 (1H, t, J = 2.0 Hz), 8.47 (2H, d, J = 1.2 Hz), 8.78 (2H, d, J = 1.2 Hz).

MS (ESI) m/z: 489.14439 $(M+H)^+$.

EJEMPLO 105

(5S)-2-[5-(3-[(1S)-2-Hidroxi-1-metiletoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4(5H)-ona



(105a) (5S)-2-[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4(5H)-ona

El (5S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-ol (80.0 mg, 0.159 mmol) sintetizado en el ejemplo (103d) se disolvió en cloruro de metileno (10 mL), y se les agregó dicromato de piridinio (240 mg, 0.638 mmol) y tamices moleculares de 4A (200mg), seguido por agitación a temperatura ambiente durante 2 horas bajo una atmósfera de nitrógeno. Después de filtración en Celite, el disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-70%), para producir el producto deseado como un sólido blanco (44.1 mg, rendimiento de 55%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.36 (3H, d, J = 6.3 Hz), 1.62 (3H, d, J = 7.0 Hz), 3.25 (3H, s), 3.42 (3H, s), 3.52 (1H, dd, J = 3.9, 10.2 Hz), 3.62

(1H, dd, J = 5.9, 10.2 Hz), 4.62 (1H, m), 4.81 (1H, q, J = 7.0 Hz), 6.68 (1H, d, J = 3.9 Hz), 6.76 (1H, t, J = 2.4 Hz), 7.03 (1H, t, J = 2.0 Hz), 7.17 (1H, t, J = 2.0 Hz), 7.26 (1H, d, J = 3.9 Hz), 8.52 (2H, d, J = 1.2 Hz), 8.82 (2H, d, J = 1.2 Hz).

(105b) (5S)-2-[5-(3-[(1S)-2-Hidroxi-1-metiletoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4(5H)-ona

La (5S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4(5H)-ona (100 mg, 0.200 mmol) sintetizada en el ejemplo (105a) se disolvió en cloruro de metileno (10 mL) y se enfrió a -78°C. Se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 0.260 mL, 0.260 mmol) y se agitó durante 2 horas, aumentando la temperatura gradualmente a la temperatura ambiente. Se le agregó una solución acuosa saturada de carbonato ácido de sodio (10 mL) y se extrajo dos veces con cloruro de metileno (10 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-10%), para producir el producto deseado como un sólido blanco (98.0 mg, rendimiento de ~100%).

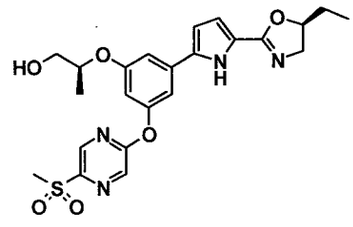
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 1.63 (3H, dd, J = 2.7, 7.0 Hz), 3.26 (3H, s), 3.80-3.84 (2H, m), 4.62 (1H, m), 4.84 (1H, q, J = 7.0 Hz), 6.66 (1H, d, J = 3.9 Hz), 6.69 (1H, m), 7.03 (1H, m), 7.20 (1H, m),

7.26 (1H, brd, J = 3.9 Hz), 8.51 (2H, d, J = 1.2 Hz), 8.81 (2H, d, J = 1.2 Hz).

MS (ESI) m/z: 487.12874 $(M+H)^+$.

EJEMPLO 106

(2S)-2-(3-{5-[(5S)-5-Etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol



(106a) 5-{3-Hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-carboxilato de bencilo

El 3-[(1S)-2-metoxi-1-metiletoxi]-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenol (26.79 g, 86.9 mmol) sintetizado en el ejemplo (78d), y el 5-bromo-1H-pirrol-1,2-dicarboxilato de 2-bencilo-1-t-butilo (32.32 g, 85.0 mmol) sintetizado en el ejemplo (78f), se disolvieron en 1,4-dioxano (360 mL) + agua (90 mL), y se les agregó complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio (II)-diclorometano (2.34 g, 2.87 mmol) y carbonato de potasio (30.40 g, 220 mmol), seguido por agitación a 60°C durante 3 horas bajo una atmósfera de nitrógeno. Después de que la solución de reacción se enfrió a temperatura ambiente, se le agregó agua (1000 mL) y se extrajo con acetato de etilo (700 mL). La capa orgánica se lavó con salmuera saturada; subsiguientemente se secó sobre sulfato de sodio anhidro

y el disolvente se removió por destilación bajo presión reducida.

El residuo resultante se disolvió en cloruro de metileno (100 mL) y se le agregó ácido trifluoroacético (120 mL), seguido por agitación a temperatura ambiente durante 1 hora. Después de que la solución de reacción se concentró bajo presión reducida, se diluyó con acetato de etilo (500 mL), se lavó con solución acuosa saturada de carbonato ácido de sodio y salmuera saturada; subsiguientemente se secó sobre sulfato de sodio anhidro y el disolvente se removió por destilación bajo presión reducida. El residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-50%), para producir el compuesto deseado como un aceite pardo (17.40 g, rendimiento de 54%).

^{1}H -RMN ($CDCl_3$, 400 Hz): δ 1.31 (3H, d, J = 6.3 Hz), 3.42 (3H, s), 3.49 (1H, dd, J = 9.8, 4.3 Hz), 3.59 (1H, dd, J = 10.2, 6.3 Hz), 4.52-4.59 (1H, m), 5.35 (2H, s), 6.42 (1H, t, J = 2.0 Hz), 6.47 (1H, dd, J = 3.9, 2.7 Hz), 6.72 (1H, s), 6.77 (1H, br s), 6.80 (1H, s), 6.98 (1H, dd, J = 3.9, 2.7 Hz), 7.45-7.33 (5H, m), 9.94 (1H, br s).

MS (FAB) m/z: 382 $(M+H)^+$.

(106b) 5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]-fenil}-1H-pirrol-2-carboxilato de bencilo

El 5-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-2-carboxilato de bencilo (27.35 g, 71.7 mmol) sintetizado en el ejemplo (106a) se disolvió en cloruro de metileno (350 mL), y se le agregó cloruro de triisopropilsililo (18.4 mL, 86.0 mmol), trietilamina (30.0 mL, 215 mmol) y 4-

dimetilaminopiridina (10.53 g, 86.2 mmol), seguido por agitación a temperatura ambiente durante 4 horas bajo una atmósfera de nitrógeno. Se le agregó agua (400 mL) para separar la solución y la capa orgánica se lavó con salmuera saturada, seguido por secado sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 3%-20%), para producir el producto deseado como un aceite amarillo pálido (34.41 g, rendimiento de 89%).

^{1}H-RMN ($CDCl_3$, 400 Hz): δ 1.11 (18H, d, J = 7.0 Hz), 1.22-1.30 (3H, m), 1.32 (3H, d, J = 6.3 Hz), 3.41 (3H, s), 3.49 (1H, dd, J = 10.2, 4.3 Hz), 3.58 (1H, dd, J = 10.2, 5.9 Hz), 4.49-4.56 (1H, m), 5.33 (2H, s), 6.43 (1H, t, J = 2.3 Hz), 6.47 (1H, dd, J = 3.9, 2.7 Hz), 6.66 (1H, t, J = 2.0 Hz), 6.71 (1H, t, J = 1.8 Hz), 6.98 (1H, dd, J = 3.9, 2.7 Hz), 7.32-7.45 (5H, m), 9.19 (1H, br s).

MS (FAB) m/z: 538 $(M+H)^+$.

(106c) Acido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)-oxi]fenil}-1H-pirrol-2-carboxílico

El 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]fenil}-1H-pirrol-2-carboxilato de bencilo (34.40 g, 64.0 mmol) sintetizado en el ejemplo (106b) se disolvió en etanol (320 mL), y se le agregó un catalizador de paladio al 10% en carbón (3.54 g), seguido por agitación durante 2 horas bajo una atmósfera de hidrógeno. El catalizador de paladio en carbón se removió por filtración en Celite y el disolvente se removió por destilación bajo presión reducida, para producir el compuesto deseado como un sólido blanco

(27.31 g, rendimiento de 95%).

^{1}H-RMN ($CDCl_3$, 400 Hz): δ 1.11 (18H, d, J = 7.4 Hz), 1.22-1.30 (3H, m), 1.33 (3H, d, J = 6.3 Hz), 3.46 (1H, s), 3.51 (1H, dd, J = 10.2, 4.7 Hz), 3.66 (1H, dd, J = 10.2, 5.9 Hz), 4.61-4.69 (1H, m), 6.43 (1H, t, J = 2.0 Hz), 6.51 (1H, dd, J = 3.7, 2.2 Hz), 6.74 (1H, t, J = 1.6 Hz), 6.98 (1H, t, J = 1.6 Hz), 7.05 (1H, dd, J = 3.9, 2.3 Hz), 10.02 (1H, br s).

MS (FAB) m/z: 448 $(M+H)^+$.

(106d) N-[(2R)-2-Hidroxibutil]-5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-carboxamida

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]-fenil}-1H-pirrol-2-carboxílico (1.03 g, 2.30 mmol) sintetizado en el ejemplo (106c) se disolvió en cloruro de metileno (20 mL), y se le agregó (2R)-1-aminobutan-2-ol (0.40 g, 4.49 mmol), sintetizado de acuerdo con un método conocido (*Angew. Chem. Int. Ed.* 2007, 46, 2245), WSC·HCl (1.15 g, 6.00 mmol) y 4-dimetilaminopiridina (280 mg, 2.29 mmol), seguido por agitación a temperatura ambiente durante la noche bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo con cloruro de metileno (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 60%-80%), para producir el compuesto deseado como un sólido blanco (1.01

g, rendimiento de 85%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 0.99 (3H, t, J = 7.4 Hz), 1.11 (18H, d, J = 7.0 Hz), 1.23-1.30 (3H, m), 1.31 (3H, d, J = 6.3 Hz), 1.49-1.60 (2H, m), 3.27-3.35 (1H, m), 3.42 (3H, s), 3.49 (1H, dd, J = 10.2, 4.3 Hz), 3.59 (1H, dd, J = 10.2, 5.9 Hz), 3.62-3.69 (1H, m), 3.70-3.76 (1H, m), 4.49-4.56 (1H, m), 6.33 (1H, t, J = 5.7 Hz), 6.41 (1H, t, J = 2.2 Hz), 6.45 (1H, dd, J = 3.5, 3.1 Hz), 6.61 (1H, dd, J = 3.7, 2.5 Hz), 6.67 (1H, t, J = 1.8 Hz), 6.73 (1H, t, J = 1.8 Hz), 9.58 (1H, s).

(106e) (5S)-5-Etil-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol

La N-[(2R)-2-hidroxibutil]-5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-carboxamida (1.01 g, 1.95 mmol) sintetizada en el ejemplo (106d) se disolvió en tetrahidrofurano (40 mL), y se le agregó ácido metanosulfónico anhidro (600 mg, 3.44 mmol) y trietilamina (1.60 mL, 11.48 mmol), seguido por agitación a 50°C durante 8 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con cloruro de metileno (80 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-70%), para producir el compuesto deseado como un sólido amarillo (980 mg, rendimiento de 100%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.01 (3H, t, J = 7.4 Hz), 1.09-1.14 (18H, m), 1.24-1.30 (3H, m), 1.32 (3H, d, J = 6.3 Hz), 1.71-1.82 (2H, m), 3.42 (3H, s), 3.49 (1H, dd, J = 10.2, 4.3 Hz), 3.57-3.63 (2H, m), 4.04 (2H, dd, J = 14.1,9.4 Hz), 4.51-4.56 (1H, m), 4.62-4.68 (1H, m), 6.39 (1H, t, J = 2.2 Hz), 6.46 (1H, d, J = 3.9 Hz), 6.71 (1H, s), 6.75 (1H, s), 6.76 (1H, s).

(106f) 2-(3-{5-[(5S)-5-Etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[(2S)-1-metoxipropan-2-il]oxi}fenoxi)-5-(metilsulfonil)pirazina

El (5S)-5-etil-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol (980 mg, 1.95 mmol) sintetizado en el ejemplo (106e) se disolvió en tetrahidrofurano (20 mL), y se le agregó fluoruro de tetrabutilamonio (solución en tetrahidrofurano 1.0 mol/L, 4.00 mL, 4.00 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante 1.5 horas bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo con cloruro de metileno (40 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida para producir un sólido amarillo.

Este se disolvió en acetonitrilo (20 mL) y se le agregó 2-cloro-5-(metilsulfonil)pirazina (420 mg, 2.18 mmol), sintetizada en el ejemplo (97c), y carbonato de cesio (1.42 g, 4.36 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante 2 horas bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó agua (30 mL) y se extrajo

con cloruro de metileno (40 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo = 100%), para producir el compuesto deseado como un sólido amarillo (860 mg, rendimiento de 88%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.08 (3H, t, J = 7.4 Hz), 1.38 (3H, d, J = 6.3 Hz), 1.81-1.94 (2H, m), 3.24 (3H, s), 3.42 (3H, s), 3.56 (1H, dd, J = 10.6, 3.9 Hz), 3.62 (1H, dd, J = 10.6, 5.9 Hz), 3.74 (1H, dd, J = 12.7, 7.6 Hz), 4.17 (1H, dd, J = 12.1,9.8 Hz), 4.74 (1H, br s), 4.99 (1H, br s), 6.61 (1H, d, J = 4.3 Hz), 6.74 (1H, s), 7.06 (1H, s), 7.20 (1H, s), 7.40 (1H, s), 8.50 (1H, d, J = 1.2 Hz), 8.82 (1H, d, J = 1.2 Hz).

(106g) (2S)-2-(3-{5-[(5S)-5-Etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol

La 2-(3-{5-[(5S)-5-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[(2S)-1-metoxipropan-2-il]oxi}fenoxi)-5-(metilsulfonil)pirazina (860 mg, 1.72 mmol) sintetizada en el ejemplo (106f) se disolvió en cloruro de metileno (20 mL), y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 2.50 mL, 2.50 mmol), gota a gota a -78°C, seguido por agitación a temperatura ambiente durante 2 horas bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio (20 mL) y se extrajo con cloruro de metileno (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se

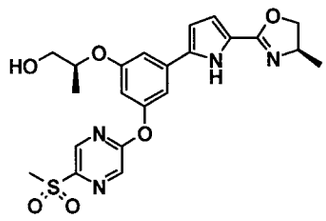
secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 2%-4%), para producir el compuesto deseado como un sólido amarillo (764 mg, rendimiento de 91%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.02 (3H, t, J = 7.4 Hz), 1.33 (3H, d, J = 6.3 Hz), 1.67-1.85 (2H, m), 3.23 (3H, s), 3.63 (1H, dd, J = 13.7, 7.8 Hz), 3.73-3.83 (2H, m), 4.07 (1H, dd, J = 13.7, 9.4 Hz), 4.60 (1H, br s), 4.72 (1H, br s), 6.51 (1H, d, J = 3.9 Hz), 6.60 (1H, s), 6.81 (1H, d, J = 3.5 Hz), 6.96 (1H, s), 7.12 (1H, s), 8.48 (1H, d, J = 1.2 Hz), 8.80 (1H, d, J = 1.2 Hz).

MS (ESI) m/z: 487.16397 $(M+H)^+$.

EJEMPLO 107

(2S)-2-(3-{5-[(4R)-4-Metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol



(107a) N-[(2R)-1-Hidroxipropan-2-il]-5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-carboxamida

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]-fenil}-1H-pirrol-2-carboxílico (2.25 g, 5.03 mmol) sintetizado en el ejemplo

(106c) se disolvió en metanol (50 mL), y se le agregó D-alaninol (0.70 mL, 8.97 mmol) y cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio n-hidratado (3.05 g, 11.02 mmol), seguido por agitación a temperatura ambiente durante 1 día, bajo una atmósfera de nitrógeno. Después de que el disolvente se removió por destilación bajo presión reducida, se le agregó una solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con acetato de etilo (80 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 80%-100%), para producir el compuesto deseado como un sólido blanco (1.95 g, rendimiento de 75%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.11 (18H, d, J = 7.4 Hz), 1.23-1.28 (3H, m), 1.28 (3H, d, J = 7.0 Hz), 1.32 (3H, d, J = 5.9 Hz), 3.42 (3H, s), 3.49 (1H, dd, J = 10.2, 4.3 Hz), 3.59 (1H, dd, J = 10.2, 5.9 Hz), 3.64 (1H, dd, J = 11.1, 6.1 Hz), 3.77 (1H, dd, J = 10.9, 3.5 Hz), 4.24 (1H, br s), 4.53 (1H, br s), 6.05 (1H, s), 6.41 (1H, t, J = 2.0 Hz), 6.45 (1H, t, J = 3.3 Hz), 6.60 (1H, dd, J = 3.7, 2.5 Hz), 6.67 (1H, t, J = 1.8 Hz), 6.74 (1H, t, J = 1.8 Hz), 9.60 (1H, s).

(107b) (4R)-2-[5-(3-{[(2S)-1-Metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-il]-4-metil-4,5-dihidro-1,3-oxazol

La N-[(2R)-1-hidroxipropan-2-il]-5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-carboxamida (1.95 g, 3.76 mmol) sintetizada en el ejemplo (107a) se disolvió en tetrahidrofurano (30 mL), y se le agregó ácido metanosulfónico anhidro (1.25 g, 7.18 mmol) y

trietilamina (2.80 mL, 20.09 mmol), seguido por agitación a 50°C durante 1 día, bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (80 mL) y se extrajo con cloruro de metileno (120 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-80%), para producir el compuesto deseado como un sólido amarillo (1.18 g, rendimiento de 64%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.12 (18H, d, J = 7.4 Hz), 1.23-1.31 (3H, m), 1.31-1.35 (6H, m), 3.42 (3H, s), 3.49 (1H, dd, J = 10.2, 4.7 Hz), 3.59 (1H, dd, J = 10.2, 5.9 Hz), 3.93 (1H, t, J = 7.8 Hz), 4.33 (1H, br s), 4.49 (1H, dd, J = 9.0, 8.2 Hz), 4.54 (1H, br s), 6.40 (1H, t, J = 2.2 Hz), 6.46 (1H, d, J = 3.5 Hz), 6.72 (1H, t, J = 1.8 Hz), 6.74 (1H, d, J = 3.9 Hz), 6.77 (1H, t, J = 1.8 Hz).

(107c) 3-{[(2S)-1-Metoxipropan-2-il]oxi}-5-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenol

El (4R)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-il]-4-metil-4,5-dihidro-1,3-oxazol (1.18 g, 2.42 mmol) sintetizado en el ejemplo (107b) se disolvió en tetrahidrofurano (10 mL), y se le agregó fluoruro de tetrabutilamonio (solución en tetrahidrofurano 1.0 mol/L, 3.00 mL, 3.00 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante 30 minutos bajo una atmósfera de nitrógeno. A

esta solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo con cloruro de metileno (40 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 1%-3%), para producir el compuesto deseado como un sólido amarillo (720 mg, rendimiento de 90%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 1.49 (3H, d, J = 6.3 Hz), 3.42 (3H, s), 3.48 (1H, dd, J = 10.2, 4.7 Hz), 3.59 (1H, dd, J = 10.2, 5.9 Hz), 4.02 (1H, t, J = 7.6 Hz), 4.47-4.61 (3H, m), 6.38 (1H, t, J = 2.2 Hz), 6.48 (1H, d, J = 3.9 Hz), 6.73 (1H, t, J = 1.8 Hz), 6.76 (1H, d, J = 3.9 Hz), 7.09 (1H, s), 11.09 (1H, s).

(107d) 2-Bromo-5-(metilsulfonil)pirazina

Se disolvió 2,5-dibromopirazina (270 mg, 1.14 mmol) en tetrahidrofurano (10 mL) y se le agregó tiometóxido de sodio (320 mg, 4.57 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante 2.5 horas bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó agua (10 mL) y se extrajo con éter dietílico (10 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 5%-

10%) para producir un sólido amarillo.

Este se disolvió en cloruro de metileno (10 mL) y se le agregó ácido m-cloroperbenzoico (aproximadamente 65%, 580 mg, aproximadamente 2.2 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante 1 hora bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio (10 mL) y se extrajo con cloruro de metileno (10 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 15%-25%), para producir el compuesto deseado como un sólido blanco (190 mg, rendimiento de 70%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 3.26 (3H, s), 8.80 (1H, d, J = 1.2 Hz), 9.06 (1H, d, J = 1.2 Hz).

(107e) 2-(3-{[(2S)-1-Metoxipropan-2-il]oxi}-5-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-5-(metilsulfonil)pirazina

El 3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenol (340 mg, 1.03 mmol) sintetizado en el ejemplo (107c) se disolvió en acetonitrilo (10 mL) y se le agregó 2-bromo-5-(metilsulfonil)pirazina (300 mg, 1.27 mmol), sintetizada en el ejemplo (107d), y carbonato de cesio (850 mg, 2.61 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante 4.5 horas bajo una atmósfera de

nitrógeno. A esta solución de reacción, se le agregó agua (20 mL) y se extrajo con cloruro de metileno (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo = 100%), para producir el compuesto deseado como un sólido blanco (456 mg, rendimiento de 91%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 4.3 Hz), 1.35 (3H, d, J = 3.9 Hz), 3.24 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 10.2, 3.9 Hz), 3.60 (1H, dd, J = 10.4, 6.1 Hz), 3.93 (1H, t, J = 7.8 Hz), 4.33 (1H, br s), 4.51 (1H, t, J = 8.6 Hz), 4.58 (1H, br s), 6.52 (1H, d, J = 3.9 Hz), 6.66 (1H, t, J = 2.2 Hz), 6.76 (1H, d, J = 3.9 Hz), 6.92 (1H, t, J = 1.8 Hz), 7.07 (1H, d, J = 1.6 Hz), 8.49 (1H, d, J = 1.2 Hz), 8.81 (1H, d, J = 1.6 Hz).

(107f) (2S)-2-(3-{5-[(4R)-4-Metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol

La 2-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-5-(metilsulfonil)pirazina (456 mg, 0.94 mmol) sintetizada en el ejemplo (107e) se disolvió en cloruro de metileno (5.0 mL), y se le agregó a gotas a -78°C tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 1.50 mL, 1.50 mmol), seguido por agitación a temperatura ambiente durante 3 horas bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio (10 mL) y se extrajo con cloruro de metileno (20

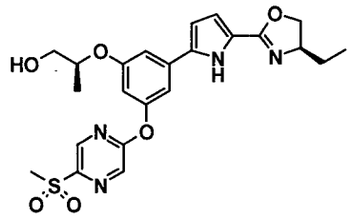
mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 4%-6%), para producir el compuesto deseado como un sólido blanco (330 mg, rendimiento de 74%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 1.40 (3H, d, J = 6.6 Hz), 3.22 (3H, s), 3.71 (1H, dd, J = 11.7, 4.3 Hz), 3.81 (1H, dd, J = 11.7, 6.6 Hz), 4.05-4.14 (1H, m), 4.38-4.45 (1H, m), 4.59-4.67 (2H, m), 6.53 (1H, d, J = 3.9 Hz), 6.62 (1H, t, J = 2.2 Hz), 6.87 (1H, d, J = 3.9 Hz), 6.98 (1H, s), 7.27 (1H, s), 8.47 (1H, d, J = 1.2 Hz), 8.79 (1H, d, J = 1.2 Hz).

MS (ESI) m/z: 473.14930 $(M+H)^+$.

EJEMPLO 108

(2S)-2-(3-{5-[(4R)-4-Etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol



(108a) (4R)-4-Etil-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)-

oxi]fenil}-1H-pirrol-2-carboxílico (1.40 g, 3.13 mmol) sintetizado en el ejemplo (106c) se disolvió en metanol (20 mL), y se le agregó (R)-(-)-2-amino-1-butanol (0.65 g, 7.29 mmol) y cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio n-hidratado (1.75 g, 6.32 mmol), seguido por agitación a temperatura ambiente durante 2 días bajo una atmósfera de nitrógeno. Después de que el disolvente se removió por destilación bajo presión reducida, se le agregó una solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con cloruro de metileno (100 mL). La capa orgánica se lavó con solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-80%), para producir el compuesto como una espuma blanca.

Esta se disolvió en tetrahidrofurano (20 mL) y se le agregó ácido metanosulfónico anhidro (0.80 g, 4.59 mmol) y trietilamina (1.20 mL, 8.61 mmol), seguido por agitación a 50°C durante la noche bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (60 mL) y se extrajo con cloruro de metileno (100 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 70%-90%), para producir el compuesto deseado

como un sólido blanco (965 mg, rendimiento de 62%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.00 (3H, t, J = 7.6 Hz), 1.07-1.14 (18H, m), 1.23-1.31 (3H, m), 1.32 (3H, d, J = 6.3 Hz), 1.56-1.65 (1H, m), 1.68-1.77 (1H, m), 3.41 (3H, s), 3.48 (1H, dd, J = 10.0, 4.6 Hz), 3.59 (1H, dd, J = 10.0, 5.6 Hz), 4.01 (1H, t, J = 7.8 Hz), 4.15-4.21 (1H, m), 4.44 (1H, t, J = 8.8 Hz), 4.49-4.54 (1H, m), 6.39 (1H, t, J = 2.0 Hz), 6.46 (1H, d, J = 3.9 Hz), 6.71 (1H, t, J = 1.7 Hz), 6.74 (1H, d, J = 3.4 Hz), 6.76 (1H, t, J = 1.7 Hz).

(108b) 3-{5-[(4R)-4-Etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[(2S)-1-metoxipropan-2-il]oxi}fenol

El (4R)-4-etil-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol (965 mg, 1.93 mmol) sintetizado en el ejemplo (108a) se disolvió en tetrahidrofurano (10 mL) y se le agregó fluoruro de tetrabutilamonio (solución en tetrahidrofurano 1.0 mol/L, 2.50 mL, 2.50 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante 1 hora bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo con cloruro de metileno (40 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 2%-4%), para producir el compuesto deseado como un sólido blanco (550 mg, rendimiento de 83%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.10 (3H, t, J = 7.4 Hz), 1.32 (3H, d, J = 6.3 Hz), 1.73 (1H, td, J = 14.1,7.0 Hz), 1.85 (1H, td, J = 14.0, 7.0 Hz), 3.41 (3H, s), 3.48 (1H, dd, J = 10.2, 4.7 Hz), 3.59 (1H, dd, J = 10.2, 5.9 Hz), 4.09-4.15 (1H, m), 4.32-4.40 (1H, m), 4.48-4.57 (2H, m), 6.36 (1H, t, J = 2.2 Hz), 6.47 (1H, d, J = 3.5 Hz), 6.72 (1H, t, J = 1.8 Hz), 6.76 (1H, d, J = 3.9 Hz), 7.10 (1H, t, J = 1.8 Hz), 11.12 (1H, br s).

(108c) 2-(3-{5-[(4R)-4-Etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[(2S)-1-metoxipropan-2-il]oxi}fenoxi)-5-(metilsulfonil)pirazina

El 3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[(2S)-1-metoxipropan-2-il]oxi}fenol (272 mg, 0.79 mmol) sintetizado en el ejemplo (108b) se disolvió en acetonitrilo (5.0 mL) y se le agregó 2-cloro-5-(metilsulfonil)pirazina (220 mg, 1.14 mmol), sintetizada en el ejemplo (97c), y carbonato de cesio (640 mg, 1.96 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante 3.5 horas bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó agua (20 mL) y se extrajo con cloruro de metileno (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 2%-3%), para producir el compuesto deseado como un sólido amarillo pálido (417 mg, rendimiento de ~100%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 0.96 (3H, t, J = 7.4 Hz), 1.34 (3H, d, J = 6.3 Hz), 1.53-1.60 (1H, m), 1.65-1.72 (1H, m), 3.23 (3H, s), 3.41 (3H, s),

3.50 (1H, dd, J = 10.2, 4.3 Hz), 3.59 (1H, dd, J = 10.6, 5.9 Hz), 4.01 (1H, t, J = 7.8 Hz), 4.11-4.19 (1H, m), 4.41-4.46 (1H, m), 4.57 (1H, br s), 6.50 (1H, d, J = 3.9 Hz), 6.64 (1H, t, J = 2.2 Hz), 6.73 (1H, d, J = 3.5 Hz), 6.94 (1H, d, J = 1.6 Hz), 7.09 (1H, d, J = 1.6 Hz), 8.47 (1H, d, J = 0.8 Hz), 8.80 (1H, d, J = 0.8 Hz).

(108d) (2S)-2-(3-{5-[(4R)-4-Etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol

La 2-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[(2S)-1-metoxipropan-2-il]oxi}fenoxi)-5-(metilsulfonil)pirazina (417 mg, 0.83 mmol) sintetizada en el ejemplo (108c) se disolvió en cloruro de metileno (10 mL) y se le agregó a gotas a -78°C tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 1.00 mL, 1.00 mmol), seguido por agitación a temperatura ambiente durante 1 hora bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa de hidróxido de sodio 1N (20 mL) y se extrajo con cloruro de metileno (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 3%-4%), para producir el compuesto deseado como un sólido blanco (325 mg, rendimiento de 80%).

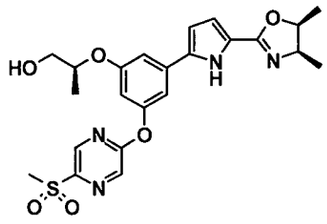
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.01 (3H, t, J = 7.4 Hz), 1.30 (3H, d, J = 6.3 Hz), 1.57-1.64 (1H, m), 1.68-1.75 (1H, m), 3.23 (3H, s), 3.78-3.80 (2H, m), 4.02 (1H, t, J = 8.0 Hz), 4.16-4.22 (1H, m), 4.47 (1H, t, J = 8.8 Hz), 4.57-4.63 (1H, m), 6.45 (1H, d, J = 3.5 Hz), 6.49 (1H, s), 6.73 (1H, d, J = 3.9

Hz), 6.90 (1H, s), 7.01 (1H, s), 8.44 (1H, s), 8.79 (1H, s).

MS (ESI) m/z: 487.16468 $(M+H)^+$.

EJEMPLO 109

(2S)-2-(3-{5-[(4R,5S)-4,5-Dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol



(109a) N-[(2R,3R)-3-Hidroxibutan-2-il]-5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-carboxamida

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]-fenil}-1H-pirrol-2-carboxílico (0.89 g, 1.99 mmol) sintetizado en el ejemplo (106c) se disolvió en metanol (20 mL) y se le agregó (2R,3R)-3-aminobutan-2-ol (0.41 g, 4.60 mmol), sintetizado en el ejemplo (88a), y cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio n-hidratado (1.20 g, 4.34 mmol), seguido por agitación a temperatura ambiente durante 3 días bajo una atmósfera de nitrógeno. Después de que el disolvente se removió por destilación bajo presión reducida, se le agregó una solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con cloruro de metileno (80 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El residuo resultante se purificó por

cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 60%-80%), para producir el compuesto deseado como una espuma blanca (722 mg, rendimiento de 70%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.11 (18H, d, J = 7.0 Hz), 1.22-1.29 (3H, m), 1.24 (3H, d, J = 6.3 Hz), 1.28 (3H, d, J = 7.0 Hz), 1.32 (3H, d, J = 6.3 Hz), 2.34 (1H, br s), 3.42 (3H, s), 3.49 (1H, dd, J = 10.2, 4.3 Hz), 3.59 (1H, dd, J = 10.2, 5.5 Hz), 3.84 (1H, br s), 4.03-4.13 (1H, m), 4.49-4.56 (1H, m), 6.06 (1H, d, J = 8.6 Hz), 6.41 (1H, t, J = 2.2 Hz), 6.45 (1H, dd, J = 3.7, 2.9 Hz), 6.61 (1H, dd, J = 3.9, 2.3 Hz), 6.67 (1H, t, J = 1.8 Hz), 6.73 (1H, t, J = 2.0 Hz), 9.49 (1H, br s).

(109b) (4R,5S)-2-[5-(3-{[(2S)-1-Metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-il]-4,5-dimetil-4,5-dihidro-1,3-oxazol

La N-[(2R,3R)-3-hidroxibutan-2-il]-5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-carboxamida (722 mg, 1.39 mmol) sintetizada en el ejemplo (109a) se disolvió en tetrahidrofurano (30 mL), se le agregó ácido metanosulfónico anhidro (430 mg, 2.47 mmol) y trietilamina (1.20 mL, 8.61 mmol), y se agitó a 50°C durante la noche bajo una atmósfera de nitrógeno. La solución de reacción se llevó de vuelta a la temperatura ambiente y se le agregó una solución acuosa saturada de cloruro de amonio (50 mL), seguido por extracción con cloruro de metileno (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en

columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 40%-70%), para producir el compuesto deseado como un líquido amarillo (700 mg, rendimiento de 100%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.11 (18H, d, J = 7.0 Hz), 1.21 (3H, d, J = 7.0 Hz), 1.23-1.30 (3H, m), 1.31 (3H, d, J = 6.3 Hz), 1.33 (3H, d, J = 6.6 Hz), 3.42 (3H, s), 3.48 (1H, dd, J = 10.2, 4.3 Hz), 3.58 (1H, dd, J = 10.2, 5.9 Hz), 4.24-4.32 (1H, m), 4.48-4.56 (1H, m), 4.78-4.85 (1H, m), 6.39 (1H, t, J = 2.2 Hz), 6.46 (1H, d, J = 3.5 Hz), 6.70 (1H, s), 6.73-6.75 (2H, m).

(109c) 3-{5-[(4R,5S)-4,5-Dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[(2S)-1-metoxipropan-2-il]oxi}fenol

El (4R,5S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-il]-4,5-dimetil-4,5-dihidro-1,3-oxazol (700 mg, 1.39 mmol) sintetizado en el ejemplo (109b) se disolvió en tetrahidrofurano (10 mL), y se le agregó fluoruro de tetrabutilamonio (solución en tetrahidrofurano 1.0 mol/L, 2.00 mL, 2.00 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante 30 minutos bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo con cloruro de metileno (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 2%-3%), para producir el compuesto deseado como un líquido amarillo (420

mg, rendimiento de 88%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 1.35-1.40 (6H, m), 3.41 (3H, s), 3.48 (1H, dd, J = 10.0, 4.5 Hz), 3.59 (1H, dd, J = 10.2, 5.5 Hz), 4.40-4.48 (1H, m), 4.48-4.56 (1H, m), 4.86-4.94 (1H, m), 6.38 (1H, t, J = 2.0 Hz), 6.47 (1H, d, J = 3.9 Hz), 6.72 (1H, s), 6.75 (1H, d, J = 3.9 Hz), 7.09 (1H, s).

(109d) 2-(3-{5-[(4R,5S)-4,5-Dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[(2S)-1-metoxipropan-2-il]oxi}fenoxi)-5-(metilsulfonil)pirazina

El 3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[(2S)-1-metoxipropan-2-il]oxi}fenol (420 mg, 1.22 mmol) sintetizado en el ejemplo (109c) se disolvió en acetonitrilo (20 mL), y se le agregó 2-cloro-5-(metilsulfonil)pirazina (345 mg, 1.46 mmol), sintetizada en el ejemplo (97c), y carbonato de cesio (1.02 g, 3.13 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante la noche bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó agua (30 mL) y se extrajo con cloruro de metileno (40 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 2%-3%), para producir el compuesto deseado como un sólido blanco (513 mg, rendimiento de 84%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.19-1.28 (6H, m), 1.35 (3H, d, J = 6.6 Hz), 3.24 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 10.2, 4.3 Hz), 3.61 (1H,

dd, J = 10.4,5.7 Hz), 4.25-4.35 (1H, m), 4.57-4.63 (1H, m), 4.81-4.91 (1H, m), 6.52 (1H, d, J = 3.9 Hz), 6.76 (1H, s), 6.96 (1H, s), 7.12 (1H, s), 8.49 (1H, d, J = 1.2 Hz), 8.81 (1H, d, J = 1.6 Hz).

(109e) ((2S)-2-(3-{5-[(4R,5S)-4,5-Dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol

La 2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[(2S)-1-metoxipropan-2-il]oxi}fenoxi)-5-(metilsulfonil)pirazina (513 mg, 1.02 mmol) sintetizada en el ejemplo (109d) se disolvió en cloruro de metileno (10 mL), y se le agregó a gotas a -78°C tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 1.50 mL, 1.50 mmol), seguido por agitación a temperatura ambiente durante 2 horas bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio (20 mL) y se extrajo con cloruro de metileno (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 4%-5%), para producir el compuesto deseado como un sólido amarillo pálido (390 mg, rendimiento de 79%).

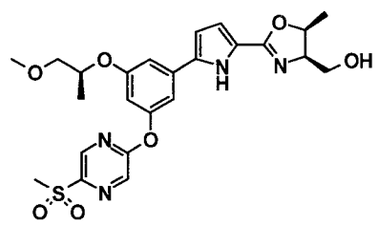
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.22 (3H, d, J = 7.0 Hz), 1.32 (3H, d, J = 6.3 Hz), 1.34 (3H, d, J = 6.6 Hz), 3.23 (3H, s), 3.76-3.79 (2H, m), 4.25-4.33 (1H, m), 4.54-4.60 (1H, m), 4.81-4.88 (1H, m), 6.49 (1H, d, J = 3.9 Hz), 6.59 (1H, s), 6.75 (1H, d, J = 3.9 Hz), 6.95 (1H, s), 7.09 (1H, s), 8.47 (1H, s),

8.80 (1H, d, J = 1.2 Hz).

MS (ESI) m/z: 487.16580 $(M+H)^+$.

EJEMPLO 110

{(4R,5S)-2-[5-(3-{[(2S)-1-Metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol



(110a) N-[(2R,3R)-1,3-Dihidroxibutan-2-il]-5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-carboxamida

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]-fenil}-1H-pirrol-2-carboxílico (2.05 g, 4.58 mmol) sintetizado en el ejemplo (106c) se disolvió en metanol (20 mL), y se le agregó L-treoninol (1.50 g, 14.27 mmol), disponible comercialmente, y cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio n-hidratado (2.85 g, 10.30 mmol), seguido por agitación a temperatura ambiente durante 3 días bajo una atmósfera de nitrógeno. Después de que el disolvente se removió por destilación bajo presión reducida, se le agregó una solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con cloruro de metileno (80 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El residuo resultante se purificó por

cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 3%-7%), para producir el compuesto deseado como una espuma blanca (2.10 g, rendimiento de 86%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.11 (18H, d, J = 7.4 Hz), 1.21-1.33 (6H, m), 1.22 (3H, d, J = 6.3 Hz), 3.44 (3H, s), 3.49 (1H, dd, J = 10.2, 3.9 Hz), 3.57 (1H, dd, J = 10.2, 6.3 Hz), 3.83 (2H, br s), 3.96 (1H, br s), 4.26 (1H, ddd, J = 12.5,6.3,2.0 Hz), 4.45-4.53 (1H, m), 6.41 (1H, t, J = 2.2 Hz), 6.44 (1H, dd, J = 3.5, 2.7 Hz), 6.68-6.72 (3H, m), 6.72-6.77 (1H, m), 10.36 (1H, s).

(110b) N-{(2R,3R)-3-Hidroxi-1-[(tripropan-2-ilsilil)oxi]butan-2-il}-5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-carboxamida

La N-[(2R,3R)-1,3-dihidroxibutan-2-il]-5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-carboxamida (2.10 g, 3.93 mmol) sintetizada en el ejemplo (110a) se disolvió en cloruro de metileno (50 mL), y se le agregó triisopropilclorosilano (1.50 mL, 7.01 mmol), 4-dimetilaminopiridina (1.50 g, 12.27 mmol) y trietilamina (5.00 mL, 35.87 mmol), seguido por agitación a temperatura ambiente durante 1 día bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con cloruro de metileno (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución:

acetato de etilo/hexano = 25-40%), para producir el compuesto deseado como un sólido blanco (2.52 g, rendimiento de 93%).

^{1}H-RMN ($CDCl_3$, 500 MHz): δ 1.07 (18H, d, J = 6.8 Hz), 1.12 (18H, d, J = 7.3 Hz), 1.21-1.31 (9H, m), 1.32 (3H, d, J = 6.3 Hz), 3.42 (3H, s), 3.49 (1H, dd, J = 10.3, 4.4 Hz), 3.55 (1H, br s), 3.59 (1H, dd, J = 10.3, 5.9 Hz), 4.00-4.04 (1H, m), 4.04-4.06 (2H, m), 4.29-4.34 (1H, m), 4.49-4.55 (1H, m), 6.41 (1H, t, J = 2.2 Hz), 6.46 (1H, dd, J = 3.9, 2.9 Hz), 6.60 (1H, s), 6.61 (1H, dd, J = 3.4, 2.4 Hz), 6.67 (1H, t, J = 2.0 Hz), 6.72 (1H, t, J = 2.0 Hz), 9.34 (1H, s).

(110c) (4R,5S)-2-[5-(3-{[(2S)-1-Metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-il]-5-metil-4-{[(tripropan-2-ilsilil)oxi]-metil}-4,5-dihidro-1,3-oxazol

La N-{(2R,3R)-3-hidroxi-1-[(tripropan-2-ilsilil)oxi]butan-2-il}-5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-carboxamida (2.52 g, 3.65 mmol) sintetizada en el ejemplo (110b) se disolvió en tetrahidrofurano (20 mL), y se le agregó ácido metanosulfónico anhidro (1.05 g, 6.03 mmol) y trietilamina (2.00 mL, 14.35 mmol), seguido por agitación a 50°C durante 1 día bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con cloruro de metileno (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de

gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-30%), para producir el compuesto deseado como un líquido amarillo pálido (2.30 g, rendimiento de 94%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.06 (18H, d, J = 5.1 Hz), 1.11 (18H, d, J = 7.4 Hz), 1.22-1.30 (6H, m), 1.31 (3H, d, J = 6.3 Hz), 1.52 (3H, d, J = 6.3 Hz), 3.42 (3H, s), 3.48 (1H, dd, J = 10.2, 4.7 Hz), 3.59 (1H, dd, J = 10.4,5.7 Hz), 3.82 (1H, dd, J = 10.2, 9.0 Hz), 3.98 (1H, dd, J = 10.2, 3.9 Hz), 4.24 (1H, td, J = 8.7, 3.9 Hz), 4.48-4.55 (1H, m), 4.86-4.96 (1H, m), 6.39 (1H, t, J = 2.2 Hz), 6.45 (1H, d, J = 3.9 Hz), 6.67 (1H, s), 6.71 (1H, s), 6.75 (1H, d, J = 3.9 Hz).

(110d) {(4R,5S)-2-[5-(3-{[(2S)-1-Metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol

El (4R,5S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-il]-5-metil-4-{[(tripropan-2-ilsilil)oxi]metil}-4,5-dihidro-1,3-oxazol (2.30 g, 3.42 mmol) sintetizado en el ejemplo (110c) se disolvió en tetrahidrofurano (20 mL), y se le agregó fluoruro de tetrabutilamonio (solución en tetrahidrofurano 1.0 mol/L, 8.00 mL, 8.00 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante 30 minutos bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (60 mL) y se extrajo con cloruro de metileno (80 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El

disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/acetato de etilo = 5%-10%), para producir un sólido blanco (2.10 g).

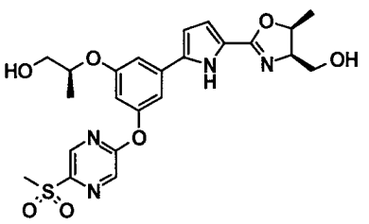
Se disolvieron 1.20 g del compuesto resultante en acetonitrilo (15 mL), y se le agregó a 0°C 2-cloro-5-(metilsulfonil)pirazina (410 mg, 2.13 mmol), sintetizada en el ejemplo (97c), y carbonato de potasio (0.85 g, 6.15 mmol), seguido por agitación bajo una atmósfera de nitrógeno a 0°C durante 5 horas y luego a temperatura ambiente durante 3 horas. A esta solución de reacción se le agregó agua (30 mL) y se extrajo con cloruro de metileno (40 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/acetato de etilo = 4%-6%), para producir el compuesto deseado como un sólido blanco (964 mg, rendimiento de 95%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.35 (3H, d, J = 6.3 Hz), 1.40 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.50 (1H, dd, J = 10.2, 4.3 Hz), 3.60 (1H, dd, J = 10.2, 5.9 Hz), 3.77 (1H, dd, J = 11.5, 6.1 Hz), 3.85 (1H, dd, J = 11.7, 3.5 Hz), 4.22-4.28 (1H, m), 4.54-4.60 (1H, m), 4.82-4.88 (1H, m), 6.45 (1H, d, J = 3.5 Hz), 6.65 (1H, t, J = 2.2 Hz), 6.67 (1H, d, J = 2.3 Hz), 6.94 (1H, t, J = 1.8 Hz), 7.10 (1H, t, J = 1.8 Hz), 8.48 (1H, d, J = 1.2 Hz), 8.80 (1H, d, J = 1.2 Hz).

MS (ESI) m/z: 517.17452 $(M+H)^+$.

EJEMPLO 111

(2S)-2-(3-{5-[(4R,5S)-4-(Hidroximetil)-5-metil-4,5-dihidro-1,3-oxazol-2-il)]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol



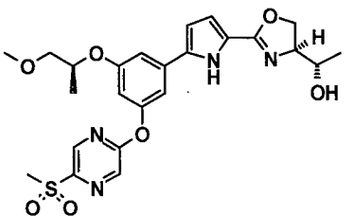
El {(4R,5S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol (209 mg, 0.40 mmol) sintetizado en el ejemplo (110d) se disolvió en cloruro de metileno (5.0 mL), y se le agregó a gotas a -78°C tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 0.80 mL, 0.80 mmol), seguido por agitación a temperatura ambiente durante 40 minutos bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa de hidróxido de sodio 1N (10 mL) y se extrajo con cloruro de metileno (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 4%-6%), para producir el compuesto deseado como un sólido blanco (169 mg, rendimiento de 83%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J = 6.3 Hz), 1.41 (3H, d, J = 6.6 Hz), 3.23 (3H, s), 3.76 (2H, d, J = 4.7 Hz), 3.70-3.80 (1H, m), 3.85 (1H, dd, J = 11.7, 3.9 Hz), 4.21-4.25 (1H, m), 4.49-4.60 (1H, m), 4.82-4.89 (1H, m), 6.43 (1H, d, J = 2.7 Hz), 6.59 (1H, s), 6.67 (1H, d, J = 2.7 Hz), 6.95 (1H, s), 7.07 (1H, s), 8.47 (1H, s), 8.78 (1H, s).

MS (ESI) m/z: 503.15957 $(M+H)^+$.

EJEMPLO 112

(1S)-1-{(4S)-2-[5-(3-{[(2S)-1-Metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol



(112a) N-[(2S,3S)-1,3-Dihidroxibutan-2-il]-5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-carboxamida

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]-fenil}-1H-pirrol-2-carboxílico (1.75 g, 3.91 mmol) sintetizado en el ejemplo (106c) se disolvió en metanol (30 mL), y se le agregó D-treoninol (1.00 g, 9.51 mmol) y cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio n-hidratado (2.85 g, 10.30 mmol), seguido por agitación a temperatura ambiente durante 5 días bajo una atmósfera de nitrógeno. Después de que el disolvente se removió por destilación bajo presión reducida, se le agregó una

solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con cloruro de metileno (80 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 3%-7%), para producir el compuesto deseado como un sólido blanco (1.76 g, rendimiento de 84%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.08 (18H, d, J = 7.4 Hz), 1.18-1.25 (6H, m), 1.27 (3H, d, J = 6.3 Hz), 2.83 (2H, br s), 3.38 (3H, s), 3.45 (1H, dd, J = 10.2, 4.3 Hz), 3.55 (1H, dd, J = 10.2, 5.9 Hz), 3.87 (2H, s), 3.94-4.01 (2H, m), 4.22 (1H, br s), 4.46-4.52 (1H, m), 6.37 (1H, br s), 6.40-6.43 (1H, m), 6.59-6.66 (3H, m), 6.70 (1H, s), 9.78 (1H, br s).

(112b) (1S)-1-{(4S)-2-[5-(3-{[(2S)-1-Metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol

La N-[(2S,3S)-1,3-dihidroxibutan-2-il]-5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-carboxamida (1.76 g, 3.29 mmol) sintetizada en el ejemplo (112a) se disolvió en tetrahidrofurano (20 mL), y se le agregó ácido metanosulfónico anhidro (0.54 g, 3.10 mmol) y trietilamina (1.00 mL, 7.17 mmol) a -40°C, seguido por agitación a la misma temperatura durante 4 horas bajo una atmósfera de nitrógeno, y luego a 50°C durante la noche. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con cloruro de metileno (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente

se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 2%-5%), para producir el compuesto deseado como una espuma blanca (880 mg, rendimiento de 52%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.12 (18H, d, J = 7.0 Hz), 1.22-1.30 (6H, m), 1.32 (3H, d, J = 6.3 Hz), 3.42 (3H, s), 3.48 (1H, dd, J = 10.2, 4.3 Hz), 3.59 (1H, dd, J = 10.2, 5.9 Hz), 3.69-3.75 (1H, m), 4.10-4.20 (2H, m), 4.45 (1H, br s), 4.53 (1H, br s), 6.40 (1H, t, J = 1.6 Hz), 6.47 (1H, d, J = 3.9 Hz), 6.70 (1H, s), 6.75 (1H, s), 6.77 (1H, d, J = 3.9 Hz).

(112c) 3-(5-{(4S)-4-[(1S)-1-Hidroxietil]-4,5-dihidro-1,3-oxazol-2-il}-1H-pirrol-2-il)-5-{[(2S)-1-metoxipropan-2-il]oxi}fenol

El (1S)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol (1.48 g, 2.88 mmol) sintetizado en el ejemplo (112b) se disolvió en tetrahidrofurano (20 mL), y se le agregó fluoruro de tetrabutilamonio (solución en tetrahidrofurano 1.0 mol/L, 3.50 mL, 3.50 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante 1.5 horas bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con cloruro de metileno (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente

de elución: metanol/cloruro de metileno = 3%-6%), para producir el compuesto deseado como un sólido blanco (880 mg, rendimiento de 85%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 1.37 (3H, d, J = 6.3 Hz), 3.42 (3H, s), 3.46 (1H, dd, J = 10.2, 4.7 Hz), 3.61 (1H, dd, J = 10.0, 5.7 Hz), 3.85-3.92 (1H, m), 4.25-4.36 (2H, m), 4.49-4.56 (2H, m), 6.48 (1H, d, J = 3.9 Hz), 6.54 (1H, t, J = 2.0 Hz), 6.73 (1H, t, J = 1.8 Hz), 6.79 (1H, d, J = 3.5 Hz), 7.06 (1H, s).

(112d) (1S)-1-{(4S)-2-[5-(3-{[(2S)-1-Metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol

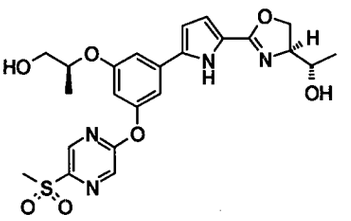
El 3-(5-{(4S)-4-[(1S)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-il}-1H-pirrol-2-il)-5-{[(2S)-1-metoxipropan-2-il]oxi}fenol (880 mg, 2.44 mmol) sintetizado en el ejemplo (112c) se disolvió en acetonitrilo (20 mL), y se le agregó 2-cloro-5-(metilsulfonil)pirazina (630 mg, 3.27 mmol), sintetizada en el ejemplo (97c), y carbonato de potasio (1.20 g, 8.68 mmol), seguido por agitación a temperatura ambiente durante 4 horas bajo una atmósfera de nitrógeno. Se le agregó agua (50 mL) y se extrajo con cloruro de metileno (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 1%-3%), para producir el compuesto deseado como un sólido blanco (1.00 g, rendimiento de 79%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.28 (3H, d, J = 6.3 Hz), 1.35 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.41 (3H, s), 3.51 (1H, dd, J = 10.2, 4.3 Hz), 3.60 (1H, dd, J = 10.2, 6.3 Hz), 3.73 (1H, br s), 4.11-4.22 (2H, m), 4.46 (1H, br s), 4.60 (1H, br s), 6.52 (1H, d, J = 3.9 Hz), 6.67 (1H, t, J = 2.0 Hz), 6.78 (1H, d, J = 3.9 Hz), 6.96 (1H, s), 7.12 (1H, s), 8.49 (1H, s), 8.81 (1H, s).

MS (ESI) m/z: 517.17608 $(M+H)^+$.

EJEMPLO 113

(2S)-2-[3-(5-{(4S)-4-[(1S)-1-Hidroxietil]-4,5-dihidro-1,3-oxazol-2-il}-1H-pirrol-2-il)-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi]propan-1-ol



El (1S)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol (204 mg, 0.395 mmol) sintetizado en el ejemplo (112d) se disolvió en cloruro de metileno (5.0 mL), y se le agregó a gotas a -78°C tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 0.80 mL, 0.80 mmol), seguido por agitación a temperatura ambiente durante 1.5 horas bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa de hidróxido de sodio 1N (10 mL) y se extrajo con cloruro de metileno (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó

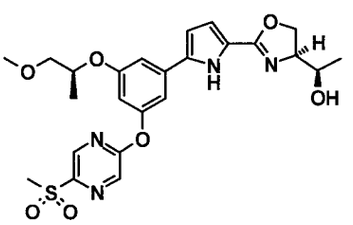
sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 3%-5%), para producir el compuesto deseado como un sólido blanco (159 mg, rendimiento de 80%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.28 (3H, d, J = 6.3 Hz), 1.32 (3H, d, J = 6.3 Hz), 3.24 (3H, s), 3.73-3.78 (3H, m), 4.12-4.23 (2H, m), 4.46 (1H, br s), 4.52-4.59 (1H, m), 6.50 (1H, d, J = 3.9 Hz), 6.62 (1H, t, J = 2.0 Hz), 6.76 (1H, d, J = 3.9 Hz), 6.94 (1H, t, J = 1.8 Hz), 7.08 (1H, s), 8.49 (1H, d, J = 1.2 Hz), 8.80 (1H, d, J = 1.2 Hz).

MS (ESI) m/z: 503.15930 $(M+H)^+$.

EJEMPLO 114

(1R)-1-{(4S)-2-[5-(3-{[(2S)-1-Metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)-pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol



(114a) N-[(2S,3R)-1,3-Dihidroxibutan-2-il]-5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-carboxamida

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]-fenil}-1H-pirrol-2-carboxílico (1.63 g, 3.64 mmol) sintetizado en el ejemplo

(106c) se disolvió en metanol (20 mL), y se le agregó D-alo-treoninol (1.05 g, 9.99 mmol) y cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio n-hidratado (2.00 g, 7.23 mmol), seguido por agitación a temperatura ambiente durante 1 día bajo una atmósfera de nitrógeno. Después de que el disolvente se removió por destilación bajo presión reducida, se le agregó una solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con cloruro de metileno (80 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 3%-7%), para producir el compuesto deseado como una espuma blanca (1.70 g, rendimiento de 87%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.07 (18H, d, J = 7.0 Hz), 1.17-1.27 (9H, m), 2.01 (1H, br s), 3.37 (3H, s), 3.44 (1H, dd, J = 10.0, 4.1 Hz), 3.44 (1H, s), 3.53 (1H, dd, J = 10.4, 6.1 Hz), 3.72-3.78 (1H, m), 3.88-3.93 (1H, m), 3.93-3.95 (1H, m), 3.96-4.04 (2H, m), 4.44-4.52 (1H, m), 6.35 (1H, t, J = 2.0 Hz), 6.39 (1H, t, J = 3.1 Hz), 6.67 (1H, t, J = 1.8 Hz), 6.70 (1H, s), 6.72 (1H, s), 6.99 (1H, d, J = 7.8 Hz), 10.34 (1H, br s).

(114b) (1R)-1-{(4S)-2-[5-(3-{[(2S)-1-Metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol

La N-[(2S,3R)-1,3-dihidroxibutan-2-il]-5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-carboxamida (1.70 g, 3.18 mmol) sintetizada en el ejemplo (114a) se disolvió en tetrahidrofurano (20 mL), y se le agregó ácido metanosulfónico anhidro (0.78 g, 4.48 mmol) y

trietilamina (1.50 mL, 10.76 mmol) a 0°C, seguido por agitación a la misma temperatura durante 1.5 horas bajo una atmósfera de nitrógeno, seguido por agitación a 50°C durante la noche. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con cloruro de metileno (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 2%-4%), para producir el compuesto deseado como una espuma blanca (1.30 g, rendimiento de 79%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.10-1.14 (18H, m), 1.20 (3H, d, J = 6.6 Hz), 1.23-1.32 (3H, m), 1.34 (3H, d, J = 6.3 Hz), 3.41 (3H, s), 3.48 (1H, dd, J = 10.2, 4.3 Hz), 3.59 (1H, dd, J = 10.2, 5.9 Hz), 4.20-4.34 (4H, m), 4.53 (1H, br s), 6.33 (1H, d, J = 3.9 Hz), 6.40 (1H, t, J = 2.0 Hz), 6.44 (1H, br s), 6.74 (1H, t, J = 1.8 Hz), 6.78 (1H, t, J = 1.8 Hz).

(114c) 3-(5-{(4S)-4-[(1R)-1-Hidroxietil]-4,5-dihidro-1,3-oxazol-2-il}-1H-pirrol-2-il)-5-{[(2S)-1-metoxipropan-2-il]oxi}fenol

El (1R)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-[(tripropan-2-ilsilil)oxi]fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol (1.30 g, 2.52 mmol) sintetizado en el ejemplo (114b) se disolvió en tetrahidrofurano (15 mL), y se le agregó fluoruro de tetrabutilamonio (solución en tetrahidrofurano 1.0 mol/L, 4.00 mL, 4.00 mmol) a temperatura ambiente, seguido por agitación a temperatura ambiente durante 1 hora bajo una

atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (50 mL) y se extrajo con cloruro de metileno (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/acetato de etilo = 8%-12%), para producir el compuesto deseado como una espuma blanca (766 mg, rendimiento de 85%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (6H, d, J = 6.3 Hz), 3.28 (1H, br s), 3.42 (3H, s), 3.47 (1H, dd, J = 10.2, 4.3 Hz), 3.61 (1H, dd, J = 10.2, 5.9 Hz), 4.23 (1H, br s), 4.35-4.43 (1H, m), 4.47-4.56 (3H, m), 6.46-6.49 (2H, m), 6.72 (1H, s), 6.78 (1H, d, J = 3.5 Hz), 7.04 (1H, t, J = 1.8 Hz), 11.07 (1H, s).

(114d) (1R)-1-{(4S)-2-[5-(3-{[(2S)-1-Metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol

El 3-(5-{(4S)-4-[(1R)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-il}-1H-pirrol-2-il)-5-{[(2S)-1-metoxipropan-2-il]oxi}fenol (766 mg, 2.13 mmol) sintetizado en el ejemplo (114c) se disolvió en acetonitrilo (15 mL), y se le agregó 2-cloro-5-(metilsulfonil)pirazina (590 mg, 3.06 mmol), sintetizada en el ejemplo (97c), y carbonato de potasio (870 mg, 6.29 mmol), seguido por agitación a temperatura ambiente durante 4 horas bajo una atmósfera de nitrógeno. Se le agregó agua (50 mL) y se extrajo con cloruro de metileno (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se

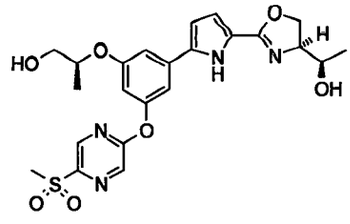
secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/acetato de etilo = 5%-8%), para producir el compuesto deseado como un sólido blanco (890 mg, rendimiento de 81%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.17 (3H, d, J = 6.6 Hz), 1.36 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 10.4, 4.1 Hz), 3.60 (1H, dd, J = 10.2, 5.9 Hz), 4.10-4.26 (2H, m), 4.28-4.35 (2H, m), 4.58 (1H, br s), 6.42 (1H, d, J = 3.9 Hz), 6.56 (1H, d, J = 3.5 Hz), 6.66 (1H, t, J = 2.2 Hz), 6.96 (1H, d, J = 1.6 Hz), 7.11 (1H, s), 8.49 (1H, d, J = 1.2 Hz), 8.81 (1H, d, J = 1.2 Hz).

MS (ESI) m/z: 517.17565 $(M+H)^+$.

EJEMPLO 115

(2S)-2-[3-(5-{(4S)-4-[(1R)-1-Hidroxietil]-4,5-dihidro-1,3-oxazol-2-il}-1H-pirrol-2-il)-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi]propan-1-ol



El (1R)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol (213 mg, 0.412 mmol) sintetizado en el ejemplo (114d) se disolvió en

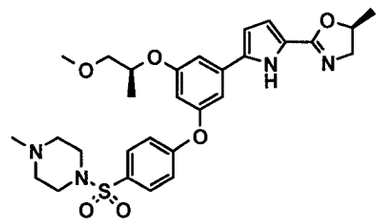
cloruro de metileno (5.0 mL), y se le agregó a gotas a -78°C tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 0.80 mL, 0.80 mmol), seguido por agitación a temperatura ambiente durante 1.5 horas bajo una atmósfera de nitrógeno. A esta solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio (10 mL) y se extrajo con cloruro de metileno (20 mL). La capa orgánica se lavó con una solución acuosa de hidróxido de sodio 1N (10 mL) y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 4%-5%), para producir el compuesto deseado como un sólido blanco (147 mg, rendimiento de 71%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.18 (3H, d, J = 6.3 Hz), 1.33 (3H, d, J = 6.3 Hz), 1.61 (2H, br s), 3.23 (3H, s), 3.73-3.82 (2H, m), 4.16-4.26 (2H, m), 4.30-4.36 (2H, m), 4.54-4.61 (1H, m), 6.39 (1H, d, J = 3.9 Hz), 6.53 (1H, d, J = 3.5 Hz), 6.61 (1H, s), 6.95 (1H, s), 7.07 (1H, s), 8.48 (1H, d, J = 1.2 Hz), 8.80 (1H, d, J = 1.6 Hz).

MS (ESI) m/z: 503.15973 $(M+H)^+$.

EJEMPLO 116

1-{[4-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)fenil]sulfonil}-4-metilpiperazina



(116a) 1-[(4-Fluorofenil)sulfonil]-4-metilpiperazina

Se suspendió en agua (15 mL) cloruro de 4-fluorobencenosulfonilo (1.00 g, 5.14 mmol), disponible comercialmente, y se le agregó N-metilpiperazina (0.68 mL, 6.17 mmol) y carbonato de potasio (1.56 g, 11.3 mmol), seguido por agitación a temperatura ambiente durante 14 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó agua (50 mL) seguido por extracción con acetato de etilo (50 mL); subsiguientemente la capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 50%-90%), para producir el compuesto deseado como un sólido blanco (491 mg, rendimiento de 37%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.28 (3H, s), 2.49 (4H, t, J = 4.9 Hz), 3.04 (4H, br s), 7.21 (2H, dd, J = 9.4, 7.8 Hz), 7.76-7.79 (2H, m).

(116b) N-[(2R)-2-Hidroxipropil]-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]fenil}-1H-pirrol-2-carboxamida

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]-fenil}-1H-pirrol-2-carboxílico (51.4 g, 115 mmol) sintetizado en el ejemplo (106c) se disolvió en metanol (600 mL), y se le agregó (R)-(-)-1-amino-2-propanol (19.9 mL, 253 mmol) y cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio n-hidratado (63.7 g, 230 mmol), seguido por agitación durante 15 horas bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y se le agregó agua (500 mL), seguido por extracción dos veces con acetato de etilo (500 mL). Subsiguientemente, la capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 25%-67%), para producir el compuesto deseado como un sólido blanco (48.7 g, rendimiento de 84%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.12 (18H, d, J = 7.8 Hz), 1.27 (3H, q, J = 8.3 Hz), 1.32 (3H, d, J = 6.3 Hz), 2.60 (1H, s), 3.27-3.33 (1H, m), 3.42 (3H, s), 3.49 (1H, dd, J = 10.3, 4.4 Hz), 3.56-3.65 (2H, m), 4.03 (1H, s), 4.53 (1H, td, J = 6.1,4.4 Hz), 6.31 (1H, br s), 6.41 (1H, t, J = 2.2 Hz), 6.46 (1H, t, J = 3.2 Hz), 6.61 (1H, t, J = 3.2 Hz), 6.67 (1H, t, J = 1.7 Hz), 6.73 (1H, t, J = 2.0 Hz), 9.51 (1H, br s).

(116c) (5S)-2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol

La N-[(2R)-2-hidroxipropil]-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]fenil}-1H-pirrol-2-carboxamida (48.7 g, 96.5 mmol) sintetizada en el ejemplo (116b) se disolvió en tetrahidrofurano (600 mL), y se le agregó ácido metanosulfónico anhidro (33.6 g, 193 mmol) y trietilamina (40.4 mL, 289 mmol), seguido por agitación a 50°C durante 3 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (500 mL) y se extrajo dos veces con acetato de etilo (500 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y al residuo resultante se le agregó éter diisopropílico (300 mL); la suspensión se agitó para producir un sólido blanco que se separó por filtración. El disolvente del licor madre se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-50%). Este se secó al vacío junto con el producto filtrado para producir el compuesto deseado como un sólido blanco (34.8 g, rendimiento de 74%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.11 (18H, d, J = 7.8 Hz), 1.25-1.34 (3H, m), 1.38 (3H, d, J = 6.3 Hz), 1.65 (3H, d, J = 5.9 Hz), 3.43 (3H, s), 3.58-3.65 (2H, m), 3.76 (1H, dd, J = 10.9, 7.8 Hz), 4.28 (1H, dd, J = 11.3, 9.8 Hz), 4.81-4.87 (1H, m), 5.28-5.37 (1H, m), 6.51 (1H, t, J = 2.2 Hz), 6.62 (1H, d, J =

2.0 Hz), 6.91 (1H, s), 7.19 (1H, s), 7.35 (1H, s).

(116d) 3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenol

El (5S)-2-(5-{3-[(1*S*)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]-fenil}-1H-pirrol-2-il)-5-metil-4,5-dihidro-1,3-oxazol (29.5 g, 60.7 mmol) sintetizado en el ejemplo (116c) se disolvió en tetrahidrofurano (400 mL), y se le agregó fluoruro de tetrabutilamonio (solución en tetrahidrofurano 1.0 mol/L, 66 mL, 66 mmol), seguido por agitación durante 1 hora bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y al residuo se le agregó agua (400 mL) y se extrajo dos veces con acetato de etilo (400 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-50%), para producir el compuesto deseado como un sólido blanco (16.7 g, rendimiento de 83%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 1.49 (4H, d, J = 6.3 Hz), 3.42 (3H, s), 3.49 (1H, dd, J = 10.2, 4.7 Hz), 3.59 (1H, dd, J = 10.2, 5.5 Hz), 3.68 (1H, dd, J = 13.3, 7.4 Hz), 4.22 (1H, dd, J = 13.5, 9.2 Hz), 4.52-4.57 (1H, m), 4.97-4.88 (1H, m), 6.34 (1H, t, J = 2.0 Hz), 6.47 (1H, d, J = 3.5 Hz), 6.72 (1H, s), 6.76 (1H, d, J = 3.5 Hz), 7.10 (1H, s).

(116e) 1-{[4-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)fenil]sulfonil}-4-metilpiperazina

El 3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenol (40 mg, 0.12 mmol) sintetizado en el ejemplo (116d), y la 1-[(4-fluorofenil)sulfonil]-4-metilpiperazina (25 mg, 0.15 mmol) sintetizada en el ejemplo (116a), se disolvieron en N,N-dimetilformamida (2 mL) y se les agregó carbonato de potasio (51 mg, 0.37 mmol), seguido por agitación a 100°C durante 1 hora bajo una atmósfera de nitrógeno. Se le agregó nuevamente 1-[(4-fluorofenil)sulfonil]-4-metilpiperazina (30 mg), y la mezcla se agitó a 90°C durante la noche. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (10 mL) y se extrajo dos veces con acetato de etilo (10 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido blanco (25 mg, rendimiento de 35%).

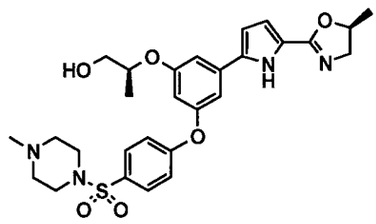
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 5.9 Hz), 1.43 (3H, d, J = 6.3 Hz), 2.29 (3H, s), 2.50 (4H, br s), 3.06 (4H, br s), 3.43 (3H, d, J = 2.4 Hz), 3.50-3.61 (3H, m), 4.10 (1H, dd, J = 14.2, 9.3 Hz), 4.58 (1H, dd, J = 10.5, 6.1 Hz), 4.82-4.86 (1H, m), 6.52 (1H, d, J = 3.4 Hz), 6.55 (1H, t, J = 2.2 Hz), 6.77 (1H, d, J = 3.9 Hz), 6.84 (1H, d, J = 2.0 Hz), 6.98 (1H, s), 7.09 (2H, d, J =

6.8 Hz), 7.71 (2H, d, J = 9.3 Hz).

MS (FAB) m/z: 569.2418 $(M+H)^+$.

EJEMPLO 117

(2S)-2-(3-{5-[(5S)-5-Metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{4-[(4-metilpiperazin-1-il)sulfonil]fenoxi}fenoxi)propan-1-ol



(117a) 3-[(1S)-2-Hidroxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenol

El 3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenol (60 mg, 0.18 mmol) sintetizado en el ejemplo (116d) se disolvió en cloruro de metileno (4 mL), y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 0.38 mL, 0.38 mmol) a -78°C y bajo una atmósfera de nitrógeno. Subsiguientemente, la temperatura se regresó a la temperatura ambiente, seguido por agitación durante 1 hora. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de

gel de sílice (disolvente de elución: hexano/acetato de etilo = 50%-70%), para producir el compuesto deseado como un sólido blanco (41 mg, rendimiento de 72%).

^{1}H-RMN ($CDCl_3$, 400 MHz) δ 1.29 (3H, d, J = 6.3 Hz), 1.49 (3H, d, J = 5.9 Hz), 3.66-3.78 (3H, m), 4.23 (1H, dd, J = 13.7, 9.3 Hz), 4.52 (1H, ddd, J = 14.4, 8.1,4.6 Hz), 4.93 (1H, dq, J = 17.7, 5.0 Hz), 6.32 (1H, t, J = 2.0 Hz), 6.48 (1H, d, J = 3.9 Hz), 6.71 (1H, s), 6.77 (1H, d, J = 3.4 Hz), 7.11 (1H, s), 11.09 (1H, s).

(117b) (2S)-2-(3-{5-[(5S)-5-Metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{4-[(4-metilpiperazin-1-il)sulfonil]fenoxi}fenoxi)propan-1-ol

El 3-[(1S)-2-hidroxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenol (40 mg, 0.13 mmol) sintetizado en el ejemplo (117a), y la 1-[(4-fluorofenil)sulfonil]-4-metilpiperazina (49 mg, 0.19 mmol) sintetizada en el ejemplo (116a), se disolvieron en N,N-dimetilformamida (2 mL) y se les agregó carbonato de potasio (52 mg, 0.38 mmol), seguido por agitación a 100°C durante 4 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (10 mL) y se extrajo dos veces con acetato de etilo (10 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido blanco (17 mg,

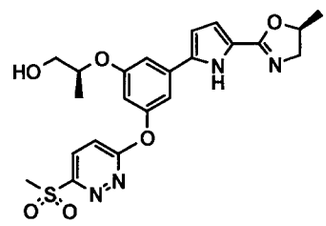
rendimiento de 25%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.29 (3H, d, J = 6.3 Hz), 1.43 (3H, d, J = 6.3 Hz), 2.28 (3H, s), 2.48-2.51 (4H, br m), 3.03 (4H, br s), 3.55 (1H, dd, J = 13.9, 7.2 Hz), 3.77 (2H, d, J = 5.1 Hz), 4.09 (1H, dd, J = 14.1, 9.4 Hz), 4.55-4.60 (1H, m), 4.87-4.81 (1H, m), 6.42 (1H, s), 6.50 (1H, d, J = 3.9 Hz), 6.76 (1H, d, J = 3.5 Hz), 6.83 (1H, s), 6.95 (1H, s), 7.07 (2H, d, J = 8.6 Hz), 7.70 (2H, d, J = 8.6 Hz).

MS (FAB) m/z: 555.2271 $(M+H)^+$.

EJEMPLO 118

(2S)-2-(3-{5-[(5S)-5-Metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridazin-3-il]oxi}fenoxi)propan-1-ol



(118a) 6-Cloropiridazin-3-tiol

Bajo una atmósfera de nitrógeno, se disolvió dicloropiridazina (1.00 g, 6.71 mmol) en metanol (20 mL) y se le agregó una solución acuosa de sulfuro ácido de potasio al 10-20% (20 mL), seguido por calentamiento a reflujo durante 2 horas. El disolvente se removió por destilación bajo presión reducida y el residuo se diluyó con agua, seguido por neutralización con ácido clorhídrico 1N. El precipitado amarillo resultante se separó por filtración, se

lavó con agua y hexano, y subsiguientemente se secó al vacío para producir el compuesto deseado como un sólido amarillo (500 mg, rendimiento de 51%).

^{1}H-RMN ($CDCl_3$, 400 MHz) δ 7.00 (1H, d, J = 9.4 Hz), 7.60 (1H, d, J = 9.4 Hz), 11.68 (1H, br s).

(118b) 3-Cloro-6-(metiltio)piridazina

El 6-cloropiridazin-3-tiol (500 mg, 3.41 mmol) sintetizado en el ejemplo (118a) se disolvió en metanol (20 mL), y se le agregó metóxido de sodio (203 mg, 3.75 mmol) y yodometano (234 mL, 3.75 mmol), seguido por agitación a 60°C durante 30 minutos bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (50 mL) y se extrajo dos veces con acetato de etilo (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-50%), para producir el compuesto deseado como un sólido amarillo (515 mg, rendimiento de 94%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.71 (3H, s), 7.25 (1H, d, J = 9.6 Hz), 7.30 (1H, d, J = 9.0 Hz).

(118c) 3-Cloro-6-(metilsulfonil)piridazina

La 3-cloro-6-(metiltio)piridazina (90 mg, 0.50 mmol) sintetizada en el ejemplo (118b) se disolvió en cloruro de metileno (10 mL) y se le agregó ácido m-cloroperbenzoico (220 mg, 1.00 mmol), seguido por agitación a 0°C

durante 30 minutos bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó agua (20 mL) y se extrajo dos veces con cloruro de metileno (10 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-100%), para producir el compuesto deseado como un sólido blanco (77 mg, rendimiento de 71%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 3.45 (3H, s), 7.81 (1H, d, J = 8.2 Hz), 8.16 (1H, d, J = 8.4 Hz).

(118d) 3-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-6-(metilsulfonil)piridazina

La 3-cloro-6-(metilsulfonil)piridazina (41 mg, 0.27 mmol) sintetizada en el ejemplo (118c), y el 3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenol (80 mg, 0.24 mmol) sintetizado en el ejemplo (116d), se disolvieron en acetonitrilo (2 mL) y se les agregó carbonato de cesio (158 mg, 0.48 mmol), seguido por agitación durante 1 hora bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó agua (10 mL) y se extrajo con acetato de etilo (10 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno =

0%-4%), para producir el compuesto deseado como un sólido blanco (116 mg, rendimiento de 98%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 1.42 (3H, d, J = 6.3 Hz), 3.40 (3H, s), 3.42 (3H, s), 3.48-3.62 (3H, m), 4.07 (1H, dd, J = 13.9, 9.2 Hz), 4.58 (1H, td, J = 6.2, 4.4 Hz), 4.82 (1H, dt, J = 11.7, 4.6 Hz), 6.50 (1H, d, J = 3.5 Hz), 6.69 (1H, t, J = 2.2 Hz), 6.74 (1H, d, J = 3.9 Hz), 6.99 (1H, q, J = 2.0 Hz), 7.09 (1H, t, J = 1.8 Hz), 7.40 (1H, d, J = 9.0 Hz), 8.17 (1H, d, J = 9.0 Hz).

(118e) (2S)-2-(3-{5-[(5S)-5-Metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridazin-3-il]oxi}fenoxi)propan-1-ol

La 3-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-6-(metilsulfonil)piridazina (116 mg, 0.24 mmol) sintetizada en el ejemplo (118d) se disolvió en cloruro de metileno (5 mL), y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 0.26 mL, 0.26 mmol), a -78°C y bajo una atmósfera de nitrógeno. Subsiguientemente la temperatura se regresó a la temperatura ambiente, seguido por agitación durante 4 horas. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado

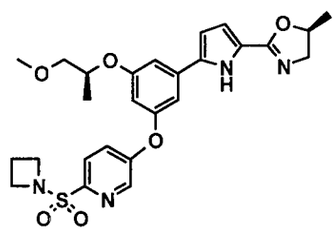
como un sólido blanco (100 mg, rendimiento de 89%).

^{1}H-RMN ($CDCl_3$, 400 MHz) δ 1.30 (3H, d, J = 6.3 Hz), 1.41 (3H, d, J = 6.3 Hz), 3.39 (3H, s), 3.53 (1H, dd, J = 13.7, 7.4 Hz), 3.76-3.77 (2H, m), 4.07 (1H, dd, J = 13.9, 9.2 Hz), 4.56 (1H, dd, J = 10.8, 6.1 Hz), 4.82 (1H, dt, J = 12.0, 4.6 Hz), 6.47 (1H, d, J = 3.5 Hz), 6.61 (1H, t, J = 2.2 Hz), 6.74 (1H, d, J = 3.9 Hz), 6.99 (1H, t, J = 1.6 Hz), 7.03 (1H, t, J = 1.6 Hz), 7.39 (1H, d, J = 9.4 Hz), 8.16 (1H, d, J = 9.4 Hz).

MS (ESI) m/z: 473.15056 $(M+H)^+$.

EJEMPLO 119

2-(Azetidin-1-ilsulfonil)-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-piridina



(119a) 5-Cloropiridin-2-tiol

Bajo una atmósfera de nitrógeno, se disolvió 2,5-dicloropiridina (5.00 g, 33.8 mmol) en sulfóxido de dimetilo (35 mL) y se le agregó disulfuro de sodio nonahidratado (9.00 g, 37.2 mmol), seguido por agitación a 120°C durante 2 horas. La solución de reacción se enfrió a temperatura ambiente y se le agregó agua (50 mL), seguido por neutralización con ácido clorhídrico 5N. El precipitado resultante se separó por filtración, seguido por lavado con

agua y hexano, y subsiguientemente el sólido resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-10%), para producir el compuesto deseado como un sólido amarillo (2.28 g, rendimiento de 46%).

^{1}H-RMN ($CDCl_3$, 400 MHz) δ 2.63 (1H, s), 7.34 (1H, dd, J = 9.0, 2.2 Hz), 7.41 (1H, d, J = 9.3 Hz), 7.70 (1H, s).

(119b) 2-(Azetidin-1-ilsulfonil)-5-cloropiridina

El 5-cloropiridin-2-tiol (1.00 g, 6.87 mmol) sintetizado en el ejemplo (119a) se disolvió en cloruro de metileno (30 mL)/ácido clorhídrico 1N (30 mL), y se enfrió a -5°C. A la solución de reacción se le agregó a gotas una solución acuosa de perclorato de sodio al 7% (30 mL) enfriada con hielo, manteniéndola a 0°C o menos, y se agitó así durante 15 minutos. La capa orgánica se extrajo en un embudo de separación previamente enfriado con hielo, se enfrió a -78°C y se le agregó una solución de clorhidrato de azetidina (2.24 mg, 17.7 mmol), disponible comercialmente, en cloruro de metileno (10 mL), y trietilamina (1.8 mL, 12.9 mmol), y la temperatura se elevó a 0°C, seguido por agitación durante 30 minutos. A la solución de reacción se le agregó agua (50 mL) y se extrajo dos veces con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 5%-

60%), para producir el compuesto deseado como un sólido blanco (735 mg, rendimiento de 46%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.19-2.25 (2H, m), 4.10 (4H, t, J = 7.8 Hz), 7.91 (1H, dd, J = 8.3, 2.0 Hz), 7.95 (1H, d, J = 7.8 Hz), 8.72 (1H, d, J = 2.0 Hz).

(119c) 2-(Azetidin-1-ilsulfonil)-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-piridina

La 2-(azetidin-1-ilsulfonil)-5-cloropiridina (170 mg, 0.73 mmol) sintetizada en el ejemplo (119b), y el 3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenol (230 mg, 0.70 mmol) sintetizado en el ejemplo (116d), se disolvieron en N,N-dimetilformamida (3.5 mL) y se les agregó carbonato de cesio (454 mg, 1.39 mmol), seguido por agitación a 100°C durante 2 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) y se extrajo dos veces con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 5%-50%), para producir el compuesto deseado como un sólido blanco (273 mg, rendimiento de 75%).

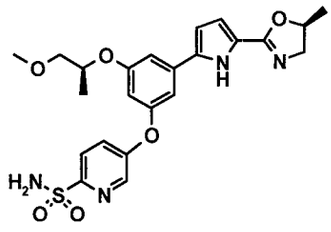
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 1.43 (3H, d, J = 6.3 Hz), 2.18-2.24 (2H, m), 3.42 (3H, s), 3.49-3.61 (3H, m), 4.10 (4H, t, J

= 7.6 Hz), 4.56-4.62 (1H, m), 4.82-4.86 (1H, m), 6.51 (1H, d, J = 3.9 Hz), 6.58 (1H, t, J = 2.0 Hz), 6.76 (1H, d, J = 3.9 Hz), 6.88 (1H, s), 7.04 (1H, s), 7.43 (1H, dd, J = 8.8, 2.9 Hz), 7.94 (1H, d, J = 8.8 Hz), 8.53 (1H, d, J = 2.9 Hz).

MS (ESI) m/z: 527.20527 $(M+H)^+$.

EJEMPLO 120

5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)piridin-2-sulfonamida



(120a) 5-Cloro-N-(4-metoxibencil)piridin-2-sulfonamida

El 5-cloropiridin-2-tiol (1.00 g, 6.87 mmol) sintetizado en el ejemplo (119a) se disolvió en cloruro de metileno (30 mL)/ácido clorhídrico 1N (30 mL) y se enfrió a -5°C. A la solución de reacción se le agregó una solución acuosa de perclorato de sodio al 7% (35 mL) enfriada con hielo, gota a gota, manteniendo la temperatura a 0°C o menos, y se agitó así durante 15 minutos. La capa orgánica se extrajo en un embudo de separación previamente enfriado con hielo y se enfrió a -78°C; se le agregó 4-metoxibencilamina (2.24 mL, 17.7 mmol), disponible comercialmente, y la temperatura se elevó a 0°C, seguido por agitación durante 30 minutos. A la

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solución de reacción se le agregó ácido clorhídrico 0.1N (30 mL) y se extrajo dos veces con cloruro de metileno (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 5%-100%), para producir el compuesto deseado como un sólido blanco (983 mg, rendimiento de 46%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 3.78 (3H, s), 4.20 (2H, d, J = 6.3 Hz), 5.07 (1H, s), 6.79 (2H, dt, J = 9.4, 2.5 Hz), 7.14 (2H, d, J = 8.6 Hz), 7.83 (1H, dd, J = 8.6, 2.3 Hz), 7.90 (1H, d, J = 7.8 Hz), 8.60 (1H, dd, J = 2.3, 0.8 Hz).

(120b) 5-Cloro-N,N-bis(4-metoxibencil)piridin-2-sulfonamida

La 5-cloro-N-(4-metoxibencil)piridin-2-sulfonamida (983 mg, 3.14 mmol) sintetizada en el ejemplo (120a) se disolvió en N,N-dimetilformamida (5 mL), y se le agregó hidruro de sodio (132 mg, 3.30 mmol). Después de enfriar con hielo, se le agregó cloruro de p-metoxibencilo (1.02 mL, 3.37 mmol) y la temperatura se elevó a la temperatura ambiente, seguido por agitación durante 2 horas. A la solución de reacción se le agregó agua (20 mL) y se extrajo dos veces con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-100%), para producir el

compuesto deseado como un sólido blanco (1.14 g, rendimiento de 84%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 3.78 (6H, s), 4.40 (4H, s), 6.75 (4H, dt, J = 9.3,2.5 Hz), 7.05 (4H, dt, J = 8.2, 2.0 Hz), 7.78 (1H, dd, J = 8.2, 2.3 Hz), 7.84 (1H, d, J = 7.8 Hz), 8.55 (1H, d, J = 2.7 Hz).

(120c) N,N-Bis(4-metoxibencil)-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)piridin-2-sulfonamida

La 5-cloro-N,N-bis(4-metoxibencil)piridin-2-sulfonamida (288 mg, 0.67 mmol) sintetizada en el ejemplo (120b), y el 3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenol (220 mg, 0.67 mmol) sintetizado en el ejemplo (116d), se disolvieron en N,N-dimetilformamida (3 mL) y se les agregó carbonato de cesio (434 mg, 1.33 mmol), seguido por agitación a 100°C durante 1 hora bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) y se extrajo dos veces con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0.5%-5%), para producir el compuesto deseado como un sólido blanco (160 mg, rendimiento de 33%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 5.9 Hz), 1.43 (3H, d, J = 6.3 Hz), 3.42 (3H, s), 3.50-3.62 (3H, m), 3.77 (6H, s), 4.09 (1H, dd, J =

13.9, 9.0 Hz), 4.41 (4H, s), 4.56-4.63 (1H, m), 4.81-4.86 (1H, m), 6.52 (1H, d, J = 3.9 Hz), 6.56 (1H, t, J = 2.0 Hz), 6.76 (4H, d, J = 8.8 Hz), 7.07 (4H, d, J = 8.8 Hz), 7.33 (1H, dd, J = 8.5, 2.7 Hz), 7.88 (1H, d, J = 8.8 Hz), 8.39 (1H, d, J = 2.9 Hz).

(120d) 5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)piridin-2-sulfonamida

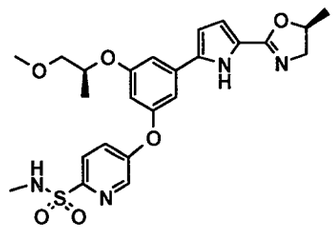
La N,N-bis(4-metoxibencil)-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)piridin-2-sulfonamida (160 mg, 0.24 mmol) sintetizada en el ejemplo (120c), se disolvió en ácido trifluoroacético (2 mL) y se agitó a 40°C durante 8 horas. El disolvente se removió por destilación bajo presión reducida; al residuo se le agregó cloruro de metileno y trietilamina en pequeñas porciones y nuevamente el disolvente se removió por destilación bajo presión reducida. El residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido blanco (106 mg, rendimiento de 99%).

^{1}H-RMN ($CDCl_3$, 400 MHz) δ 1.33 (3H, d, J = 6.3 Hz), 1.42 (3H, d, J = 5.9 Hz), 3.42 (3H, s), 3.49-3.53 (2H, m), 3.59 (1H, dd, J = 10.3, 5.9 Hz), 4.05 (1H, dd, J = 14.2, 9.3 Hz), 4.55-4.61 (1H, m), 4.79-4.86 (1H, m), 5.30 (2H, br s), 6.50 (1H, d, J = 3.9 Hz), 6.56 (1H, t, J = 2.2 Hz), 6.75 (1H, d, J = 3.9 Hz), 6.85 (1H, t, J = 1.7 Hz), 7.03 (1H, t, J = 1.7 Hz), 7.42 (1H, dd, J = 8.5, 2.7 Hz), 7.95 (1H, d, J = 8.8 Hz), 8.42 (1H, d, J = 2.4 Hz).

MS (ESI) m/z: 487.16619 $(M+H)^+$.

EJEMPLO 121

5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-N-metilpiridin-2-sulfonamida



(121a) 5-Cloro-N-metilpiridin-2-sulfonamida

El 5-cloropiridin-2-tiol (1.00 g, 6.87 mmol) sintetizado en el ejemplo (119a) se disolvió en cloruro de metileno (30 mL)/ácido clorhídrico 1N (30 mL), y se enfrió a -5°C. A la solución de reacción se le agregó una solución acuosa de perclorato de sodio al 7% (30 mL) enfriada con hielo, gota a gota, manteniendo la temperatura a 0°C o menos, y se agitó así durante 15 minutos. La capa orgánica se extrajo en un embudo de separación previamente enfriado con hielo, se enfrió a -78°C y se le agregó una solución de metilamina 40% /metanol (1.33 mL, 17.2 mmol), disponible comercialmente, en cloruro de metileno (10 mL), y la temperatura se elevó a 0°C, seguido por agitación durante 2 horas. A la solución de reacción se le agregó agua (50 mL) y se extrajo dos veces con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en

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columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 30%-80%), para producir el compuesto deseado como un sólido blanco (889 mg, rendimiento de 63%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.77 (3H, d, J = 4.9 Hz), 4.81 (1H, s), 7.90 (1H, dd, J = 8.3, 2.4 Hz), 7.97 (1H, d, J = 8.3 Hz), 8.65 (1H, d, J = 2.4 Hz).

(121b) 5-Cloro-N-(4-metoxibencil)-N-metilpiridin-2-sulfonamida

La 5-cloro-N-metilpiridin-2-sulfonamida (889 mg, 4.30 mmol) sintetizada en el ejemplo (121a) se disolvió en N,N-dimetilformamida (15 mL), y se le agregó hidruro de sodio (172 mg, 4.30 mmol). Después de enfriamiento con hielo, se le agregó cloruro de p-metoxibencilo (0.70 mL, 5.16 mmol) y la temperatura se elevó a temperatura ambiente, seguido por agitación durante 3 horas. A la solución de reacción se le agregó agua (20 mL) y se extrajo dos veces con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-20%), para producir el compuesto deseado como un aceite incoloro (817 mg, rendimiento de 58%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.79 (3H, s), 3.81 (3H, s), 4.36 (2H, s), 6.87 (2H, dt, J = 9.4, 2.4 Hz), 7.25 (2H, d, J = 7.3 Hz), 7.88 (1H, dd, J = 8.3,2.4 Hz), 7.94 (1H, d, J = 8.3 Hz), 8.66 (1H, d, J = 2.4 Hz).

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(121c) N-(4-Metoxibencil)-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-N-metilpiridin-2-sulfonamida

La 5-cloro-N-(4-metoxibencil)-N-metilpiridin-2-sulfonamida (228 mg, 0.70 mmol) sintetizada en el ejemplo (121b), y el 3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenol (220 mg, 0.67 mmol) sintetizado en el ejemplo (116d), se disolvieron en N,N-dimetilformamida (3 mL) y se les agregó carbonato de cesio (434 mg, 1.33 mmol), seguido por agitación a 100°C durante 3 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (20 mL) y se extrajo dos veces con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0.5%-5%), para producir el compuesto deseado como un sólido blanco (293 mg, rendimiento de 71%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 1.43 (3H, d, J = 5.9 Hz), 2.79 (3H, s), 3.42 (3H, s), 3.49-3.61 (3H, m), 3.81 (3H, s), 4.08 (1H, dd, J = 13.7, 9.3 Hz), 4.37 (2H, s), 4.55-4.62 (1H, m), 4.80-4.87 (1H, m), 6.51 (1H, d, J = 3.9 Hz), 6.57 (1H, t, J = 2.2 Hz), 6.75 (1H, d, J = 3.9 Hz), 6.87-6.89 (3H, m), 7.03 (1H, s), 7.28 (2H, d, J = 8.8 Hz), 7.41 (1H, dd, J = 8.5, 2.7 Hz), 7.94 (1H, d, J = 8.3 Hz), 8.47 (1H, d, J = 2.4 Hz).

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(121d) 5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-N-metilpiridin-2-sulfonamida

La N-(4-metoxibencil)-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-N-metilpiridin-2-sulfonamida (292 mg, 0.47 mmol) sintetizada en el ejemplo (121c) se disolvió en ácido trifluoroacético (2 mL) y se agitó a 45°C durante 1 hora. El disolvente se removió por destilación bajo presión reducida y al residuo se le agregó cloruro de metileno y trietilamina en pequeñas porciones, y nuevamente el disolvente se removió por destilación bajo presión reducida. El residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-4%), para producir el compuesto deseado como un sólido blanco (208 mg, rendimiento de 88%).

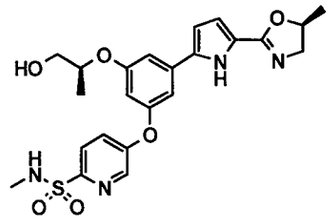
^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 5.9 Hz), 1.43 (3H, d, J = 6.3 Hz), 2.76 (3H, s), 3.41 (3H, s), 3.49-3.61 (3H, m), 4.08 (1H, dd, J = 13.9, 9.0 Hz), 4.61-4.55 (1H, m), 4.84 (1H, dd, J = 15.1, 7.3 Hz), 6.50 (1H, d, J = 3.9 Hz), 6.56 (1H, t, J = 2.2 Hz), 6.76 (1H, d, J = 3.9 Hz), 6.86 (1H, s), 7.04 (1H, s), 7.41 (1H, dd, J = 8.5, 2.7 Hz), 7.96 (1H, d, J = 8.8 Hz), 8.45 (1H, d, J = 2.4 Hz).

MS (ESI) m/z: 501.18090 $(M+H)^+$.

1384

EJEMPLO 122

5-(3-[(1S)-2-Hidroxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-N-metilpiridin-2-sulfonamida



La 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-N-metilpiridin-2-sulfonamida (166 mg, 0.32 mmol) sintetizada en el ejemplo (121d) se disolvió en cloruro de metileno (5 mL), y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 0.34 mL, 0.34 mmol), a -78°C y bajo una atmósfera de nitrógeno. Subsiguientemente, la temperatura se regresó a la temperatura ambiente, seguido por agitación durante 1.5 horas. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con cloruro de metileno. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-4%), para producir el compuesto deseado como un sólido blanco (119 mg, rendimiento de 78%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.30 (3H, d, J = 6.3 Hz), 1.43 (3H, d, J = 6.8 Hz), 2.75 (3H, s), 3.54 (1H, dd, J = 13.7, 7.3 Hz), 3.75-3.77 (2H, m),

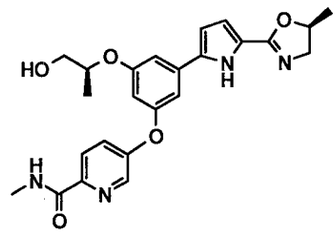
1385

4.08 (1H, dd, J = 9.3, 13.7 Hz), 4.52-4.58 (1H, m), 4.81-4.88 (1H, m), 6.43 (1H, s), 6.47 (1H, d, J = 3.9 Hz), 6.75 (1H, d, J = 4.4 Hz), 6.83 (1H, s), 7.00 (1H, s), 7.39 (1H, dd, J = 8.8, 2.0 Hz), 7.95 (1H, d, J = 8.8 Hz), 8.39 (1H, s).

MS (ESI) m/z: 487.16369 $(M+H)^+$.

EJEMPLO 123

5-(3-[(1S)-2-Hidroxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-N-metilpiridin-2-carboxamida



(123a) 5-Fluoro-N-metilpiridin-2-carboxamida

Se disolvió ácido 5-fluoropiridin-2-carboxílico (495 mg, 3.51 mmol) en cloruro de metileno (10 mL), y se le agregó HOBt·H_2O (591 mg, 3.86 mmol), WSCI·HCl (1.35 g, 7.02 mmol), trietilamina (2.44 mL, 17.5 mmol) y solución de metilamina 40% /metanol (0.82 mL, 10.5 mmol), seguido por agitación durante 15 horas. A la solución de reacción se le agregó agua (30 mL) y se extrajo dos veces con cloruro de metileno (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-50%), para

producir el compuesto deseado como un sólido blanco (490 mg, rendimiento de 91%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 3.03 (3H, d, J = 5.5 Hz), 7.53 (1H, dt, J = 2.7, 8.6 Hz), 7.85 (1H, br s), 8.24 (1H, dd, J = 8.2, 4.7 Hz), 8.38 (1H, d, J = 2.7 Hz).

(123b) 5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-N-metilpiridin-2-carboxamida

La 5-fluoro-N-metilpiridin-2-carboxamida (122 mg, 0.79 mmol) sintetizada en el ejemplo (123a), y el 3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenol (275 mg, 0.83 mmol) sintetizado en el ejemplo (116d), se disolvieron en N,N-dimetilformamida (3 mL) y se les agregó carbonato de potasio (219 mg, 1.58 mmol), seguido por agitación a 100°C durante 3 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (30 mL) y se extrajo dos veces con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido blanco (283 mg, rendimiento de 77%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 1.42 (3H, d, J = 6.3 Hz), 3.03 (3H, d, J = 5.1 Hz), 3.41 (3H, s), 3.48-3.61 (3H, m), 4.08

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(1H, dd, J = 13.9, 9.2 Hz), 4.53-4.60 (1H, m), 4.80-4.86 (1H, m), 6.49 (1H, d, J = 3.9 Hz), 6.53 (1H, t, J = 2.2 Hz), 6.74 (1H, d, J = 3.5 Hz), 6.83 (1H, d, J = 1.6 Hz), 7.00 (1H, s), 7.41 (1H, dd, J = 8.6, 2.7 Hz), 7.86 (1H, br s), 8.17 (1H, d, J = 8.6 Hz), 8.31 (1H, d, J = 2.7 Hz).

(123c) 5-(3-[(1S)-2-Hidroxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-N-metilpiridin-2-carboxamida

La 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-N-metilpiridin-2-carboxamida (176 mg, 0.38 mmol) sintetizada en el ejemplo (123b) se disolvió en cloruro de metileno (5 mL), y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 0.50 mL, 0.50 mmol) a -78°C. Subsiguientemente, la temperatura se regresó a la temperatura ambiente, seguido por agitación durante 1 hora. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con cloruro de metileno. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido blanco (118 mg, rendimiento de 69%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.28 (3H, d, J = 5.9 Hz), 1.42 (3H, d, J = 6.3 Hz), 3.03 (3H, d, J = 5.1 Hz), 3.54 (1H, dd, J = 13.9, 7.2 Hz), 3.76 (2H, d, J = 4.7 Hz), 4.07 (1H, dd, J = 13.9, 9.2 Hz), 4.57 (1H, dd, J = 11.1, 6.1 Hz), 4.83 (1H, dt, J = 11.7, 4.6 Hz), 6.38 (1H, s), 6.45 (1H, d, J = 3.5 Hz), 6.73

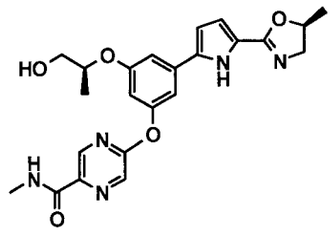
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(1H, d, J = 3.9 Hz), 6.80 (1H, s), 6.93 (1H, s), 7.35 (1H, dd, J = 8.6, 2.7 Hz), 7.87 (1H, d, J = 5.5 Hz), 8.15 (1H, d, J = 8.6 Hz), 8.27 (1H, d, J = 2.7 Hz).

MS (ESI) m/z: 451.19720 $(M+H)^+$.

EJEMPLO 124

5-(3-[(1S)-2-Hidroxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-N-metilpirazin-2-carboxamida



(124a) 5-Cloro-N-metilpirazin-2-carboxamida

Se disolvió ácido 5-cloropirazin-2-carboxílico (1.99 g, 12.6 mmol) en N,N-dimetilformamida (10 mL) y se le agregó HOBt·H_2O (591 mg, 3.86 mmol), WSCI·HCl (1.35 g, 7.02 mmol), N-metilmorfolina (2.76 mL, 25.1 mmol) y solución de metilamina 40% /metanol (2.92 mL, 37.6 mmol), seguido por agitación durante 18 horas. A la solución de reacción se le agregó agua (50 mL) y se extrajo dos veces con acetato de etilo (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-75%), para producir el compuesto deseado como un sólido blanco (585 mg, rendimiento

de 27%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 3.03 (3H, d, J = 4.9 Hz), 7.60 (1H, br s), 8.09 (1H, d, J = 1.5 Hz), 8.93 (1H, d, J = 1.0 Hz).

(124b) 5-(3-[(1S)-2-Hidroxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-N-metilpirazin-2-carboxamida

La 5-cloro-N-metilpirazin-2-carboxamida (171 mg, 1.00 mmol) sintetizada en el ejemplo (124a), y el 3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenol (300 mg, 0.91 mmol) sintetizado en el ejemplo (116d), se disolvieron en N,N-dimetilformamida (3 mL) y se les agregó carbonato de potasio (376 mg, 2.72 mmol), seguido por agitación a 100°C durante 5 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó 5-cloro-N-metilpirazin-2-carboxamida (110 mg, 0.64 mmol) y se agitó durante 3 horas. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (30 mL) y se extrajo dos veces con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir un sólido blanco (206 mg).

Este producto se disolvió en cloruro de metileno (5 mL) y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 0.57 mL, 0.57 mmol) a -78°C. Subsiguientemente, la temperatura se regresó a la

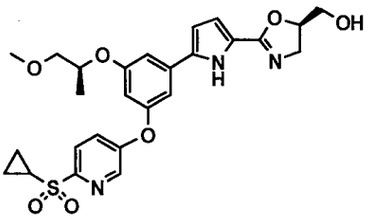
temperatura ambiente, seguido por agitación durante 1.5 horas. La solución de reacción se enfrió nuevamente a -78°C, se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 1.00 mL, 1.00 mmol), y la temperatura se regresó a la temperatura ambiente, seguido por agitación durante 3 horas. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con cloruro de metileno. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido blanco (87.8 mg, rendimiento de 21%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J = 5.9 Hz), 1.43 (3H, d, J = 6.3 Hz), 3.05 (3H, d, J = 5.4 Hz), 3.55 (1H, dd, J = 13.9, 7.6 Hz), 3.77 (2H, d, J = 5.4 Hz), 4.09 (1H, dd, J = 13.9, 9.0 Hz), 4.56 (1H, dd, J = 11.2, 5.9 Hz), 4.87-4.80 (1H, m), 6.49 (1H, d, J = 3.4 Hz), 6.60 (1H, s), 6.75 (1H, d, J = 3.9 Hz), 6.93 (1H, s), 7.00 (1H, s), 7.62 (1H, d, J = 4.9 Hz), 8.29 (1H, s), 8.93 (1H, d, J = 1.0 Hz).

MS (ESI) m/z: 452.19252 $(M+H)^+$.

EJEMPLO 125

{(5R)-2-[5-(3-{[6-(Ciclopropilsulfonil)piridin-3-il]oxi}-5-[(1S)-2-metoxi-1-metiletoxi]fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol



(125a) 5-Cloro-2-[(3-cloropropil)tio]piridina

El 5-cloropiridin-2-tiol (600 mg, 4.12 mmol) sintetizado en el ejemplo (119a) se disolvió en metanol (15 mL), y se le agregó una solución de metóxido de sodio 28% /metanol (0.95 mL, 4.94 mmol) y 1-bromo-3-cloropropano (0.61 mL, 6.18 mmol), seguido por agitación a 60°C durante 1.5 horas. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (40 mL) y se extrajo dos veces con acetato de etilo (40 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida; se secó al vacío para producir el compuesto deseado como un aceite incoloro (849 mg, rendimiento de 92%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.26-2.31 (2H, m), 3.55-3.58 (2H, m), 3.67 (2H, t, J = 6.3 Hz), 7.96 (1H, dd, J = 8.3,2.0 Hz), 8.06 (1H, d, J = 7.8 Hz), 8.70 (1H, d, J = 2.4 Hz).

(125b) 5-Cloro-2-[(3-cloropropil)sulfonil]piridina

La 5-cloro-2-[(3-cloropropil)tio]piridina (846 mg, 3.80 mmol)

sintetizada en el ejemplo (125a) se disolvió en cloruro de metileno (20 mL) y subsiguientemente se le agregó ácido m-cloroperbenzoico (2.02 g, 7.62 mmol) enfriando con hielo, seguido por agitación así durante 1 hora. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio (40 mL) y se extrajo dos veces con cloruro de metileno (40 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-20%), para producir el compuesto deseado como un aceite incoloro (733 mg, rendimiento de 76%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.21-2.14 (2H, m), 3.30 (2H, t, J = 6.8 Hz), 3.67 (2H, t, J = 6.3 Hz), 7.13 (1H, dd, J = 8.6, 0.8 Hz), 7.45 (1H, dd, J = 8.6, 2.3 Hz), 8.37 (1H, dd, J = 5.1,3.1 Hz).

(125c) 5-Cloro-2-(ciclopropilsulfonil)piridina

La 5-cloro-2-[(3-cloropropil)sulfonil]piridina (732 mg, 3.05 mmol) sintetizada en el ejemplo (125b) se disolvió en tetrahidrofurano (10 mL) y se enfrió a -30°C; subsiguientemente se le agregó t-butóxido de potasio (582 mg, 5.18 mmol), seguido por agitación así durante 30 minutos. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (40 mL) y se extrajo dos veces con cloruro de metileno (40 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión

reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-25%), para producir el compuesto deseado (397 mg, rendimiento de 60%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.07-1.12 (2H, m), 1.37-1.41 (2H, m), 2.76-2.83 (1H, m), 7.91 (1H, dd, J = 8.2, 2.3 Hz), 7.98 (1H, d, J = 8.2 Hz), 8.71 (1H, dd, J = 2.3, 0.8 Hz).

(125d) N-[(2S)-2,3-Dihidroxipropil]-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]fenil}-1H-pirrol-2-carboxamida

El ácido 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]-fenil}-1H-pirrol-2-carboxílico (9.32 g, 20.8 mmol) sintetizado en el ejemplo (106c) se disolvió en metanol (200 mL), y se le agregó (S)-(-)-3-amino-1,2-propanodiol (5.01 g, 55.0 mmol) y cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio n-hidratado (10.13 g, 32.3 mmol), seguido por agitación a temperatura ambiente durante la noche bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y al residuo resultante se le agregó agua (300 mL) y acetato de etilo (200 mL), y la solución se separó. La capa orgánica se lavó con salmuera saturada; subsiguientemente se secó sobre sulfato de magnesio anhidro y el disolvente se removió por destilación bajo presión reducida. El residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 70%-100%), para producir el producto deseado como un aceite incoloro (9.32 g, rendimiento de 86%).

^{1}H-RMN ($CDCl_3$, 400 Hz): δ 1.11 (18H, d, J = 7.0 Hz), 1.22-1.29

1394

(3H, m), 1.31 (3H, d, J = 6.3 Hz), 3.07-3.14 (2H, m), 3.42 (3H, s), 3.50 (1H, dd, J = 10.2, 4.3 Hz), 3.54-3.66 (5H, m), 3.83-3.90 (1H, m), 4.49-4.57 (1H, m), 6.34 (1H, t, J = 6.5 Hz), 6.42 (1H, t, J = 2.3 Hz), 6.46 (1H, dd, J = 3.9, 2.7 Hz), 6.63 (1H, dd, J = 3.9, 2.3 Hz), 6.67 (1H, t, J = 1.6 Hz), 6.73 (1H, t, J = 1.6 Hz), 9.55 (1H, br s).

(125e) N-{(2S)-2-Hidroxi-3-[(triisopropilsilil)oxi]propil}-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]fenil}-1H-pirrol-2-carboxamida

La N-[(2S)-2,3-dihidroxipropil]-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]fenil}-1H-pirrol-2-carboxamida (9.30 g, 17.9 mmol) sintetizada en el ejemplo (125d) se disolvió en cloruro de metileno (180 mL), y se le agregó cloruro de triisopropilsililo (4.25 mL, 19.9 mmol), trietilamina (7.45 mL, 53.5 mmol) y 4-dimetilaminopiridina (2.20 g, 18.0 mmol), seguido por agitación a temperatura ambiente durante 2.5 horas bajo una atmósfera de nitrógeno. Se le agregó agua (300 mL) para separar la solución, y la capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 10%-35%), para producir el compuesto deseado como un aceite incoloro (10.56 g, rendimiento de 87%).

^{1}H-RMN ($CDCl_3$, 400 Hz): δ 1.18-1.06 (39H, m), 1.22-1.30 (3H, m), 1.32 (3H, d, J = 6.3 Hz), 3.20 (1H, d, J = 4.3 Hz), 3.38-3.44 (1H, m), 3.42 (3H, s), 3.49 (1H, dd, J = 10.2, 4.3 Hz), 3.59 (1H, dd, J = 10.2, 5.5 Hz), 3.66-

3.79 (3H, m), 3.85-3.91 (1H, m), 4.49-4.56 (1H, m), 6.30 (1H, t, J = 5.9 Hz), 6.41 (1H, t, J = 2.0 Hz), 6.45 (1H, dd, J = 3.9, 2.7 Hz), 6.59 (1H, dd, J = 3.9, 2.3 Hz), 6.66 (1H, t, J = 2.0 Hz), 6.72 (1H, t, J = 2.0 Hz), 9.34 (1H, br s).

(125f) (5R)-2-(5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-[(triisopropilsilil)-oxi]fenil}-1H-pirrol-2-il)-5{[(triisopropilsilil)oxi]metil}-4,5-dihidro-1,3-oxazol

La N-{(2S)-2-hidroxi-3-[(triisopropilsilil)oxi]propil}-5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]fenil}-1H-pirrol-2-carboxamida (10.54 g, 15.6 mmol) sintetizada en el ejemplo (125e) se disolvió en tetrahidrofurano (160 mL), y se le agregó ácido metanosulfónico anhidro (5.51 g, 31.6 mmol) y trietilamina (8.70 mL, 62.4 mmol), seguido por agitación a temperatura ambiente durante 3 horas bajo una atmósfera de nitrógeno; subsiguientemente la temperatura se elevó a 60°C, seguido por agitación durante 3 horas. A la solución de reacción se le agregó agua (200 mL) y se extrajo con acetato de etilo (300 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 5%-30%), para producir el compuesto deseado como un aceite pardo (9.72 g, rendimiento de 95%).

^{1}H-RMN ($CDCl_3$, 400 Hz): δ 1.04-1.14 (39H, m), 1.22-1.29 (3H, m), 1.32 (3H, d, J = 6.3 Hz), 3.42 (3H, s), 3.48 (1H, dd, J = 10.2, 4.3 Hz), 3.59 (1H, dd, J = 10.2, 5.9 Hz), 3.85-3.90 (3H, m), 4.02 (1H, dd, J = 14.1,9.8 Hz), 4.48-4.54 (1H, m), 4.72-4.78 (1H, m), 6.39 (1H, t, J = 2.0 Hz), 6.45 (1H, d, J =

3.9 Hz), 6.67 (1H, t, J = 2.0 Hz), 6.71 (1H, t, J = 2.0 Hz), 6.73 (1H, d, J = 3.9 Hz).

(125g) 3-{5-[(5R)-5-(Hidroxilmetil)-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenol

El (5R)-2-(5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-[(triisopropilsilil)oxi]-fenil}-1H-pirrol-2-il)-5{[(triisopropilsilil)oxi]metil}-4,5-dihidro-1,3-oxazol (9.69 g, 14.7 mmol) sintetizado en el ejemplo (125f) se disolvió en tetrahidrofurano (150 mL), y se le agregó a gotas fluoruro de tetrabutilamonio (solución en tetrahidrofurano 1 mol/L, 30.0 mL, 30 mmol), a 0°C, seguido por agitación a 0°C durante 30 minutos. Se le agregó una solución acuosa saturada de cloruro de amonio (200 mL) y se extrajo con acetato de etilo (200 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 3%-7%), para producir el compuesto deseado como un sólido amarillo pálido (6.50 g, rendimiento de ~100%).

^{1}H-RMN ($CDCl_3$, 400 Hz): δ 1.31 (3H, d, J = 6.3 Hz), 3.41 (3H, s), 3.48 (1H, dd, J = 10.2, 4.3 Hz), 3.58 (1H, dd, J = 10.2, 5.9 Hz), 3.78 (1H, dd, J = 12.5,5.5 Hz), 3.92-3.97 (2H, m), 4.12 (1H, dd, J = 13.7, 9.8 Hz), 4.51-4.59 (1H, m), 4.88-4.94 (1H, m), 6.39 (1H, t, J = 2.0 Hz), 6.47 (1H, d, J = 3.5 Hz), 6.72 (1H, s), 6.82 (1H, d, J = 3.9 Hz), 7.06 (1H, s), 11.05 (1H, br s).

(125h) {(5R)-2-[5-(3-{[6-(Ciclopropilsulfonil)piridin-3-il]oxi}-5-[(1S)-2-metoxi-1-metiletoxi]fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol

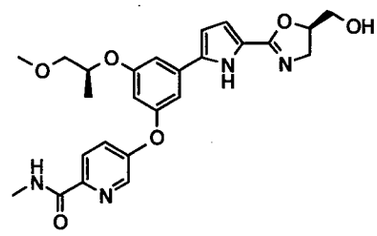
La 5-cloro-2-(ciclopropilsulfonil)piridina (168 mg, 0.77 mmol) sintetizada en el ejemplo (125c), y el 3-{5-[(5R)-5-(hidroxilmetil)-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenol (401 mg, 1.16 mmol) sintetizado en el ejemplo (125g), se disolvieron en N,N-dimetilformamida (2 mL) y se les agregó carbonato de potasio (213 mg, 154 mmol), seguido por agitación a 100°C durante 3 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (30 mL) y se extrajo dos veces con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0.5%-5%), para producir el compuesto deseado como un sólido blanco (139 mg, rendimiento de 34%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.06-1.11 (2H, m), 1.31 (3H, d, J = 6.3 Hz), 1.37-1.41 (2H, m), 2.76-2.83 (1H, m), 3.42 (3H, d, J = 2.3 Hz), 3.50 (1H, dd, J = 10.2, 3.9 Hz), 3.59 (1H, dd, J = 10.2, 6.3 Hz), 3.68-3.79 (2H, m), 3.87 (1H, dd, J = 12.3, 2.9 Hz), 4.03 (1H, dd, J = 14.1, 9.8 Hz), 4.60-4.53 (1H, m), 4.84-4.77 (1H, m), 6.49 (1H, d, J = 3.9 Hz), 6.57 (1H, t, J = 2.2 Hz), 6.75 (1H, d, J = 3.9 Hz), 6.86 (1H, t, J = 1.8 Hz), 7.03 (1H, s), 7.42 (1H, dd, J = 8.6, 2.7 Hz), 7.97 (1H, d, J = 8.6 Hz), 8.51 (1H, d, J = 2.7 Hz).

MS (ESI) m/z: 528.17975 $(M+H)^+$.

EJEMPLO 126

5-(3-{5-[(5R)-5-(Hidroximetil)-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)-N-metilpiridin-2-carboxamida



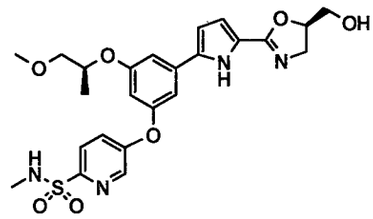
La 5-fluoro-N-metilpiridin-2-carboxamida (150 mg, 0.97 mmol) sintetizada en el ejemplo (123a), y el 3-{5-[(5R)-5-(hidroxilmetil)-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenol (438 mg, 1.27 mmol) sintetizado en el ejemplo (125 g), se disolvieron en N,N-dimetilformamida (3 mL) y se les agregó carbonato de potasio (269 mg, 1.95 mmol), seguido por agitación a 100°C durante 3 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (30 mL) y se extrajo dos veces con acetato de etilo (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido blanco (281 mg, rendimiento de 60%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.30 (3H, d, J = 6.3 Hz), 3.03 (3H, d, J = 4.9 Hz), 3.41 (3H, s), 3.49 (1H, dd, J = 10.3, 3.9 Hz), 3.58 (1H, dd, J = 10.3, 6.3 Hz), 3.69 (1H, dd, J = 11.7, 5.4 Hz), 3.76 (1H, dd, J = 13.9, 7.1 Hz), 3.85 (1H, d, J = 12.2 Hz), 4.02 (1H, dd, J = 14.2, 9.3 Hz), 4.58-4.52 (1H, m), 4.78 (1H, s), 6.47 (1H, d, J = 3.9 Hz), 6.54 (1H, t, J = 2.2 Hz), 6.73 (1H, d, J = 3.4 Hz), 6.83 (1H, t, J = 1.7 Hz), 6.98 (1H, s), 7.40 (1H, dd, J = 8.8, 2.9 Hz), 7.86 (1H, d, J = 4.4 Hz), 8.16 (1H, d, J = 8.3 Hz), 8.30 (1H, d, J = 2.4 Hz).

MS (ESI) m/z: 481.20954 $(M+H)^+$.

EJEMPLO 127

5-(3-{5-[(5R)-5-(Hidroximetil)-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)-N-metilpiridin-2-sulfonamida



(127a) 5-(3-{5-[(5R)-5-Hidroximetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)-N-(4-metoxibencil)-N-metilpiridin-2-sulfonamida

La 5-cloro-N-(4-metoxibencil)-N-metilpiridin-2-sulfonamida (427 mg, 1.31 mmol) sintetizada en el ejemplo (121b), y el 3-{5-[(5R)-5-(hidroxilmetil)-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenol (568 mg, 1.64 mmol) sintetizado en el ejemplo (125g), se

disolvieron en N,N-dimetilformamida (5 mL) y se les agregó carbonato de potasio (361 mg, 2.61 mmol), seguido por agitación a 100°C durante 2 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (40 mL) y se extrajo dos veces con acetato de etilo (40 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-3.5%), para producir el compuesto deseado como un sólido blanco (228 mg, rendimiento de 27%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.31 (3H, d, J = 5.9 Hz), 2.79 (3H, s), 3.43 (3H, s), 3.51 (1H, dd, J = 10.3, 3.9 Hz), 3.59 (1H, dd, J = 10.3, 6.3 Hz), 3.69-3.73 (1H, m), 3.75-3.81 (4H, m), 3.87 (1H, d, J = 12.2 Hz), 4.04 (1H, dd, J = 14.2, 9.8 Hz), 4.37 (2H, s), 4.55-4.58 (1H, m), 4.79-4.84 (1H, m), 6.50 (1H, d, J = 3.9 Hz), 6.58 (1H, t, J = 2.2 Hz), 6.76 (1H, d, J = 3.9 Hz), 6.85 (1H, s), 6.88 (2H, d, J = 8.8 Hz), 6.99 (1H, s), 7.28 (3H, d, J = 8.8 Hz), 7.42 (1H, dd, J = 8.8, 2.9 Hz), 7.94 (1H, d, J = 8.8 Hz), 8.47 (1H, d, J = 2.4 Hz).

(127b) 5-(3-{5-[(5R)-5-(Hidroximetil)-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)-N-metilpiridin-2-sulfonamida

La 5-(3-{5-[(5R)-5-hidroximetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)-N-(4-metoxibencil)-N-metilpiridin-2-sulfonamida (292 mg, 0.47 mmol) sintetizada en el ejemplo (127a) se disolvió en ácido trifluoroacético (2 mL) y se agitó a 45°C durante 6

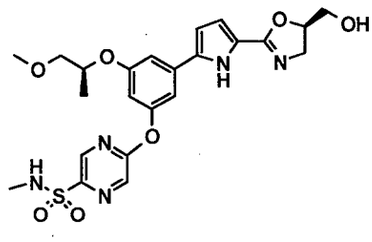
horas. El disolvente se removió por destilación bajo presión reducida y al residuo se le agregó cloruro de metileno y trietilamina en pequeñas porciones, y nuevamente el disolvente se removió por destilación bajo presión reducida. El residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-4%), para producir el compuesto deseado como un sólido blanco (184 mg, rendimiento de 100%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 5.9 Hz), 1.43 (3H, d, J = 6.3 Hz), 2.76 (3H, s), 3.41 (3H, s), 3.49-3.61 (3H, m), 4.08 (1H, dd, J = 13.9, 9.0 Hz), 4.61-4.55 (1H, m), 4.84 (1H, dd, J = 15.1, 7.3 Hz), 6.50 (1H, d, J = 3.9 Hz), 6.56 (1H, t, J = 2.2 Hz), 6.76 (1H, d, J = 3.9 Hz), 6.86 (1H, s), 7.04 (1H, s), 7.41 (1H, dd, J = 8.5, 2.7 Hz), 7.96 (1H, d, J = 8.8 Hz), 8.45 (1H, d, J = 2.4 Hz).

MS (ESI) m/z: 517.17549 $(M+H)^+$.

EJEMPLO 128

5-(3-{5-[(5R)-5-(Hidroximetil)-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)-N-metilpirazin-2-sulfonamida



(128a) 5-Bromopirazin-2-tiol

Bajo una atmósfera de nitrógeno, se disolvió 2,5-dibromopirazina

(300 mg, 1.26 mmol) en sulfóxido de dimetilo (3 mL), y se le agregó disulfuro de sodio nonahidratado (454 mg, 1.89 mmol), seguido por agitación a 100°C durante 1.5 horas. La solución de reacción se enfrió a temperatura ambiente y se le agregó agua (30 mL), seguido por neutralización con ácido clorhídrico 5N. Después, el precipitado resultante se separó por filtración y se lavó con agua; el sólido resultante se disolvió en éter dietílico/tetrahidrofurano y el material insoluble se separó por filtración. El disolvente se removió por destilación bajo presión reducida y el residuo se secó al vacío para producir el compuesto deseado como un sólido anaranjado (163 mg, rendimiento de 68%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 3.19 (1H, s), 7.97 (1H, d, J = 1.0 Hz), 8.34 (1H, d, J = 1.0 Hz).

(128b) 5-Bromo-N-metilpirazin-2-sulfonamida

El 5-bromopirazin-2-tiol (988 mg, 5.17 mmol) sintetizado en el ejemplo (128a) se disolvió en cloruro de metileno (15 mL) /ácido clorhídrico 1N (15 mL), y se enfrió a -10°C. A la solución de reacción se le agregó a gotas una solución acuosa de perclorato de sodio al 7% (15 mL) enfriada con hielo, manteniendo la temperatura a -5°C o menos, y se agitó así durante 1 hora. La capa orgánica se extrajo en un embudo de separación previamente enfriado con hielo y se enfrió a 0°C; se le agregó una solución de metilamina 40% /metanol (1.00 mL, 12.9 mmol), y la temperatura se regresó a la temperatura ambiente, seguido por agitación durante 17 horas. A la solución de reacción

se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo dos veces con cloruro de metileno (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-30%), para producir el compuesto deseado como un sólido blanco (147 mg, rendimiento de 11%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.83 (3H, d, J = 5.5 Hz), 4.80 (1H, s), 8.76 (1H, d, J = 1.6 Hz), 8.96 (1H, d, J = 1.2 Hz).

(128c) 5-(3-{5-[(5R)-5-(Hidroximetil)-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)-N-metilpirazin-2-sulfonamida

La 5-bromo-N-metilpirazin-2-sulfonamida (147 mg, 0.58 mmol) sintetizada en el ejemplo (128b), y el 3-{5-[(5R)-5-(hidroxilmetil)-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenol (262 mg, 0.76 mmol) sintetizado en el ejemplo (125g), se disolvieron en acetonitrilo (6 mL) y se les agregó carbonato de potasio (161 mg, 1.17 mmol), seguido por agitación durante 4 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó agua (20 mL) y se extrajo dos veces con acetato de etilo (20 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se

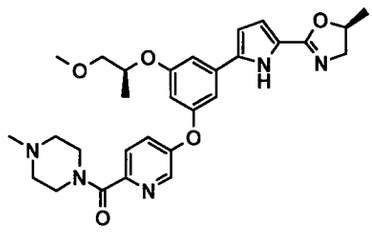
purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-3.5%), para producir el compuesto deseado como un sólido blanco (161 mg, rendimiento de 54%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 2.81 (3H, s), 3.42 (3H, s), 3.51 (1H, dd, J = 10.3, 3.9 Hz), 3.60 (1H, dd, J = 10.3, 5.9 Hz), 3.68-3.76 (2H, m), 3.85 (1H, dd, J = 12.2, 3.4 Hz), 4.00 (1H, dd, J = 14.2, 9.8 Hz), 4.60-4.54 (1H, m), 4.76-4.82 (1H, m), 5.23 (1H, s), 6.49 (1H, d, J = 3.9 Hz), 6.66 (1H, t, J = 2.0 Hz), 6.75 (1H, d, J = 3.4 Hz), 6.96 (1H, t, J = 1.7 Hz), 7.06 (1H, t, J = 2.0 Hz), 8.44 (1H, d, J = 1.5 Hz), 8.70 (1H, d, J = 1.0 Hz).

MS (ESI) m/z: 518.17036 $(M+H)^+$.

EJEMPLO 129

1-{[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)piridin-2-il]carbonil}-4-metilpiperazina



(129a) 5-Fluoro-piridin-2-carboxilato de metilo

Se disolvió 2-bromo-5-fluoro-piridina (3.80 g, 21.6 mmol), disponible comercialmente, en metanol (50 mL), y se le agregó N,N-dimetilformamida (50 mL), acetato de paladio (484 mg, 2.16 mmol), 1,1-bis(difenilfosfino)ferroceno (2.39 g, 4.32 mmol) y trietilamina (6.0 mL, 43.2

mmol), seguido por agitación a temperatura ambiente durante 3 días bajo una atmósfera de monóxido de carbono; el material insoluble se separó de la solución de reacción por filtración. Se le agregó agua (100 mL), seguido por extracción con acetato de etilo (100 mL); la capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-50%), para producir el compuesto deseado como un sólido amarillo pálido (2.87 g, rendimiento de 86%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 4.01 (3H, s), 7.54 (1H, dt, J = 8.6, 3.9 Hz), 8.20 (1H, dd, J = 8.6, 4.7 Hz), 8.59 (1H, d, J = 2.7 Hz).

(129b) 5-(3-{5-[(Benciloxi)carbonil]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)piridin-2-carboxilato de metilo

El 5-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-1,2-dicarboxilato de 2-bencilo-1-t-butilo (4.08 g, 8.47 mmol) sintetizado en el ejemplo (78g), y el 5-fluoro piridin-2-carboxilato de metilo (1.45 g, 9.32 mmol) sintetizado en el ejemplo (129a), se disolvieron en N,N-dimetilformamida (30 mL) y se les agregó carbonato de potasio (3.51 g, 25.4 mmol), seguido por agitación a 100°C durante 3 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (100 mL) y se extrajo con acetato de etilo (100 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión

reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: acetato de etilo/hexano = 0%-35%).

El sólido amarillo resultante se disolvió en cloruro de metileno (5 mL) y se le agregó ácido trifluoroacético (7.5 mL), seguido por agitación a temperatura ambiente durante 1 hora. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio (50 mL) y se extrajo dos veces con acetato de etilo (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido amarillo pálido (3.26 g, rendimiento de 75%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 3.40 (3H, s), 3.50 (1H, dd, J = 10.2, 3.9 Hz), 3.58 (1H, dd, J = 10.4, 6.5 Hz), 4.00 (3H, s), 4.52-4.59 (1H, m), 5.32 (2H, s), 6.50 (1H, t, J = 2.9 Hz), 6.59 (1H, s), 6.83 (1H, s), 6.99-6.97 (2H, m), 7.34-7.44(5H, m), 8.12 (1H, d, J = 8.6 Hz), 8.52 (1H, d, J = 2.7 Hz), 9.22 (1H, s).

(129c) Acido 5-(3-{[6-(metoxicarbonil)]piridin-3-il]oxi}-5-[(1S)-2-metoxi-1-metiletoxi]fenil)-1H-pirrol-2-carboxílico

El 5-(3-{5-[(benciloxi)carbonil]-1H-pirrol-2-il}-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi)piridin-2-carboxilato de metilo (3.18 g, 6.16 mmol) sintetizado en el ejemplo (129b) se disolvió en ácido fórmico 5% /etanol (200 mL), y se le

agregó un catalizador de paladio al 10% en carbón (2.00 g), seguido por agitación durante 2 horas bajo una atmósfera de hidrógeno. El catalizador de paladio en carbón se removió por filtración en Celite, seguido por lavado con tetrahidrofurano. El disolvente se removió por destilación bajo presión reducida, seguido por dilución con cloruro de metileno (100 mL), lavado con agua y secado sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida para producir el compuesto deseado como un sólido blanco (2.41 g, rendimiento de 92%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.33 (3H, d, J = 6.3 Hz), 3.46 (3H, s), 3.54 (1H, dd, J = 10.2, 3.9 Hz), 3.66 (1H, dd, J = 10.2, 6.6 Hz), 4.00 (3H, s), 4.71 (1H, td, J = 6.3, 4.3 Hz), 6.49 (1H, dd, J = 3.9, 2.7 Hz), 6.59 (1H, d, J = 2.0 Hz), 6.92 (1H, t, J = 1.6 Hz), 7.02 (1H, dd, J = 3.9, 2.3 Hz), 7.39 (1H, dd, J = 8.8, 2.9 Hz), 8.13 (1H, d, J = 8.6 Hz), 8.57 (1H, d, J = 2.7 Hz), 10.46 (1H, s).

(129d) 5-(3-{[(2R)-2-Hidroxipropil]carbamoil}-1H-pirrol-2-il)-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi}piridin-2-carboxilato de metilo

El ácido 5-(3-{[6-(metoxicarbonil)]piridin-3-il]oxi}-5-[(1S)-2-metoxi-1-metiletoxi]fenil)-1H-pirrol-2-carboxílico (800 mg, 1.87 mmol) sintetizado en el ejemplo (129c) se disolvió en metanol (20 mL), y se le agregó (R)-(-)-1-amino-2-propanol (339 μL, 4.30 mol) y cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio n-hidratado (829 mg, 2.99 mmol), seguido por agitación a temperatura ambiente durante 16 horas bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente

de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido blanco (726 mg, rendimiento de 80%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.25 (3H, d, J = 6.6 Hz), 1.32 (3H, d, J = 6.3 Hz), 3.25-3.32 (1H, m), 3.41 (3H, s), 3.51 (1H, dd, J = 10.2, 3.9 Hz), 3.57-3.65 (2H, m), 4.05 (3H, s), 4.58 (1H, td, J = 6.3, 4.0 Hz), 6.35 (1H, s), 6.48 (1H, dd, J = 3.9, 3.1 Hz), 6.57 (1H, t, J = 2.2 Hz), 6.61 (1H, dd, J = 3.9, 2.3 Hz), 6.85 (1H, t, J = 1.8 Hz), 7.00 (1H, t, J = 1.8 Hz), 7.36 (1H, dd, J = 8.8, 2.9 Hz), 8.12 (1H, d, J = 9.0 Hz), 8.53 (1H, d, J = 2.7 Hz), 9.66 (1H, s).

(129e) 5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)piridin-2-carboxilato de metilo

El 5-(3-{[(2R)-2-hidroxipropil]carbamoil}-1H-pirrol-2-il)-5-[(1S)-2-metoxi-1-metiletoxi]fenoxi}piridin-2-carboxilato de metilo (726 mg, 1.50 mmol) sintetizado en el ejemplo (129d) se disolvió en tetrahidrofurano (20 mL), y se le agregó ácido metanosulfónico anhidro (523 mg, 3.00 mmol) y trietilamina (0.63 mL, 4.50 mmol), seguido por agitación a 50°C durante 5 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo con cloruro de metileno (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-7.5%), para producir el compuesto deseado como un sólido amarillo pálido (264 mg, rendimiento de 38%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 1.42 (3H, d, J = 6.3 Hz), 3.41 (3H, d, J = 3.1 Hz), 3.54 (3H, ddt, J = 26.4, 11.3, 4.4 Hz), 4.01 (3H, s), 4.04-4.11 (1H, m), 4.60-4.53 (1H, m), 4.87-4.78 (1H, m), 6.49 (1H, d, J = 3.9 Hz), 6.55 (1H, t, J = 2.0 Hz), 6.75 (1H, d, J = 3.9 Hz), 6.83 (1H, t, J = 1.8 Hz), 6.99 (1H, t, J = 2.0 Hz), 7.35 (1H, dd, J = 8.6, 2.7 Hz), 8.12 (1H, d, J = 9.0 Hz), 8.53 (1H, d, J = 2.7 Hz).

(129f) Acido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)piridin-2-carboxílico

El 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)piridin-2-carboxilato de metilo (264 mg, 0.57 mmol) sintetizado en el ejemplo (129e) se disolvió en metanol (20 mL), y se le agregó agua (3 mL) e hidróxido de litio monohidratado (71 mg, 1.70 mmol), seguido por agitación a 50°C durante 1 hora bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (50 mL), seguido por extracción dos veces con cloruro de metileno (40 mL), lavado con salmuera saturada y secado sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida; se secó al vacío para producir el compuesto deseado como un sólido amarillo pálido (256 mg, rendimiento de 100%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.40 (3H, d, J = 6.3 Hz), 1.67 (3H, d, J = 6.3 Hz), 3.43 (3H, s), 3.58-3.65 (2H, m), 3.78 (1H, dd, J = 11.2, 7.8 Hz), 4.29 (1H, t, J = 10.3 Hz), 4.84-4.90 (1H, m), 5.30-5.36 (1H, m), 6.65 (1H, d, J = 3.9 Hz), 6.69 (1H, t, J = 2.2 Hz), 7.21 (2H, s), 7.50 (1H, dd, J = 7.3, 3.4 Hz),

7.56 (1H, s), 8.18 (1H, s), 8.39 (1H, d, J = 2.4 Hz).

(129g) 1-{[5-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)piridin-2-il]carbonil}-4-metilpiperazina

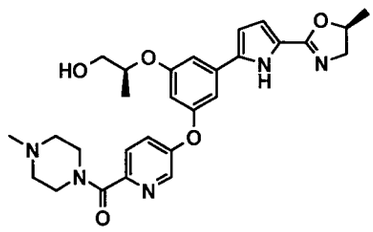
El ácido 5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)piridin-2-carboxílico (270 mg, 0.60 mmol) sintetizado en el ejemplo (129f) se disolvió en tetrahidrofurano (5 mL), y se le agregó N-metilpiperazina (199 μl, 1.79 mmol), HATU (454 mg, 1.19 mmol) y N,N-diisopropiletilamina (624 μL, 3.58 mmol), seguido por agitación a temperatura ambiente durante 3 días bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó salmuera saturada (15 mL) y se extrajo dos veces con acetato de etilo (15 mL), seguido por secado sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido amarillo pálido (208 mg, rendimiento de 65%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.32 (3H, d, J = 6.3 Hz), 1.42 (3H, d, J = 5.9 Hz), 2.33 (3H, s), 2.44 (2H, t, J = 4.9 Hz), 2.52 (2H, t, J = 4.9 Hz), 3.41 (3H, d, J = 0.8 Hz), 3.48-3.60 (3H, m), 3.73 (2H, br s), 3.84 (2H, br s), 4.08 (1H, dd, J = 14.3, 9.2 Hz), 4.56 (1H, dd, J = 10.2, 6.3 Hz), 4.83 (1H, dd, J = 15.6, 6.6 Hz), 6.49 (1H, d, J = 4.3 Hz), 6.54 (1H, t, J = 2.0 Hz), 6.75 (1H, d, J = 3.9 Hz), 6.81 (1H, t, J = 1.8 Hz), 6.95 (1H, t, J = 1.8 Hz), 7.38 (1H, dd, J = 8.6, 2.7 Hz), 7.69 (1H, d, J = 8.6 Hz), 8.36 (1H, d, J = 2.7 Hz).

MS (ESI) m/z: 534.27234 $(M+H)^+$.

EJEMPLO 130

(2S)-2-[3-{5-[(5S)-5-Metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-({6-[(4-metilpiperazin-1-il)carbonil] piridin-3-il}oxi)fenoxi]propan-1-ol



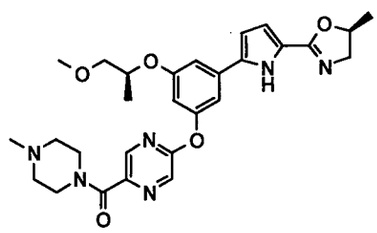
La 1-{[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)piriding-2-il]carbonil}-4-metilpiperazina (185 mg, 0.35 mmol) sintetizada en el ejemplo (129g) se disolvió en cloruro de metileno (10 mL), y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 694 μL, 0.694 mmol) a -78°C. Subsiguientemente, la temperatura se regresó a la temperatura ambiente, seguido por agitación durante 50 minutos. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-10%), para producir el compuesto deseado como un sólido blanco (51 mg, rendimiento de 28%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.28 (3H, d, J = 6.3 Hz), 1.43 (3H, d, J = 6.3 Hz), 2.34 (3H, s), 2.44 (2H, t, J = 4.9 Hz), 2.53 (2H, t, J = 4.9 Hz), 3.55 (1H, dd, J = 13.9, 7.2 Hz), 3.72 (2H, t, J = 4.7 Hz), 3.78 (2H, d, J = 5.5 Hz), 3.84 (2H, s), 4.09 (1H, dd, J = 13.9, 9.2 Hz), 4.60 (1H, dd, J = 11.3, 5.5 Hz), 4.85 (1H, dt, J = 11.6, 4.5 Hz), 6.35 (1H, s), 6.46 (1H, d, J = 3.9 Hz), 6.75 (1H, d, J = 3.9 Hz), 6.79 (1H, t, J = 1.8 Hz), 6.90 (1H, s), 7.33 (1H, dd, J = 8.6, 2.7 Hz), 7.67 (1H, dd, J = 8.6, 0.8 Hz), 8.33 (1H, t, J = 1.8 Hz).

MS (ESI) m/z: 520.25784 $(M+H)^+$.

EJEMPLO 131

2-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-5-[(4-metilpiperazin-1-il)carbonil]pirazina



(131a) 2-Cloro-5-[(4-metilpiperazin-1-il)carbonil]pirazina

Se disolvió ácido 5-hidroxipirazin-2-carboxílico (5.00 g, 39.0 mmol), disponible comercialmente, en cloruro de tionilo (64 mL), y se le agregaron unas gotas de N,N-dimetilformamida, seguido por calentamiento a reflujo durante 5 horas bajo una atmósfera de nitrógeno. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se diluyó con cloruro de metileno (50 mL). Enfriando en un baño de hielo se le agregó

diisopropiletilamina (18.7 mL, 107 mmol) y 1-metilpiperazina (4.37 mL, 39.2 mmol), y se agitó a temperatura ambiente durante 3 días bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó agua (100 mL) y se extrajo con cloruro de metileno (100 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 3%-5%), para producir el compuesto deseado como un sólido pardo (5.32 g, rendimiento de 62%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 2.34 (3H, s), 2.44 (2H, t, J = 5.1 Hz), 2.53 (2H, t, J = 5.1 Hz), 3.64 (2H, t, J = 5.1 Hz), 3.84 (2H, t, J = 4.9 Hz), 8.55 (1H, d, J = 1.2 Hz), 8.76 (1H, d, J = 1.6 Hz).

(131b) 5-{3-[(1S)-2-Metoxi-1-metiletoxi]-5-({5-[(4-metilpiperazin-1-il)carbonil]pirazin-2-il}oxi)fenil}-1H-pirrol-2-carboxilato de bencilo

El 5-{3-hidroxi-5-[(1S)-2-metoxi-1-metiletoxi]fenil}-1H-pirrol-1,2-dicarboxilato de 2-bencilo-1-t-butilo (2.00 g, 4.15 mmol) sintetizado en el ejemplo (78g), y la 2-cloro-5-[(4-metilpiperazin-1-il)carbonil]pirazina (1.10 g, 4.57 mmol) sintetizada en el ejemplo (131a), se disolvieron en N,N-dimetilformamida (20 mL) y se les agregó carbonato de potasio (1.72 g, 12.5 mmol), seguido por agitación a 80°C durante 4 horas bajo una atmósfera de nitrógeno. La solución de reacción se enfrió a temperatura ambiente, se le agregó agua (80 mL) y se extrajo dos veces con acetato de etilo (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó

sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-7.5%) para producir un compuesto como un aceite pardo (2.88 g).

Este se disolvió en cloruro de metileno (5 mL) y se le agregó ácido trifluoroacético (5 mL), seguido por agitación a temperatura ambiente durante 2 horas. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio (50 mL) y se extrajo dos veces con cloruro de metileno (50 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-7.5%), para producir el compuesto deseado como un sólido amarillo pálido (1.96 g, rendimiento de 81%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ1.34 (3H, d, J = 6.3 Hz), 2.34 (3H, s), 2.45 (2H, t, J = 4.5 Hz), 2.53 (2H, t, J = 4.9 Hz), 3.41 (3H, s), 3.51 (1H, dd, J = 10.9, 3.7 Hz), 3.59 (1H, dd, J = 9.8, 5.5 Hz), 3.71 (2H, br s), 3.84 (2H, br s), 4.53-4.60 (1H, m), 5.33 (2H, s), 6.51 (1H, dd, J = 3.9, 2.7 Hz), 6.69 (1H, t, J = 2.0 Hz), 6.93 (1H, s), 6.98 (1H, dd, J = 3.7, 2.5 Hz), 7.02 (1H, s), 7.34-7.44(5H, m), 8.35 (1H, t, J = 1.4 Hz), 8.54 (1H, d, J = 0.8 Hz), 9.21 (1H, br s).

(131c) N-[(2R)-2-Hidroxipropil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-({5-[(4-metilpiperazin-1-il)carbonil]pirazin-2-il}oxi)fenil}-1H-pirrol-2-carboxamida

El 5-{3-[(1S)-2-metoxi-1-metiletoxi]-5-({5-[(4-metilpiperazin-1-il)carbonil]pirazin-2-il}oxi)fenil}-1H-pirrol-2-carboxilato de bencilo (1.94 g, 3.32 mmol) sintetizado en el ejemplo (131b) se disolvió en metanol (100 mL), y se le agregó un catalizador de paladio al 10% en carbón (1.20 g), seguido por agitación a temperatura ambiente durante 2.5 horas bajo una atmósfera de hidrógeno. El catalizador de paladio en carbón se removió por filtración en Celite, seguido por lavado con tetrahidrofurano. El disolvente se removió por destilación bajo presión reducida para producir un sólido blanco (1.45 g).

Este sólido blanco (700 mg, 1.41 mmol) y 4-dimetilaminopiridina (86 mg, 0.71 mmol) se disolvieron en cloruro de metileno (30 mL), y se les agregó WSCI·HCl (625 mg, 2.26 mmol) y (R)-1-amino-2-propanol (256 μL, 3.25 mmol) a temperatura ambiente, seguido por agitación durante 3 días bajo una atmósfera de nitrógeno. La solución de reacción se diluyó con cloruro de metileno (60 mL), se lavó con una solución acuosa saturada de carbonato ácido de sodio y salmuera saturada, y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-10%), para producir el producto deseado como un sólido blanco (447 mg, 50%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.23 (3H, d, J = 6.3 Hz), 1.33 (3H, d, J = 8.0 Hz), 2.34 (3H, s), 2.45 (2H, t, J = 4.7 Hz), 2.53 (2H, t, J = 4.7 Hz), 3.23-3.30 (1H, m), 3.42 (3H, s), 3.51 (1H, dd, J = 10.2, 4.3 Hz), 3.58-3.63 (2H, m), 3.71 (2H, t, J = 4.7 Hz), 3.84 (2H, t, J = 5.5 Hz), 4.00 (1H, br s), 4.53-4.60 (1H, m), 6.37 (1H, s), 6.49 (1H, t, J = 3.3 Hz), 6.61 (1H, dd, J = 3.9, 2.3 Hz), 6.66 (1H, s), 6.93 (1H, t, J = 1.8 Hz), 7.02 (1H, t, J = 2.0 Hz), 8.34 (1H, s), 8.53 (1H, s), 9.66 (1H, br s).

(131d) 2-(3-[(1S)-2-Metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-5-[(4-metilpiperazin-1-il)carbonil]-pirazina

La N-[(2R)-2-hidroxipropil]-5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-({5-[(4-metilpiperazin-1-il)carbonil]pirazin-2-il}oxi)fenil}-1H-pirrol-2-carboxamida (447 mg, 0.81 mmol) sintetizada en el ejemplo (131c) se disolvió en tetrahidrofurano (20 mL), y se le agregó ácido metanosulfónico anhidro (282 mg, 1.62 mmol) y trietilamina (0.34 mL, 2.43 mmol), seguido por agitación a 50°C durante 4 horas bajo una atmósfera de nitrógeno. A la solución de reacción se le agregó una solución acuosa saturada de cloruro de amonio (30 mL) y se extrajo dos veces con cloruro de metileno (30 mL). La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de magnesio anhidro. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 0%-5%), para producir el compuesto deseado como un sólido amarillo pálido (279 mg,

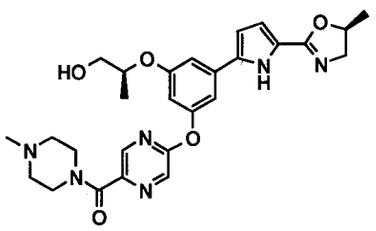
rendimiento de 65%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.34 (3H, d, J = 6.3 Hz), 1.42 (3H, d, J = 6.3 Hz), 2.34 (3H, s), 2.46 (2H, t, J = 4.7 Hz), 2.53 (2H, t, J = 4.7 Hz), 3.42 (3H, s), 3.49-3.62 (3H, m), 3.72 (2H, t, J = 4.3 Hz), 3.84 (2H, t, J = 5.1 Hz), 4.08 (1H, dd, J = 14.1, 9.0 Hz), 4.53-4.60 (1H, m), 4.87-4.78 (1H, m), 6.50 (1H, d, J = 3.9 Hz), 6.65 (1H, t, J = 2.2 Hz), 6.75 (1H, d, J = 3.9 Hz), 6.91 (1H, t, J = 1.8 Hz), 7.02 (1H, t, J = 2.0 Hz), 8.34 (1H, d, J = 1.2 Hz), 8.54 (1H, d, J = 1.2 Hz).

MS (ESI) m/z: 535.26585 $(M+H)^+$.

EJEMPLO 132

(2S)-2-[3-{5-[(5S)-5-Metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-({5-[(4-metilpiperazin-1-il)carbonil]pirazin-2-il}oxi)fenoxi]propan-1-ol



La 2-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}fenoxi)-5-[(4-metilpiperazin-1-il)carbonil]pirazina (259 mg, 0.48 mmol) sintetizada en el ejemplo (131d) se disolvió en cloruro de metileno (15 mL), y se le agregó tribromuro de boro (solución en cloruro de metileno 1.0 mol/L, 0.81 mL, 0.81 mmol) a -78°C. Subsiguientemente, la temperatura se regresó a la temperatura ambiente, seguido por agitación

durante 3 horas. A la solución de reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y subsiguientemente se secó sobre sulfato de sodio. El disolvente se removió por destilación bajo presión reducida y el residuo resultante se purificó por cromatografía en columna de gel de sílice (disolvente de elución: metanol/cloruro de metileno = 2%-8%), para producir el compuesto deseado como un sólido blanco (62.4 mg, rendimiento de 25%).

^{1}H-RMN ($CDCl_3$, 400 MHz): δ 1.28 (4H, d, J = 6.3 Hz), 1.41 (3H, d, J = 6.3 Hz), 2.34 (3H, s), 2.45 (2H, t, J = 4.5 Hz), 2.52 (2H, t, J = 4.7 Hz), 3.53 (1H, dd, J = 13.7, 7.4 Hz), 3.71 (2H, t, J = 4.7 Hz), 3.77-3.79 (2H, m), 3.83 (2H, t, J = 4.7 Hz), 4.07 (1H, dd, J = 13.7, 9.4 Hz), 4.59 (1H, td, J = 11.5, 5.7 Hz), 4.83 (1H, dq, J = 17.8, 5.1 Hz), 6.44 (1H, d, J = 3.9 Hz), 6.47 (1H, s), 6.72 (1H, d, J = 3.9 Hz), 6.88 (1H, s), 6.94 (1H, s), 8.30 (1H, s), 8.52 (1H, d, J = 0.8 Hz).

MS (ESI) m/z: 521.25002 $(M+H)^+$.

EJEMPLO DE PRUEBA 1

(1) Preparación de GK

Por medio de una reacción en cadena de polimerasa (PCR) se clonó ADNc que codifica el polipéptido GK pancreático humano (No. de registro de GenBank NM_000162, variante de glucocinasa humana 1) de una

colección de ADNc humano, y se introdujo en un vector de expresión de proteína fusionado con glutatión S-transferasa (GST) (GEX4T, GE Healthcare Bioscience). El vector se introdujo en *Escherichia coli* (tal como BL21 o JM109, Invitrogen), y la *E. coli* transformada se cultivó durante la noche a 37 °C, seguido por recuperación de las células. Después de congelar y descongelar las células recuperadas, se suspendieron en amortiguador de fosfato que contenía Triton-X a una concentración final de 1%, seguido por lisis de las células con un homogeneizador ultrasónico. El sobrenadante obtenido por centrifugación del homogenato a baja velocidad (10,000 x g, 30 minutos) se sometió adicionalmente a centrifugación de alta velocidad (100,000 x g, 10 minutos), seguido por recuperación del sobrenadante y purificación de la proteína fusionada usando un sistema de purificación de proteína GST fusionada (Bulk GST Purification Module, GE Healthcare Bioscience). La proteína GK-fusionada se dividió en alícuotas más pequeñas y se guardó a -80 °C.

(2) Prueba de actividad de GK

La actividad de GK se midió usando la GK purificada del paso (1) anterior. Más específicamente, se preparó una solución de enzima agregando la GK purificada del paso (1) anterior y glucosa-6-fosfato deshidrogenasa (Sigma) a la solución 1 de un kit de prueba de glucosa (D-Glucose UV Method, Roche Diagnostics). La solución de enzima, un diluente del compuesto de prueba y glucosa (concentración final: 5 mM), se mezclaron en una placa de ELISA de 96 pocillos y se dejaron reaccionar 30 minutos a

temperatura ambiente. Después de terminarse la reacción se midió la absorbancia a una longitud de onda de 340 nm usando SpectraMax Plus (Molecular Probe). Además, se usó la absorbancia sin reacción (cuando no se agregó glucosa) como referencia.

Las proporciones de activación de GK se indican con los valores representados por la siguiente fórmula numérica: (absorbancia después de reaccionar durante 30 minutos con el compuesto de prueba) / (absorbancia después de reaccionar durante 30 minutos sin compuesto de prueba). En el cuadro 1 se muestran los resultados de las proporciones de activación de GK obtenidas a una concentración de compuesto de prueba de 1 μM.

CUADRO 1

Ejemplo	Proporción de activación de GK
1	2.0
2	1.9
3	1.9
15	1.6
20	2.0
21	2.0
25	2.0
26	2.3
29	2.0
31	2.0
32	2.0

CUADRO 1 (Continuación)

Ejemplo	Proporción de activación de GK
33	1.7
35	2.1
41	2.1
47	2.0
60	2.0
64	1.9
65	2.4
67	1.7
68	2.0
69	2.2
70	1.9
73	2.0
74	2.0
75	1.8
76	3.0
77	2.6
81	2.2
82	2.7
84	2.7
85	2.9
86	2.5
88	2.4
89	2.3
91	2.6
93	2.4
95	2.5

CUADRO 1 (Continuación)

Ejemplo	Proporción de activación de GK
98	1.9
100	1.9
101	1.9
103	2.1
107	2.0
108	2.0
109	2.2
110	2.4
112	2.4
114	2.2
122	2.5
123	2.6
126	2.6
127	2.4

Basándose en estos resultados, los compuestos de la presente invención tienen una actividad activadora de GK superior y son útiles como agentes terapéuticos o preventivos de una enfermedad seleccionada del conjunto que consiste en diabetes, deterioro de tolerancia a la glucosa, diabetes gestacional, complicaciones crónicas de la diabetes (que incluyen neuropatía periférica diabética, nefropatía diabética, retinopatía diabética y macroangiopatía diabética), y síndrome metabólico.

EJEMPLO DE PREPARACION 1

Cápsula	
Compuesto del ejemplo 1 o 78	50 mg
Lactosa	128 mg
Almidón de maíz	70 mg
Estearato de magnesio	2 mg
	250 mg

Los polvos de esta formulación se mezclaron y se pasaron a través de un tamiz de malla 60, y después se vaciaron en una cápsula de gelatina de 250 mg para obtener una cápsula.

EJEMPLO DE PREPARACION 2

Tableta	
Compuesto del ejemplo 1 o 78	50 mg
Lactosa	126 mg
Almidón de maíz	23 mg
Estearato de magnesio	1 mg
	200 mg

Los polvos de esta formulación se mezclaron, se granularon con una pasta de almidón de maíz y se secaron; después se comprimió en tableta con una máquina tableteadora para obtener una tableta de 200 mg. Esta

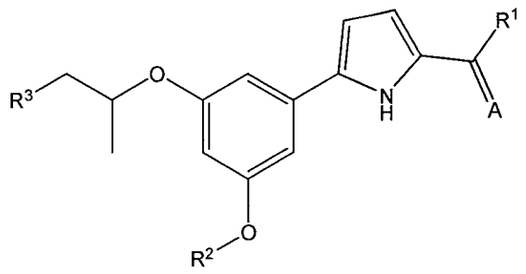
tableta se puede proveer con un recubrimiento de azúcar conforme sea necesario.

Aplicación industrial

Un compuesto representado por la fórmula general (I) de la presente invención, o una sal farmacológicamente aceptable del mismo, tiene una actividad activadora de GK superior y es útil como agente terapéutico o preventivo (particularmente terapéutico) para la diabetes, deterioro de tolerancia a la glucosa, diabetes gestacional, complicaciones crónicas de la diabetes (que incluyen neuropatía periférica diabética, nefropatía diabética, retinopatía diabética y macroangiopatía diabética), o síndrome metabólico (particularmente diabetes o deterioro de tolerancia a la glucosa), para usarse en animales de sangre caliente (particularmente en humanos).

RESUMEN DE LA INVENCION

La presente invención se refiere a un compuesto que tiene una actividad activadora de glucocinasa superior y está representado por la fórmula general (I), y las sales farmacológicamente aceptables del mismo:



(I)

[en donde: A representa, por ejemplo, un átomo de oxígeno o un átomo de azufre, R^1 representa, por ejemplo, un grupo alquilo de C_1-C_6, un grupo alcoxi de C_1-C_6 o un grupo alquilo de C_1-C_6 halogenado, A y R^1 junto con el átomo de carbono al que están unidos forman un grupo heterocíclico que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, R^2 representa un grupo fenilo que puede estar sustituido con 1 a 5 grupos seleccionados independientemente del conjunto de sustituyentes α, o un grupo heterocíclico que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, R^3 representa un grupo hidroxi o un grupo alcoxi de C_1-C_6, y el conjunto de sustituyentes α consiste, por ejemplo, en un átomo de halógeno, un grupo alquilo de C_1-C_6, un grupo

alquilo de C_1-C_6 sustituido con 1 o 2 grupos hidroxi, un grupo alquilsulfonilo de C_1-C_6 y un grupo representado por la fórmula –V-NR^5R^6 (en donde V representa un grupo carbonilo o un grupo sulfonilo, y R^5 y R^6 pueden ser iguales o diferentes entre sí y representan respectivamente un átomo de hidrógeno o un grupo alquilo de C_1-C_6, o R^5 y R^6, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros que puede estar sustituido con 1 o 2 grupos seleccionados independientemente de un grupo alquilo de C_1-C_6 y un grupo hidroxi, y el heterociclo saturado de 4 a 6 miembros también puede contener un átomo de oxígeno o un átomo de nitrógeno)].

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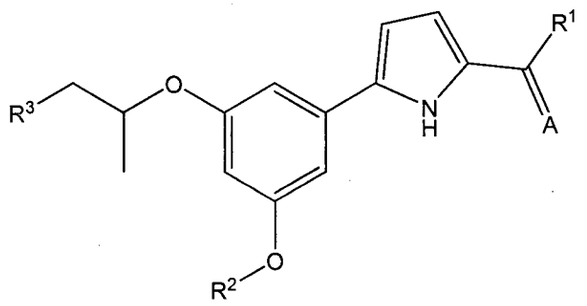
REIVINDICACIONES MODIFICADAS

PARA REALIZAR EL EXAMEN DE

PATENTABILIDAD

REIVINDICACIONES MODIFICADAS

1.- Un compuesto que tiene la fórmula general (I):



(I)

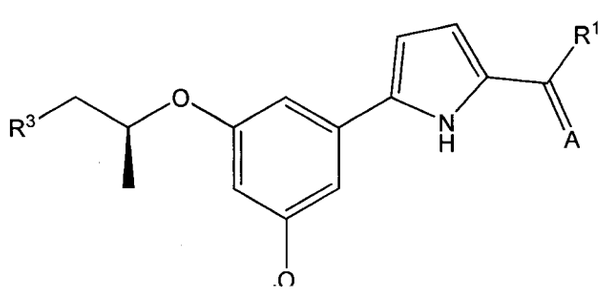
[en donde: A representa un grupo representado por la fórmula $=NOR^4$, un átomo de oxígeno o un átomo de azufre; R^4 representa un átomo de hidrógeno o un grupo alquilo de C_1-C_6; R^1 representa un grupo alquilo de C_1-C_6, un grupo alcoxi de C_1-C_6, un grupo alquilo de C_1-C_6 halogenado, un grupo alcoxi de C_1-C_6 halogenado, un grupo amino, un grupo mono-alquil(C_1-C_6)-amino, un grupo mono-alquilo halogenado (C_1-C_6)-amino, un grupo di-alquil(C_1-C_6)-amino, o un grupo di-alquilo halogenado (C_1-C_6)-amino, o A y R^1 junto con el átomo de carbono al que están unidos, forman un grupo heterocíclico que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α; R^2 representa un grupo fenilo que puede estar sustituido con 1 a 5 grupos seleccionados independientemente del conjunto de sustituyentes α, o un grupo heterocíclico que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α; R^3 representa un grupo hidroxi o un grupo alcoxi de C_1-C_6; y el conjunto de sustituyentes α comprende un átomo de halógeno, un grupo alquilo de C_1-C_6, un grupo de alquilo de C_1-C_6 halogenado, un grupo alquenilo de C_2-C_6, un grupo alquinilo de C_2-C_6, un grupo hidroxi, un grupo alquilo de C_1-C_6 sustituido con 1 o 2 grupos hidroxi, un grupo alcoxi de C_1-C_6, un grupo alcoxi de C_1-C_6 halogenado, un grupo

alcoxi(C_1-C_6)-alquilo(C_1-C_6), un grupo alcoxi(C_1-C_6)-alcoxi(C_1-C_6), un grupo formilo, un grupo carboxilo, un grupo alquilcarbonilo de C_2-C_7, un grupo alcoxicarbonilo de C_2-C_7, un grupo alquilcaboniloxi de C_2-C_7, un grupo alcoxicarboniloxi de C_2-C_7, un grupo nitro, un grupo amino, un grupo mono-alquil(C_1-C_6)-amino, un grupo di-alquil(C_1-C_6)-amino, un grupo alquiltio de C_1-C_6, un grupo alquilsulfonilo de C_1-C_6, un grupo cicloalquilsulfonilo de C_3-C_6, un grupo hidroxialquilsulfonilo de C_1-C_6, un grupo alcoxi(C_1-C_6)-alquilsulfonilo(C_1-C_6), un grupo representado por la fórmula -V-NR^5R^6 (en donde V representa un grupo carbonilo o un grupo sulfonilo, y R^5 y R^6 pueden ser iguales o diferentes y representan respectivamente un átomo de hidrógeno o un grupo alquilo de C_1-C_6, o R^5 y R^6, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros que puede estar sustituido con 1 o 2 grupos seleccionados independientemente de un grupo alquilo de C_1-C_6 y un grupo hidroxi, y el heterociclo saturado de 4 a 6 miembros puede contener también un átomo de oxígeno o un átomo de nitrógeno), un grupo mono-alquilcarbonilamino de C_2-C_7, un grupo mono-alquil(C_1-C_6)-aminocarboniloxi, un grupo di-alquil(C_1-C_6)-aminocarboniloxi, un grupo mono-alcoxicarbonilamino de C_2-C_7, un grupo mono-alquilsulfonilamino de C_1-C_6, un grupo ciano, un grupo 1,3,4-oxadiazol-2-ilo sustituido opcionalmente con un grupo alquilo de C_1-C_6 en la posición 5, un grupo 1,3,4-tiadiazol-2-ilo sustituido opcionalmente con un grupo alquilo de C_1-C_6 en la posición 5, y un grupo oxo], o una sal farmacológicamente aceptable del mismo.

2.- El compuesto o sal farmacológicamente aceptable de conformidad con la reivindicación 1, caracterizado además porque el conjunto de sustituyentes α comprende un átomo de halógeno, un grupo alquilo de C_1-C_6, un grupo alquilo de C_1-C_6 halogenado, un grupo alquenilo de C_2-C_6, un grupo alquinilo de C_2-C_6, un grupo hidroxi, un grupo alquilo de C_1-C_6 sustituido

con 1 o 2 grupos hidroxi, un grupo alcoxi de C_1-C_6, un grupo alcoxi de C_1-C_6 halogenado, un grupo alcoxi(C_1-C_6)-alquilo(C_1-C_6), un grupo alcoxi(C_1-C_6)-alcoxi(C_1-C_6), un grupo formilo, un grupo carboxilo, un grupo alquilcarbonilo de C_2-C_7, un grupo alcoxicarbonilo de C_2-C_7, un grupo alquilcaboniloxi de C_2-C_7, un grupo alcoxicarboniloxi de C_2-C_7, un grupo nitro, un grupo amino, un grupo mono-alquil(C_1-C_6)-amino, un grupo di-alquil(C_1-C_6)-amino, un grupo alquiltio de C_1-C_6, un grupo alquilsulfonilo de C_1-C_6, un grupo cicloalquilsulfonilo de C_3-C_6, un grupo hidroxialquilsulfonilo de C_1-C_6, un grupo alcoxi(C_1-C_6)-alquilsulfonilo(C_1-C_6), un grupo representado por la fórmula -V-NR^5R^6 (en donde V representa un grupo carbonilo o un grupo sulfonilo, y R^5 y R^6 pueden ser iguales o diferentes y representan respectivamente un átomo de hidrógeno o un grupo alquilo de C_1-C_6, o R^5 y R^6, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros que puede estar sustituido con 1 o 2 grupos seleccionados independientemente de un grupo alquilo de C_1-C_6 y un grupo hidroxi, y el heterociclo saturado de 4 a 6 miembros puede contener también un átomo de oxígeno o un átomo de nitrógeno), un grupo mono-alquilcarbonilamino de C_2-C_7, un grupo mono-alquil(C_1-C_6)-aminocarboniloxi, un grupo di-alquil(C_1-C_6)-aminocarboniloxi, un grupo mono-alcoxicarbonilamino de C_2-C_7, un grupo mono-alquilsulfonilamino de C_1-C_6, un grupo ciano, un grupo 1,3,4-oxadiazol-2-ilo sustituido opcionalmente con un grupo alquilo de C_1-C_6 en la posición 5, y un grupo 1,3,4-tiadiazol-2-ilo sustituido opcionalmente con un grupo alquilo de C_1-C_6 en la posición 5.

3.- El compuesto o sal farmacológicamente aceptable de conformidad con la reivindicación 1 o 2, caracterizado además porque la fórmula general (I) es la fórmula general (Ia):



4.- El compuesto o sal farmacológicamente aceptable de conformidad con cualquiera de las reivindicaciones 1 a 3, caracterizado además porque A es un átomo de oxígeno.

5.- El compuesto o sal farmacológicamente aceptable de conformidad con cualquiera de las reivindicaciones 1 a 4, caracterizado además porque R^1 es un grupo alquilo de C_1-C_6, un grupo alcoxi de C_1-C_6 o un grupo mono-alquilo halogenado (C_1-C_6)-amino.

6.- El compuesto o sal farmacológicamente aceptable de conformidad con cualquiera de las reivindicaciones 1 a 4, caracterizado además porque R^1 es un grupo metilo o un grupo 2-cloroetilamino.

7.- El compuesto o sal farmacológicamente aceptable de conformidad con cualquiera de las reivindicaciones 1 a 3, caracterizado además porque el grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están unidos, y que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, es un grupo 2-piridilo, un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo, un grupo 1,3-tiazol-2-ilo, un grupo 1,3-oxazol-2-ilo, un grupo 1,3,4-oxadiazol-2-ilo, un grupo 1,3,4-tiadiazol-2-ilo, un grupo 4,5-dihidro-1,3-tiazol-2-ilo, un grupo 4,5-dihidro-1,3-oxazol-2-ilo, o un grupo 1,3-benzotiazol-2-ilo, que pueden estar sustituidos con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes γ, y el conjunto de sustituyentes γ comprende un átomo de halógeno, un grupo alquilo de C_1-C_6, un grupo alquilo de C_1-C_6 halogenado, un grupo alquilo de C_1-C_6 sustituido con 1 o 2 grupos hidroxi, un grupo alcoxi de C_1-C_6, un grupo carboxilo, un grupo mono-alquil(C_1-C_6)-aminocarbonilo, un

grupo di-alquil(C_1-C_6)-aminocarbonilo y un grupo hidroxi.

8.- El compuesto o sal farmacológicamente aceptable de conformidad con cualquiera de las reivindicaciones 1 a 3, caracterizado además porque el grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están unidos, y que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, es un grupo 1,3-tiazol-2-ilo, un grupo 5-metil-1,3-tiazol-2-ilo, un grupo 5-metil-1,3,4-oxadiazol-2-ilo, un grupo 4,5-dihidro-1,3-tiazol-2-ilo, un grupo 4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo 5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-etil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1R)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1S)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-4-hidroxi-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4-hidroximetil-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5R)-5-hidroximetil-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo 5-carboxil-1,3-tiazol-2-ilo, un grupo 5-dimetilaminocarbonil-1,3-tiazol-2-ilo, un grupo 5-metil-1,3,4-tiadiazol-2-ilo, o un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo.

9.- El compuesto o sal farmacológicamente aceptable de conformidad con cualquiera de las reivindicaciones 1 a 3, caracterizado además porque el grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están unidos, y que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, es un grupo 4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-etil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-hidroximetil-4,5-dihidro-1,3-

oxazol-2-ilo, un grupo (5R)-5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1R)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1S)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4-hidroximetil-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5R)-5-hidroximetil-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo 1,3-tiazol-2-ilo, un grupo 5-carboxil-1,3-tiazol-2-ilo, un grupo 5-dimetilaminocarbonil-1,3-tiazol-2-ilo, un grupo 5-metil-1,3,4-tiadiazol-2-ilo, un grupo 5-metil-1,3,4-oxadiazol-2-ilo, un grupo 4,5-dihidro-1,3-tiazol-2-ilo, o un grupo 5,6-dihidro-4H-1,3-oxazin-2-ilo.

10.- El compuesto o sal farmacológicamente aceptable de conformidad con cualquiera de las reivindicaciones 1 a 3, caracterizado además porque el grupo heterocíclico formado por A y R^1 junto con el átomo de carbono al que están unidos, y que puede estar sustituido con 1 a 3 grupos seleccionados independientemente del conjunto de sustituyentes α, es un grupo 4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-etil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5S)-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R)-4-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (5R)-5-hidroximetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1R)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4S)-4-[(1S)-1-hidroxietil]-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-ilo, un grupo (4R,5S)-4-hidroximetil-5-metil-4,5-dihidro-1,3-oxazol-2-ilo, o un grupo (4R,5R)-5-hidroximetil-4-metil-4,5-dihidro-1,3-oxazol-2-ilo.

11.- El compuesto o sal farmacológicamente aceptable de conformidad con cualquiera de las reivindicaciones 1 a 10, caracterizado además porque R^2 es un grupo fenilo que puede estar sustituido con 1 a 5 grupos seleccionados independientemente del conjunto de sustituyentes δ, o un grupo 2-piridilo, 3-piridilo o 2-pirazinilo que puede estar sustituido con 1 a 3

grupos seleccionados independientemente del conjunto de sustituyentes δ, y el conjunto de sustituyentes δ comprende un átomo de halógeno, un grupo alquilo de C_1-C_6, un grupo alquilo de C_1-C_6 halogenado, un grupo alquilo de C_1-C_6 sustituido con 1 o 2 grupos hidroxi, un grupo alquilcarbonilo de C_2-C_7, un grupo alcoxicarbonilo de C_2-C_7, un grupo alquilsulfonilo de C_1-C_6, un grupo representado por la fórmula –V-NR^5R^6 (en donde V representa un grupo carbonilo o un grupo sulfonilo, y R^5 y R^6 pueden ser iguales o diferentes y representan, respectivamente, un átomo de hidrógeno o un grupo alquilo de C_1-C_6, o R^5 y R^6, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros que puede estar sustituido con 1 o 2 grupos seleccionados independientemente de un grupo alquilo de C_1-C_6 y un grupo hidroxi, y el heterociclo saturado de 4 a 6 miembros puede contener también un átomo de oxígeno o un átomo de nitrógeno), un grupo 1,3,4-oxadiazol-2-ilo sustituido opcionalmente con un grupo alquilo de C_1-C_6 en la posición 5, y un grupo 1,3,4-tiadiazol-2-ilo sustituido opcionalmente con un grupo alquilo de C_1-C_6 en la posición 5.

12.- El compuesto o sal farmacológicamente aceptable de conformidad con cualquiera de las reivindicaciones 1 a 10, caracterizado además porque R^2 es un grupo 4-metilsulfonilfenilo, un grupo 4-(1-azetidinil)carbonil-2-fluorofenilo, un grupo 2-fluoro-4-(1-pirrolidinil)-carbonilfenilo, un grupo 5-(1-azetidinil)carbonil-3-cloro-2-piridilo, un grupo 2-metilsulfonil-5-piridilo, un grupo 5-(4-metil-1-piperazinil)carbonil-2-pirazinilo, un grupo 2-metilaminocarbonil-5-piridilo, un grupo 2-metilaminosulfonil-5-piridilo, o un grupo 5-metilsulfonil-2-pirazinilo.

13.- El compuesto o sal farmacológicamente aceptable de conformidad con cualquiera de las reivindicaciones 1 a 10, caracterizado además porque R^2 es un grupo 4-metilsulfonilfenilo, un grupo 2-metilsulfonil-5-piridilo, un grupo 5-metilsulfonil-2-pirazinilo, o un grupo 5-(1-azetidinil)carbonil-

3-cloro-2-piridilo.

14.- El compuesto o sal farmacológicamente aceptable de conformidad con cualquiera de las reivindicaciones 1 a 13, caracterizado además porque R^3 es un grupo hidroxi o un grupo metoxi.

15.- El compuesto o sal farmacológicamente aceptable de conformidad con la reivindicación 1, caracterizado además porque el compuesto representado por la fórmula general (I) es: (2S)-2-{3-[5-(4,5-dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[4-(metilsulfonil)fenoxi]fenoxi}propan-1-ol; (2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[4-(metilsulfonil)fenoxi]fenoxi)propan-1-ol; (2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol; {(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}-metanol; (2S)-2-(3-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenoxi)propan-1-ol; (2S)-2-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol; {(4R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]-oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}metanol; (2S)-2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol; {(4R,5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4-metil-4,5-dihidro-1,3-oxazol-5-il}metanol; {(4R,5S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol; (1S)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol; (1R)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol; (2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)-

pirazin-2-il]oxi}fenoxi)propan-1-ol; {(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol; (2S)-2-(3-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol; (2S)-2-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}-fenoxi)propan-1-ol; (2S)-2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol; {(4R,5S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol; (1S)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol; o (1R)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol.

16.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque el compuesto representado por la fórmula general (I) es: (2S)-2-{3-[5-(4,5-dihidro-1,3-oxazol-2-il)-1H-pirrol-2-il]-5-[4-(metilsulfonil)fenoxi]fenoxi}propan-1-ol; (2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-[4-(metilsulfonil)fenoxi]fenoxi)propan-1-ol; (2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol; {(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}-metanol; (2S)-2-(3-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol; (2S)-2-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol; {(4R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)-piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}metanol; (2S)-2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenoxi)propan-1-ol; {(4R,5R)-2-[5-

(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4-metil-4,5-dihidro-1,3-oxazol-5-il}metanol; {(4R,5S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol; (1S)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol; (1R)-1-{(4S)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[6-(metilsulfonil)piridin-3-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}-etanol; (2S)-2-(3-{5-[(5S)-5-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol; {(5R)-2-[5-(3-[(1S)-2-metoxi-1-metiletoxi]-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-5-il}metanol; (2S)-2-(3-{5-[(4R)-4-metil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol; (2S)-2-(3-{5-[(4R)-4-etil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol; (2S)-2-(3-{5-[(4R,5S)-4,5-dimetil-4,5-dihidro-1,3-oxazol-2-il]-1H-pirrol-2-il}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenoxi)propan-1-ol; {(4R,5S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-5-metil-4,5-dihidro-1,3-oxazol-4-il}metanol; (1S)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol; o (1R)-1-{(4S)-2-[5-(3-{[(2S)-1-metoxipropan-2-il]oxi}-5-{[5-(metilsulfonil)pirazin-2-il]oxi}fenil)-1H-pirrol-2-il]-4,5-dihidro-1,3-oxazol-4-il}etanol.

17.- Una composición farmacéutica que contiene como ingrediente activo de la misma un compuesto o sal farmacológicamente aceptable del mismo de cualquiera de las reivindicaciones 1 a 16.

1438

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-109309- -00000-0000
Fecha: 2010-09-03 16:34:02 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 1441

: RECIBO OFICIAL DE CAJA : 10 - 65,119
FECHA : AGOSTO 9 DE 2010

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	132667006	09/08/2010	59,216,000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-03 CAMBIO DE MODALIDAD Y MODIFICA	12 MARCAS Y LEMAS COMERCIALES		114,000.00
		TOTAL :	$	114,000.00

SON: CIENTO CATORCE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

COLO: J5869-84J-022-8.

1439

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 65,122
FECHA : AGOSTO 9 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-109309- -00000-0000
Fecha: 2010-09-03 16:34:02 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1441

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	132667006	09/08/2010	59,216,000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	5000-01-01 SOLICITUDES	93	TASA ANUAL MANTENIMIENTO MODELO D	174,000.00
			TOTAL : $	174,000.00

SON: CIENTO SETENTA Y CUATRO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

C010015869-841-022-8

1440

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 10 - 69,575
FECHA : AGOSTO 23 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-109309- -00000-0000

Fecha: 2010-09-03 16:34:02 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1441

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	156799795	23/08/2010	83,297,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	5005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVCIOS ADMINISTRATIVOS	5,000.00
		TOTAL : $	5,000.00

SON: CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA ANEXADO AL EXPEDIENTE No. _____

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

0010015869-845-022-8.

1441

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-109309- -00000-0000
Fecha: 2010-09-03 16:34:02 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1441

CERTIFICACION DE EXCEDENTE : 10 - 69,576
FECHA : AGOSTO 23 DE 2010

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	156798795	23/08/2010	83,297,000.00

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

CANT.	ESTATISTICO	CONCEPTO	TOTAL CONCEPTO
1	5005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVCIOS ADMINISTRATIVOS	5,000.00
		TOTAL : $	5,000.00

SON: CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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

COLO 15869-845-022-8.

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-109309- -00000-0000
Fecha: 2010-09-03 16:34:02 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1441

PATENTE DE INVENCIÓN ☐ MODELO DE UTILIDAD ☐ Art 33 Decisión 486/00

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☑ MODELO DE UTILIDAD PCT ☐ Art.33 Decisión 486/00, Circular Única

- ☑ Indicación que se solicita una PCT
- ☑ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☑ Dibujos de ser estos pertinentes
- ☑ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☑ Incompleta ☐

DISEÑO INDUSTRIAL ☐ (Art. 119 Decisión 486/00)

- ☐ Indicación que se solicita Diseño industrial
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ (Art. 92 Decisión 486/00)

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

1442

Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
SUAREZ DE PAEZ LUZ CLEMENCIA
Apoderado(a) y/o Representante de
DAIICHI SANKYO COMPANY LIMITED

REFERENCIA		
	Radicación No.	10 109309
	Solicitud internacional	PCT/JP2009/051834
	Fecha inicio fase nacional	06/09/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	12855

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. El solicitante debe presentar un nuevo titulo que permita identificar la materia de la cual trata la solicitud, ya que el titulo relacionado no se encuentra con la precisión necesaria para identificar claramente el objeto de la solicitud de patente. (Regla 4.3 PCT, Art 26-27 D-486, Circular única 5.2.9)

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 01 OCT. 2010
adpa11

Al contestar favor indique el número de radicación que se encuentra a continuación

