Industria y Comercio

SUPERINTENDENCIA

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PCT
INVENTARIO
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Delegatura de Propiedad Industrial

División de Nue

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-132362- -00000-0000
Fecha: 2010-10-26 10:31:28 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 619

SOLICITUD

PATENTE DE INVENCIÓN

10 - 132362

21. **EXPEDIENTE No.**

54. **TÍTULO** DERIVADO DE HIDROXI-QUINOXALIN-CARBOXAMIDA

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.,**

(FORMA P-10)

26-10-2010

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-132362- -00000-0000
Fecha: 2010-10-26 10:31:28 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 619

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 CAMPANY, LIMITED**
Sociedad constituida y existente bajo las leyes de Japón.

Dirección: 3-5-1, 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. **Kayoko MOTOKI**
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Tokyo 140-8710,
Japón

3. **Shigeyuki NISHINAKA**
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Japón

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Japón

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Japón

8. **Aki YOKOMIZO**
c/o Daiichi company, Limited
1-16-13, Kitakasai, Edogawa-ku,
Tokyo 134-8630
Japón

5 PCT (86)

Solicitud Internacional No. PCT/JP2009/055741 Fecha: 24 de marzo de 2009
Publicación Internacional No. WO 2009/119537 A1 Fecha: 01/10/2009

6 Título (54)

DERIVADO DE HIDROXI-QUINOXALIN-CARBOXAMIDA

7 **Clasificación Internacional (51)** C07D 401/012

8 **Prioridad** SI☒ NO☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	JP JP	26 de marzo de 2008 26 de diciembre de 2008	2008-079919 2008-332106

9

Comprobante de pago No.: 10-87,900 **Fecha:** 20 de octubre de 2010
Comprobante de pago No.: 10-87,905 **Fecha:** 20 de octubre de 2010
Comprobante de pago No.: 10-87,906 **Fecha:** 20 de octubre 2010
Comprobante de pago No.: 10-87,932 **Fecha:** 20 de octubre de 2010
Comprobante de pago No.: 10-88,078 **Fecha:** 20 de octubre de 2010

10

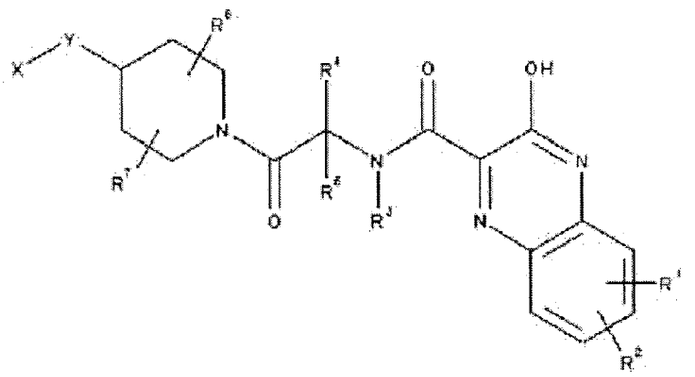
Anexos:

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por $ 554.000.oo.
- ☒ Comprobante de pago por 22 reivindicaciones adicionales después de la décima reivindicación por $572.000.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)
- ☐ 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

【1】



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

SCT

4

DOCUMENTOS ANEXOS

1. ☒ Publicación Internacional WO 2009/119537 A1

   Descripción:

   Páginas 203 en el idioma original

   Páginas 357 en español

   Reivindicaciones: Número (s) 32

   Figuras: Número (s)

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

3. ☒ Traducción Al Español De Los Anexos Presentados Junto Con El Informe Del Examen Preliminar Internacional.

4. ☒ Extracto de publicación.

NO SE REALIZARON MODIFICACIONES EN LA FASE INTERNACIONAL

Notaría Sexta 6

DEL CIRCULO DE BOGOTA, D.C.

COPIA NUMERO 6

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

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 N° 72-35
BOGOTA, D – 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 N° 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 N° 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
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BOGOTA D.C. REPUBLICA DE COLOMBIA
25 FEB. 2010
AMPARO QUINTERO ARTURO
NOTARIA

8

NOTARIAL CERTIFICATE Registration No 7255

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 BOGOTÁ, 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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AMPARO QUINTERO ARTURO
NOTARIA

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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 咏一郎

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

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
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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

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

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

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 EL TEXTO

15 A 9:38

LEGALIZACIONES BOGOTA D.C.

MINISTERIO DE RELACIONES EXTERIORES

150539

Eduardo Calvo

DOCUMENTO RESEÑADO EN EL

10

01

88226885

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
ARTURO QUINTERO ARTURO
NOTARIA

NOTARIA SEXTA DE BOGOTA

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 AL 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 TUVO 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
QUINTERO ARTURO
NOTARIA

NOTARIA SEXTA DE BOGOTA

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 RECURSOS EN VIA GUBERNATIVA.

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

EXPEDIDO EN LA CAMARA DE COMERCIO,

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
MARIO QUINTERO ARTEAGA
NOTARIA

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12

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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

Benjamin Esteban R

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
AMPARO QUINTERO ARTURO
NOTARIA

NOTARIA 6ª DE BOGOTÁ

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**

AMPARO QUINTERO ARTURO

NOTARIA SEXTA (6a) DE BOGOTA D.C.

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 SEXTA COPIA (FOTOCOPIA) TOMADA DE LA ESCRITURA PUBLICA NUMERIO 1039 DE FECHA 25 DE FEBRERO DE 2010.

COPIA QUE EXPIDO EN 08 HOJAS RUBRICADAS EN SUS MARGENES , LA CUAL CARECE DE NOTAS DE REVOCATORIA, MODIFICACION O SUSTITUCION, POR TANTO SE PRESUME VIGENTE EL PODER EN ELLA CONTENIDO.

BOGOTA, D.C. 21 DE OCTUBRE DE 2010

RESOLUCION 01 DE 2008

LA NOTARIA SEXTA DE BOGOTA D.C.



AMPARO QUINTERO ARTURO
NOTARIA SEXTA DE BOGOTA

(12) 特許協力条約に基づいて公開された国際出願

(19) 世界知的所有権機関
国際事務局

(43) 国際公開日
2009 年 10 月 1 日(01.10.2009)

PCT

(10) 国際公開番号
WO 2009/119537 A1

(51) 国際特許分類:
C07D 401/12 (2006.01)
A61K 31/498 (2006.01)
A61K 31/501 (2006.01)
A61K 31/506 (2006.01)
A61K 31/5377 (2006.01)
A61P 7/02 (2006.01)
A61P 9/00 (2006.01)
C07D 401/14 (2006.01)
C07D 417/14 (2006.01)

(21) 国際出願番号: PCT/JP2009/055741

(22) 国際出願日: 2009 年 3 月 24 日(24.03.2009)

(25) 国際出願の言語: 日本語

(26) 国際公開の言語: 日本語

(30) 優先権データ:
特願 2008-079919 2008 年 3 月 26 日(26.03.2008) JP
特願 2008-332106 2008 年 12 月 26 日(26.12.2008) JP

(71) 出願人 (米国を除く全ての指定国について): 第一三共株式会社(DAIICHI SANKYO COMPANY, LIMITED) [JP/JP]; 〒1038426 東京都中央区日本橋本町三丁目５番１号 Tokyo (JP).

(72) 発明者; および

(75) 発明者/出願人 (米国についてのみ): 本木 佳代子(MOTOKI, Kayoko). 川越 敬一(KAWAGOE, Keiichi). 西中 重行(NISHINAKA, Shigeyuki). 増田 幸枝(MASUDA, Sachie). 坂本 篤信(SAKAMOTO, Atsunobu). 金子 悟(KANEKO, Satoru). 有田 健(ARITA, Tsuyoshi). 横溝 亜紀(YOKOMIZO, Aki).

(74) 代理人: 石橋 公樹, 外(ISHIBASHI, Koki et al.); 〒1340081 東京都江戸川区北葛西一丁目１６番１３号 第一三共株式会社内 Tokyo (JP).

(81) 指定国 (表示のない限り、全ての種類の国内保護が可能): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

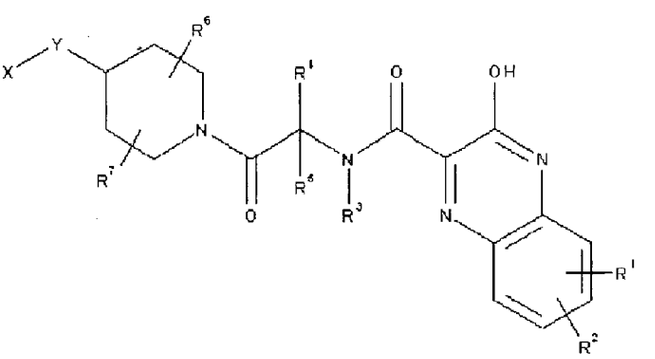
(84) 指定国 (表示のない限り、全ての種類の広域保護が可能): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), ユーラシア (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), ヨーロッパ (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[続葉有]

(54) **Title**: HYDROXYQUINOXALINECARBOXAMIDE DERIVATIVE

(54) 発明の名称: ヒドロキシキノキサリンカルボキサミド誘導体

【1】



(57) **Abstract**: Disclosed is a novel hydroxyquinoxalinecarboxamide derivative which is useful for prevention and/or treatment of blood coagulation disorders. Specifically disclosed is a compound represent by formula (i) or a pharmacologically acceptable salt thereof. (i) (In the formula, R^1 and R^2 independently represent a hydrogen atom, a halogen atom or the like; R^3 represents a hydrogen atom or the like; R^4 and R^5 independently represent a hydrogen atom, a halogen atom, a C_{1-4} alkyl group or the like; R^6 and R^7 independently represent a hydrogen atom or a C_{1-4} alkyl group; X represents a C_{3-10} cycloalkyl group, C_{6-10} aryl group or 5-10 membered heterocyclic group, which may be substituted by a member selected from the substituent group α, or the like; Y represents -CO-, -O-, -NRa- or the like; and Ra represents a hydrogen atom, a C_{1-4} alkyl group or the like.)

(57) 要約:

[続葉有]

WO 2009/119537 A1

WO 2009/119537 A1

添付公開書類:

— 国際調査報告（条約第21条(3)）

本発明は、血液凝固性疾患の予防及び／又は治療するために有用な、新規なヒドロキシキノキサリンカルボキサミド誘導体を提供する。　式（ｉ）　【化１】　[式中、R^1及びR^2は、各々独立に、水素原子、ハロゲン原子等を；R^3は、水素原子等を；R^4及びR^5は、各々独立に、水素原子、ハロゲン原子、C_{1-4}アルキル基等を；R^6及びR^7は、各々独立に、水素原子、又はC_{1-4}アルキル基を；Ｘは、置換基群αから選択される置換基で置換されていてもよい、C_{3-10}シクロアルキル基、C_{6-10}アリール基、５乃至１０員の複素環基等を；Ｙは、－ＣＯ－、－Ｏ－、－ＮＲａ－等を、Ｒａは、水素原子、C_{1-4}アルキル基等を示す。]で表される化合物又はその薬理上許容される塩。

DESCRIPTION

HYDROXYQUINOXALINECARBOXAMIDE DERIVATIVE

TECHNICAL FIELD

The present invention relates to a hydroxyquinoxalinecarboxamide derivative, and pharmacologically acceptable salts thereof, that are useful as pharmaceuticals. More particularly, the present invention relates to a hydroxyquinoxalinecarboxamide derivative, and pharmacologically acceptable salts thereof, that demonstrate anticoagulant action.

BACKGROUND ART

In recent years, average life span has become longer and the size of the elderly population has increased due to progress in medical care. In addition, the proportion of persons suffering from cardiovascular diseases has increased due to changes in eating habits and lifestyle. In particular, not only do thrombotic diseases such as cerebral infarction, myocardial infarction or peripheral circulatory disturbance demonstrate high mortality rates, but serious living restrictions caused by sequelae place a huge burden on patients. Inhibiting thrombus formation is important for preventing and treating these diseases.

Increased blood coagulation has conventionally been one of the causes of unstable angina, cerebral infarction, cerebral embolism, myocardial infarction, pulmonary infarction, pulmonary embolism, Buerger's disease, deep vein thrombosis, generalized intravascular coagulation syndrome, thrombosis following prosthetic valve replacement, reocclusion following vascular reconstruction and thrombosis during extracorporeal circulation. Accordingly, there is a need for an oral anticoagulant that has superior dose response, substantivity, low risk of hemorrhage and few side effects (Non-Patent Document 1).

Oral anticoagulants currently on the market are coumarin-based drugs as represented by warfarin (Patent Document 1). This drug inhibits the supply of reduced vitamin K by inhibiting the vitamin K metabolic cycle, and inhibits γ-carboxylation modification (Gla modification) of glutamic acid residues by γ-carboxylase. This leads the drug to inhibit activation of vitamin K-dependent blood coagulation factors (such as FII, FVII, FIX or FX) and demonstrate potent anticoagulant action. However, while warfarin demonstrates potent and stable sustained pharmacological effects, it has a narrow effective therapeutic range and requires

monitoring by frequent blood sampling in order to accommodate individual differences in the effective dose. In addition, the risk of deviating from the therapeutic range due to drug interactions and the influence of vitamin K in the diet has also been pointed out. Thus, there is a desire for an oral anticoagulant that allows pharmacological effects to be easily controlled with low-frequency monitoring, has superior safety and has high general versatility.

In recent years, a coumarin derivative ATI-5923 (Patent Document 2) has been reported that is designed to avoid the drug interaction of warfarin and is currently undergoing clinical trials. In addition, sulfaquinoxaline has been reported as a compound other than a coumarin derivative (Non-Patent Document 2). However, the hydroxyquinoxaline structure possessed by the compounds of the present application as a partial structure thereof is not disclosed or suggested in these prior art documents.

[Patent Document 1] U.S. Patent No. 2642441
[Patent Document 2] WO 2005/100336
[Non-Patent Document 1] Thrombosis Research, Vol. 68, pp. 507-512, 1992
[Non-Patent Document 2] Archive of Biochemistry and Biophysics, Vol. 269, pp. 18-24, 1989

DISCLOSURE OF THE INVENTION

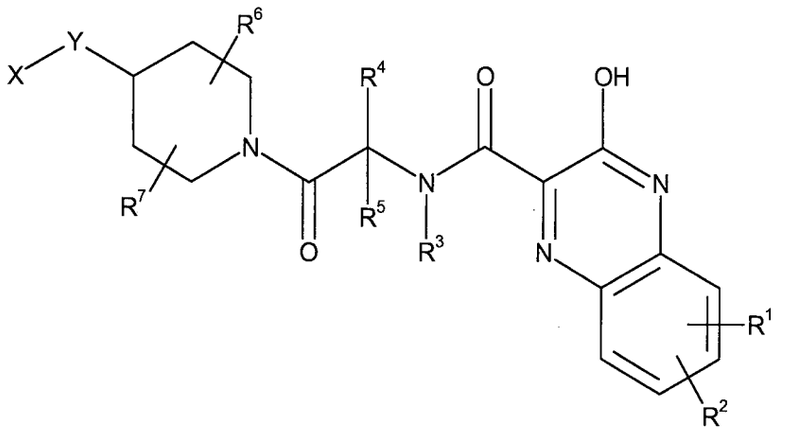
[Problems to be Solved by the Invention]

As a result of conducting studies on the synthesis of compounds which are able to inhibit activation of blood coagulation factors as described above along with the pharmacological action thereof, the inventors of the present invention found that a group of compounds having for the basic structure thereof a hydroxyquinoxalinecarboxamide derivative has superior anticoagulant action, thereby leading to completion of the present invention.

[Means for Solving the Problems]

The present invention is directed to:

(1) a compound represented by the following general formula (i):



wherein,

each of R^1 and R^2 independently represents a hydrogen atom, a halogen atom, a cyano group, a C_{1-4} alkyl group or a C_{1-4} alkoxy group,

R^3 represents a hydrogen atom or a C_{1-4} alkyl group,

each of R^4 and R^5 independently represents a hydrogen atom, a halogen atom, a C_{1-4} alkyl group, a C_{2-4} alkenyl group, a C_{2-4} alkynyl group, a C_{3-5} cycloalkyl group or a hydroxy C_{1-4} alkyl group,

each of R^6 and R^7 independently represents a hydrogen atom or a C_{1-4} alkyl group,

X represents a monocyclic or bicyclic C_{3-10} cycloalkyl group, a monocyclic or bicyclic C_{6-10} aryl group or a monocyclic or bicyclic 5- to 10-membered heterocyclic group (in which the heterocyclic group includes aromatic heterocycles and non-aromatic heterocycles and contains 1 to 3 atoms selected from the group consisting of a nitrogen atom, a sulfur atom and an oxygen atom), which may be substituted with 1 to 3 substituents selected from substituent group α,

Y represents -CHRa-, -C(OH)Ra-, -CO-, -O-, -NRa-, -S-, -SO- or -SO_2-,

Ra represents a hydrogen atom, a C_{1-4} alkyl group, a halogeno C_{1-4} alkyl group or a C_{1-4} alkanoyl group, or

in the case where Ra in Y is a C_{1-4} alkyl group, a halogeno C_{1-4} alkyl group or a C_{1-4} alkanoyl group, Ra may form a 5- or 6-membered ring by bonding with an atom that is a component of X,

substituent group α represents:

a halogen atom, a cyano group, a nitro group, a hydroxy group;

a C_{1-4} alkyl group, a C_{2-4} alkenyl group, a C_{2-4} alkynyl group, a C_{3-6} cycloalkyl group, a C_{1-4} alkoxy group or a C_{3-6} cycloalkoxy group, which may be substituted with substituent(s) selected from substituent group β;

-OCORb, -CORb, -COORb, -CONRbRc, -NRbRc, -NRbCORc, -NRbSORc, -$NRbSO_2Rc$, -SRb, -SORb, -SO_2Rb;

a phenyl group, and

a 5- or 6-membered heterocyclic group, which may be substituted with a C_{1-4} alkyl group(s) (in which the heterocyclic group includes aromatic heterocycles and non-aromatic heterocycles and contains 1 to 3 atoms selected from the group consisting of a nitrogen atom, a sulfur atom and an oxygen atom),

each of Rb and Rc independently represents a hydrogen atom, a C_{1-4} alkyl group or a halogeno C_{1-4} alkyl group, and

substituent group β represents a halogen atom, a hydroxy group, a C_{1-4} alkoxy group and a C_{1-4} alkanoyloxy group,

or a pharmacologically acceptable salt thereof,

(2) a compound or a pharmacologically acceptable salt thereof, described in (1) above, wherein each of R^1 and R^2 independently represents a hydrogen atom or a halogen atom,

(3) a compound or a pharmacologically acceptable salt thereof, described in (1) above, wherein each of R^1 and R^2 independently represents a hydrogen atom or a fluorine atom,

(4) a compound or a pharmacologically acceptable salt thereof, described in (1) above, wherein R^1 and R^2 both represent a hydrogen atom,

(5) a compound or a pharmacologically acceptable salt thereof, described in any one of (1) to (4) above, wherein R^3 represents a hydrogen atom or a methyl group,

(6) a compound or a pharmacologically acceptable salt thereof, described in any one of (1) to (4) above, wherein R^3 represents a hydrogen atom,

(7) a compound or a pharmacologically acceptable salt thereof, described in any one of (1) to (6) above, wherein R^4 represents a hydrogen atom, a fluorine atom, a C_{1-4} alkyl group, a C_{2-4} alkenyl group, a C_{2-4} alkynyl group, a C_{3-5} cycloalkyl group or a hydroxy C_{1-4} alkyl group, and R^5 represents a hydrogen atom,

(8) a compound or a pharmacologically acceptable salt thereof, described in any one of (1) to (6) above, wherein R^4 represents a methyl group, an ethyl group, an isopropyl group, an isobutyl group, a t-butyl group, a cyclopropyl group or a 1-hydroxy-1-methylethyl group, and R^5 represents a hydrogen atom,

(9) a compound or a pharmacologically acceptable salt thereof, described in any one of (1) to (6) above, wherein R^4 represents a methyl group, an ethyl group, an isopropyl group, a t-butyl group, a cyclopropyl group or a 1-hydroxy-1-methylethyl group, and R^5 represents a hydrogen atom,

(10) a compound or a pharmacologically acceptable salt thereof,

described in any one of (1) to (6) above, wherein R^4 represents an ethyl group, an isopropyl group, a cyclopropyl group or a 1-hydroxy-1-methylethyl group, and R^5 represents a hydrogen atom,

(11) a compound or a pharmacologically acceptable salt thereof, described in any one of (1) to (6) above, wherein each of R^4 and R^5 independently represents a hydrogen atom, a halogen atom, a C_{1-4} alkyl group, a C_{2-4} alkenyl group, a C_{2-4} alkynyl group or a C_{3-5} cycloalkyl group,

(12) a compound or a pharmacologically acceptable salt thereof, described in any one of (1) to (6) above, wherein R^4 represents a hydrogen atom, a methyl group, an ethyl group, an isopropyl group, an isobutyl group, a t-butyl group or a cyclopropyl group, and R^5 represents a hydrogen atom,

(13) a compound or a pharmacologically acceptable salt thereof, described in any one of (1) to (12) above, wherein each of R^6 and R^7 independently represents a hydrogen atom or methyl group,

(14) a compound or a pharmacologically acceptable salt thereof, described in any one of (1) to (12) above, wherein R^6 and R^7 both represent a hydrogen atom,

(15) a compound or a pharmacologically acceptable salt thereof, described in any one of (1) to (14) above, wherein X represents a phenyl group, a naphthyl group, a pyridyl group, a pyridazinyl group, a pyrimidinyl group, a pyrazinyl group, a quinolyl group, an isoquinolyl group, a benzimidazolyl group, a benzoxazolyl group or a benzothiazolyl group, which may be substituted with 1 or 2 substituents selected from substituent group α, and

substituent group α represents a halogen atom, a cyano group, a nitro group, a hydroxy group, a methyl group, an ethyl group, a propyl group, an isopropyl group, a t-butyl group, a hydroxymethyl group, a fluoromethyl group, a difluoromethyl group, a trifluoromethyl group, a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, an acetoxy group, a trifluoromethoxy group, an acetyl group, a methoxycarbonyl group, an ethoxycarbonyl group, a dimethylcarbamoyl group, a piperidyl group, a pyrrolidyl group, a morpholino group, a pyrazolyl group, a methylpyrazolyl group, an oxadiazolyl group, a methyloxadiazolyl group, a phenyl group and a pyridyl group,

(16) a compound or a pharmacologically acceptable salt thereof, described in any one of (1) to (14) above, wherein X represents a phenyl group, a naphthyl group, a pyridyl group, a pyridazinyl group, a pyrimidinyl group, a pyrazinyl group, a quinolyl group or an isoquinolyl

group, which may be substituted with 1 or 2 substituents selected from substituent group α, and

substituent group α represents a fluorine atom, a chlorine atom, a bromine atom, a cyano group, a hydroxy group, a methyl group, an ethyl group, a propyl group, an isopropyl group, a t-butyl group, a hydroxymethyl group, a fluoromethyl group, a difluoromethyl group, a trifluoromethyl group, a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, a trifluoromethoxy group, a piperidyl group, a pyrrolidyl group, a phenyl group and a pyridyl group,

(17) a compound or a pharmacologically acceptable salt thereof, described in any one of (1) to (14) above, wherein X represents a phenyl group, a 2-pyridyl group, a 3-pyridyl group, a 3-pyridazinyl group, a 2-pyrimidinyl group or a 5-pyrimidinyl group, which may be substituted with 1 or 2 substituents selected from substituent group α, and

substituent group α represents a fluorine atom, a chlorine atom, a bromine atom, a cyano group, a hydroxy group, a methyl group, an ethyl group, a t-butyl group, a trifluoromethyl group, a methoxy group, an ethoxy group, a trifluoromethoxy group, a phenyl group and a pyridyl group,

(18) a compound or a pharmacologically acceptable salt thereof, described in any one of (1) to (14) above, wherein X represents a phenyl group or a 2-pyridyl group, which may be substituted with 1 or 2 substituents selected from substituent group α, and substituent group α represents a fluorine atom, a chlorine atom, a trifluoromethyl group, a methoxy group and a trifluoromethoxy group,

(19) a compound or a pharmacologically acceptable salt thereof, described in any one of (1) to (14) above, wherein X represents 4-fluorophenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 4-chlorophenyl, 2,4-dichlorophenyl, 4-trifluoromethylphenyl, 4-trifluoromethoxyphenyl, 5-fluoropyridin-2-yl, 5-chloropyridin-2-yl, 5-trifluoromethylpyridin-2-yl or 6-methoxypyridin-3-yl,

(20) a compound or a pharmacologically acceptable salt thereof, described in any one of (1) to (14) above, wherein X represents a phenyl group, a naphthyl group, a pyridyl group, a pyridazinyl group, a pyrimidinyl group, a pyrazinyl group, a quinolyl group or an isoquinolyl group, which may be substituted with 1 or 2 substituents selected from substituent group α, and substituent group α represents a fluorine atom, a chlorine atom, a bromine atom, a cyano group, a hydroxy group, a methyl group, an ethyl group, a propyl group, an isopropyl group, a t-butyl group, a hydroxymethyl group, a fluoromethyl group, a difluoromethyl

group, a trifluoromethyl group, a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, a trifluoromethoxy group, a phenyl group and a pyridyl group,

(21) a compound or a pharmacologically acceptable salt thereof, described in any one of (1) to (14) above, wherein X represents a phenyl group, a naphthyl group, a pyridyl group, a pyridazinyl group or a pyrimidinyl group, which may be substituted with 1 or 2 substituents selected from substituent group α, and substituent group α represents a fluorine atom, a chlorine atom, a bromine atom, a cyano group, a hydroxy group, a methyl group, a trifluoromethyl group, a methoxy group, a trifluoromethoxy group and a phenyl group,

(22) a compound or a pharmacologically acceptable salt thereof, described in any one of (1) to (14) above, wherein X represents a phenyl group or a pyridyl group, which may be substituted with 1 or 2 substituents selected from substituent group α, and substituent group α represents a fluorine atom, a chlorine atom, a cyano group, a trifluoromethyl group and a trifluoromethoxy group,

(23) a compound or a pharmacologically acceptable salt thereof, described in any one of (1) to (22) above, wherein Y represents -CO-, -O- or -NRa-, Ra represents a hydrogen atom, a methyl group or an ethyl group, and Ra may form a 5-membered ring by bonding with an atom that is a component of X in the case where Ra is an ethyl group in Y,

(24) a compound or a pharmacologically acceptable salt thereof, described in any one of (1) to (22) above, wherein Y represents -O- or -NRa-, and Ra represents a hydrogen atom, a methyl group or an ethyl group,

(25) a compound or a pharmacologically acceptable salt thereof, described in any one of (1) to (22) above, wherein Y represents -O-,

(26) a compound or a pharmacologically acceptable salt thereof, described in (1) above, which is selected from the following:

N-{(1S)-2-[4-(2-fluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,

N-{(1S)-2-[4-(3-fluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,

N-{(1S)-2-[4-(4-fluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,

N-{(1S)-2-[4-(4-chlorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,

3-hydroxy-N-[(1S)-1-methyl-2-oxo-2-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}ethyl]quinoxaline-2-carboxamide,

N-{(1S)-2-[4-(4-cyanophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,

N-{(1S)-2-[4-(2,4-difluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,

N-{(1S)-2-[4-(3,4-difluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,

N-[(1S)-2-{4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}-1-methyl-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide,

N-[(1S)-2-{4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}-1-methyl-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide,

3-hydroxy-N-[(1S)-1-methyl-2-oxo-2-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)ethyl]quinoxaline-2-carboxamide,

N-[(1S)-1-{[4-(2-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,

N-[(1S)-1-{[4-(3-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,

N-[(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,

N-[(1S)-1-{[4-(4-chlorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,

3-hydroxy-N-[(1S)-1-({4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide,

N-[(1S)-1-{[4-(4-cyanophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,

N-[(1S)-1-{[4-(2,4-difluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,

N-[(1S)-1-{[4-(3,4-difluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,

N-[(1S)-1-({4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]-3-hydroxyquinoxaline-2-carboxamide,

N-[(1S)-1-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]-3-hydroxyquinoxaline-2-carboxamide,

3-hydroxy-N-{(1S)-1-[(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide,

N-[(1S)-1-{[4-(2-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,

N-[(1S)-1-{[4-(3-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,

N-[(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,

N-[(1S)-1-{[4-(4-chlorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,

3-hydroxy-N-[(1S)-2-methyl-1-({4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide,

N-[(1S)-1-{[4-(4-cyanophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,

N-[(1S)-1-{[4-(2,4-difluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,

N-[(1S)-1-{[4-(3,4-difluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,

N-[(1S)-1-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,

N-[(1S)-1-({4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,

3-hydroxy-N-{(1S)-2-methyl-1-[(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide,

3-hydroxy-N-[(1S)-1-({4-[(6-methoxypyridin-3-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]quinoxaline-2-carboxamide,

N-[(1S)-1-{[4-(2,4-difluorobenzoyl)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,

N-[(1S)-1-({4-[(2,4-difluorophenyl)(hydroxy)methyl]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,

N-[(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-hydroxy-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,

N-{(1S)-1-cyclopropyl-2-[4-(2-fluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,

N-{(1S)-1-cyclopropyl-2-[4-(3-fluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,

N-{(1S)-1-cyclopropyl-2-[4-(4-fluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,

N-{(1S)-2-[4-(4-chlorophenoxy)piperidin-1-yl]-1-cyclopropyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,

N-[(1S)-1-cyclopropyl-2-oxo-2-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}ethyl]-3-hydroxyquinoxaline-2-carboxamide,

N-{(1S)-2-[4-(4-cyanophenoxy)piperidin-1-yl]-1-cyclopropyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,

N-{(1S)-1-cyclopropyl-2-[4-(2,4-difluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,

N-{(1S)-1-cyclopropyl-2-[4-(3,4-difluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,

N-[(1S)-1-cyclopropyl-2-{4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2-{4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}-1-cyclopropyl-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-cyclopropyl-2-oxo-2-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)ethyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2,2-dimethyl-1-{[4-(2-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2,2-dimethyl-1-{[4-(3-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2,2-dimethyl-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-chlorophenoxy)piperidin-1-yl]carbonyl}-2,2-dimethylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2,2-dimethyl-1-({4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}carbonyl)propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-cyanophenoxy)piperidin-1-yl]carbonyl}-2,2-dimethylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(2,4-difluorophenoxy)piperidin-1-yl]carbonyl}-2,2-dimethylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(3,4-difluorophenoxy)piperidin-1-yl]carbonyl}-2,2-dimethylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2,2-dimethyl-1-({4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2,2-dimethylpropyl]-3-hydroxyquinoxaline-2-carboxamide, and
N-{(1S)-2,2-dimethyl-1-[(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}-3-hydroxyquinoxaline-2-carboxamide,

(27) a compound or a pharmacologically acceptable salt thereof, described in (1) above, which is selected from the following:
N-{(1S)-2-[4-(2-fluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(3-fluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(4-fluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(4-chlorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-[(1S)-1-methyl-2-oxo-2-{4-[4-

(trifluoromethoxy)phenoxy]piperidin-1-yl}ethyl]quinoxaline-2-carboxamide,
N-{(1S)-2-[4-(4-cyanophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(2,4-difluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(3,4-difluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2-{4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}-1-methyl-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2-{4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}-1-methyl-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-[(1S)-1-methyl-2-oxo-2-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)ethyl]quinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(2-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(3-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-chlorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-[(1S)-1-({4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-cyanophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(2,4-difluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(3,4-difluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-{(1S)-1-[(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(2-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(3-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-

3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-chlorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-[(1S)-2-methyl-1-({4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-cyanophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(2,4-difluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(3,4-difluorophenoxy)piperidin-1-yl]carbonyl}-2-methyl-propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-{(1S)-2-methyl-1-[(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide,
N-{(1S)-1-cyclopropyl-2-[4-(2-fluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-1-cyclopropyl-2-[4-(3-fluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-1-cyclopropyl-2-[4-(4-fluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(4-chlorophenoxy)piperidin-1-yl]-1-cyclopropyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-cyclopropyl-2-oxo-2-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}ethyl]-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(4-cyanophenoxy)piperidin-1-yl]-1-cyclopropyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-1-cyclopropyl-2-[4-(2,4-difluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-1-cyclopropyl-2-[4-(3,4-difluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-cyclopropyl-2-{4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2-{4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}-1-cyclopropyl-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-cyclopropyl-2-oxo-2-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)ethyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2,2-dimethyl-1-{[4-(2-fluorophenoxy)piperidin-1-

yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2,2-dimethyl-1-{[4-(3-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2,2-dimethyl-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-chlorophenoxy)piperidin-1-yl]carbonyl}-2,2-dimethylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2,2-dimethyl-1-({4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}carbonyl)propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-cyanophenoxy)piperidin-1-yl]carbonyl}-2,2-dimethylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(2,4-difluorophenoxy)piperidin-1-yl]carbonyl}-2,2-dimethylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(3,4-difluorophenoxy)piperidin-1-yl]carbonyl}-2,2-dimethylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2,2-dimethyl-1-({4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2,2-dimethylpropyl]-3-hydroxyquinoxaline-2-carboxamide, and
N-{(1S)-2,2-dimethyl-1-[(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}-3-hydroxyquinoxaline-2-carboxamide,

(28) a compound or a pharmacologically acceptable salt thereof, described in (1) above, which is selected from the following:
N-{(1S)-2-[4-(4-chlorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(2,4-difluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(3,4-difluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2-{4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}-1-methyl-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2-{4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}-1-methyl-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-[(1S)-1-methyl-2-oxo-2-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)ethyl]quinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-chlorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,

N-[(1S)-1-({4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-{(1S)-1-[(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-[(1S)-2-methyl-1-({4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-{(1S)-2-methyl-1-[(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide, and
N-{(1S)-1-cyclopropyl-2-[4-(4-fluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide.

(29) a pharmaceutical composition comprising as an active ingredient a compound or a pharmacologically acceptable salt thereof, selected from those described in any one of (1) to (28) above,

(30) a pharmaceutical composition for preventing and/or treating a blood coagulation disorder, comprising as an active ingredient a compound or a pharmacologically acceptable salt thereof, selected from those described in any one of (1) to (28) above,

(31) a pharmaceutical composition for preventing and/or treating thromboembolism, congenital anticoagulant factor deficiency or plasminogen abnormality, comprising as an active ingredient a compound or a pharmacologically acceptable salt thereof, selected from those described in any one of (1) to (28) above, and,

(32) a pharmaceutical composition for preventing thrombogenesis following artificial valve replacement surgery, or thrombogenesis caused by nonvalvular atrial fibrillation or atrial fibrillation accompanying valvular heart disease, comprising as an active ingredient a compound or a pharmacologically acceptable salt thereof, selected from those described in any of (1) to (28) above.

In addition, the present invention provides a method for preventing and/or treating blood coagulation disorders, comprising administering an effective amount of a compound or a pharmacologically acceptable salt thereof, selected from those described in any one of (1) to (28) above to

a warm-blooded animal (and preferably a human) (such as a method for preventing and/or treating thromboembolism, congenital anticoagulant factor deficiency or plasminogen abnormality, or a method for preventing thrombogenesis following artificial valve replacement surgery or thrombogenesis caused by nonvalvular atrial fibrillation or atrial fibrillation accompanying valvular heart disease).

In the aforementioned general formula (i), a "halogen atom" in the definitions of R^1, R^2, R^4, R^5, α and β refers to a fluorine atom, a chlorine atom, a bromine atom or an iodine atom. It is preferably a fluorine atom or a chlorine atom, and more preferably a fluorine atom.

A "C_{1-4} alkyl group" in the definitions of R^1, R^2, R^3, R^4, R^5, R^6, R^7, Ra, Rb, Rc and α refers to a linear or branched alkyl group having 1 to 4 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, s-butyl or t-butyl.

A "halogeno C_{1-4} alkyl group" in the definitions of Ra, Rb and Rc refers to a group in which one or two or more hydrogen atoms of the aforementioned "C_{1-4} alkyl group" are substituted by the aforementioned "halogen atom(s)". Examples are fluoromethyl, difluoromethyl, trifluoromethyl and 2,2,2-trifluoroethyl, and preferably trifluoromethyl.

A "hydroxy C_{1-4} alkyl group" in the definitions of R^4 and R^5 refers to a group in which one or two or more hydrogen atoms of the aforementioned "C_{1-4} alkyl group" are substituted by hydroxy group(s). Examples are hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxy-1-methylethyl, 1-hydroxy-2-methylpropyl and 3-hydroxy-butyl. It is preferably 1-hydroxy-1-methylethyl.

A "C_{2-4} alkenyl group" in the definitions of R^4, R^5 and α refers to a linear or branched alkenyl group having 2 to 4 carbon atoms, for example, vinyl, 1-propenyl, 2-propenyl, isopropenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl, 2-butenyl, 3-butenyl or 1,3-butadienyl. It is preferably an alkenyl group having 2 or 3 carbon atoms.

A "C_{2-4} alkynyl group" in the definitions of R^4 and R^5 refers to a linear or branched alkynyl group having 2 to 4 carbon atoms, for example, an ethynyl, 2-propynyl, 1-methyl-2-propynyl, 2-methyl-2-propynyl, 2-butynyl or 3-butynyl group. It is preferably an alkynyl group having 2 or 3 carbon atoms.

A "C_{3-5} cycloalkyl group" in the definitions of R^4 and R^5 refers to a cycloalkyl group having 3 to 5 carbon atoms, for example, cyclopropyl, cyclobutyl or cyclopentyl.

A "C_{3-6} cycloalkyl group" in the definition of α refers to a cycloalkyl group having 3 to 6 carbon atoms, for example, the

aforementioned "C_{3-5} cycloalkyl group" or cyclohexyl.

A "monocyclic or bicyclic C_{3-10} cycloalkyl group" in the definition of X refers to a monocyclic or bicyclic saturated cyclic hydrocarbon group having 3 to 10 carbon atoms, for example, the aforementioned "C_{3-6} cycloalkyl group" or cyclooctyl, cyclononyl or tetrahydronaphthyl.

A "monocyclic or bicyclic C_{6-10} aryl group" in the definition of X refers to an aromatic hydrocarbon group having 6 to 10 carbon atoms, for example, phenyl or naphthyl, and preferably phenyl.

A "5- or 6-membered heterocyclic group" in the definition of α includes 5- or 6-membered monocyclic aromatic heterocycles and non-aromatic heterocycles, and the heterocyclic group contains 1 to 3 atoms selected from the group consisting of a nitrogen atom, a sulfur atom and an oxygen atom.

Aromatic heterocyclic groups which are a "5- or 6-membered heterocyclic group" include monocyclic aromatic heterocyclic groups containing 1 to 3 atoms selected from the group consisting of a nitrogen atom, a sulfur atom and an oxygen atom such as 5-membered ring groups such as pyrrolyl, thienyl, furyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl or thiadiazolyl, and 6-membered ring groups such as pyranyl, pyridyl, pyridazinyl, pyrimidinyl or pyrazinyl group. Preferred examples include 2-pyridyl, 3-pyridyl, 3-pyridazinyl, 2-pyrimidinyl and 5-pyrimidinyl, while more preferred examples include 2-pyridyl, 3-pyridyl, 3-pyridazinyl and 2-pyrimidinyl.

Among "5- or 6-membered heterocyclic groups", a non-aromatic heterocyclic group refers to a group in which 1 to 3 carbon atoms of a monocyclic cycloalkyl group or cycloalkenyl group having 5 or 6 carbon atoms are substituted with an atom selected from the group consisting of a nitrogen atom, a sulfur atom and an oxygen atom.

Non-aromatic heterocyclic groups which are of "5- or 6-membered heterocyclic groups" include monocyclic non-aromatic heterocyclic groups like a 5-membered ring group such as pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, oxazolidinyl or thiazolidinyl; and a 6-membered ring group such as piperidyl, tetrahydropyridyl, dihydropyridyl, piperazinyl, morpholinyl or thiomorpholinyl.

A "monocyclic or bicyclic 5- to 10-membered heterocyclic group" in the definition of X includes 5- to 10-membered monocyclic or bicyclic aromatic heterocycles and non-aromatic heterocycles, and the heterocyclic group contains 1 to 3 atoms selected from the group consisting of a nitrogen atom, a sulfur atom and an oxygen atom.

5- to 10-membered monocyclic or bicyclic aromatic heterocycles include, for example, aromatic heterocyclic groups in the aforementioned "5- or 6-membered heterocyclic groups", and bicyclic aromatic heterocyclic groups containing 1 to 3 atoms selected from the group consisting of a nitrogen atom, a sulfur atom and an oxygen atom, such as indolyl, isoindolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, isobenzofuranyl, indazolyl, benzimidazolyl, imidazopyridyl, benzoxazolyl, benzothiazolyl, quinolyl or isoquinolyl. Preferred examples include pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinolyl, isoquinolyl, benzimidazolyl, benzoxazolyl and benzothiazolyl, more preferred examples include pyridyl, pyridazinyl, pyrimidinyl, quinolyl and isoquinolyl, even more preferred examples include 2-pyridyl, 3-pyridyl, 3-pyridazinyl, 2-pyrimidinyl and 5-pyrimidinyl, with 2-pyridyl being even more preferred.

A 5- to 10-membered monocyclic or bicyclic non-aromatic heterocyclic group refers to a group in which 1 to 3 carbon atoms of a monocyclic cycloalkyl or cycloalkenyl group having 5 to 10 carbon atoms are substituted with an atom selected from the group consisting of a nitrogen atom, a sulfur atom and and an oxygen atom, or a group in which 1 to 3 carbon atoms of a bicycloalkyl or bicycloalkenyl group having 7 to 10 carbon atoms are substituted with an atom selected from the group consisting of a nitrogen atom, a sulfur atom or an oxygen atom. Examples include a non-aromatic heterocyclic group among the aforementioned "5- or 6-membered heterocyclic groups", and bicyclic non-aromatic heterocyclic groups such as indolinyl, isoindolinyl, thiochromanyl group or chromanyl.

A "C_{1-4} alkoxy group" in the definitions of R^1, R^2, α and β refers to a group in which an oxygen atom is bonded to the aforementioned "C_{1-4} alkyl group". Examples include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy and t-butoxy, while preferred examples include methoxy, ethoxy, propoxy and isopropoxy, with methoxy being more preferred.

A "C_{3-10} cycloalkoxy group" in the definition of α refers to a group in which an oxygen atom is bonded to the aforementioned "C_{3-6} cycloalkyl group". Examples include cyclopropoxy, cyclobutoxy, cyclopentoxy and cyclohexyloxy.

A "C_{1-4} alkanoyl group" in the definition of Ra refers to, for example, formyl, acetyl, propionyl, butyryl or isobutyryl.

A "C_{1-4} alkanoyloxy group" in the definition of β refers to a group in which an oxygen atom is bonded to the aforementioned "C_{1-4} alkanoyl group". Examples include formyloxy, acetyloxy, propionyloxy, butyryloxy and isobutyryloxy.

R^1 and R^2 of compound (i) of the present invention are each

independently, preferably a hydrogen atom or a halogen atom, more preferably a hydrogen atom or a fluorine atom, and even more preferably both R^1 and R^2 are hydrogen atoms.

The substitution positions of R^1 and R^2 are preferably the 6 or 7 positions, and are more preferably the 7 position.

R^3 of compound (i) of the present invention is preferably a hydrogen atom or a methyl group and more preferably a hydrogen atom.

R^4 and R^5 in compound (i) of the present invention are preferably such that R^4 is a hydrogen atom, a fluorine atom, a C_{1-4} alkyl group, a C_{2-4} alkenyl group, a C_{2-4} alkynyl group, a C_{3-5} cycloalkyl group or a hydroxy C_{1-4} alkyl group and R^5 is a hydrogen atom. More preferably, R^4 is a methyl group, an ethyl group, an isopropyl group, an isobutyl group, a t-butyl group, a cyclopropyl group or a 1-hydroxy-1-methylethyl group and R^5 is a hydrogen atom. Even more preferably, R^4 is a methyl group, an ethyl group, an isopropyl group, a t-butyl group, a cyclopropyl group or a 1-hydroxy-1-methylethyl group and R^5 is a hydrogen atom. Still more preferably, R^4 is an ethyl group, an isopropyl group, a cyclopropyl group or a 1-hydroxy-1-methylethyl group and R^5 is a hydrogen atom.

R^6 and R^7 of compound (i) of the present invention are each independently, preferably a hydrogen atom or a methyl group, and more preferably R^6 and R^7 are both hydrogen atoms.

The substitution positions of R^6 and R^7 are preferably the 3 position or the 5 position.

X of compound (i) of the present invention is preferably a phenyl group, a naphthyl group, a pyridyl group, a pyridazinyl group, a pyrimidinyl group, a pyrazinyl group, a quinolyl group, an isoquinolyl group, a benzimidazolyl group, a benzoxazolyl group or a benzothiazolyl group that may be substituted with 1 or 2 substituents selected from the substituent group α, and the substituent group α consists of a halogen atom, a cyano group, a nitro group, a hydroxy group, a methyl group, an ethyl group, a propyl group, an isopropyl group, a t-butyl group, a hydroxymethyl group, a fluoromethyl group, a difluoromethyl group, a trifluoromethyl group, a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, an acetoxy group, a trifluoromethoxy group, an acetyl group, a methoxycarbonyl group, an ethoxycarbonyl group, a dimethylcarbamoyl group, a piperidyl group, a pyrrolidyl group, a morpholino group, a pyrazolyl group, a methylpyrazolyl group, an oxadiazolyl group, a methyloxadiazolyl group, a phenyl group and a pyridyl group.

More preferably, X is a phenyl group, a naphthyl group, a pyridyl

group, a pyridazinyl group, a pyrimidinyl group, a pyrazinyl group, a quinolyl group or an isoquinolyl group that may be substituted with 1 or 2 substituents selected from the substituent group α, and the substituent group α consists of a fluorine atom, a chlorine atom, a bromine atom, a cyano group, a hydroxy group, a methyl group, an ethyl group, a propyl group, an isopropyl group, a t-butyl group, a hydroxymethyl group, a fluoromethyl group, a difluoromethyl group, a trifluoromethyl group, a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, a trifluoromethoxy group, a piperidyl group, a pyrrolidyl group, a phenyl group and a pyridyl group.

Even more preferably, X is a phenyl group, a naphthyl group, a pyridyl group, a pyridazinyl group, a pyrimidinyl group, a pyrazinyl group, a quinolyl group or an isoquinolyl group that may be substituted with 1 or 2 substituents selected from the substituent group α, and the substituent group α consists of a fluorine atom, a chlorine atom, a bromine atom, a cyano group, a hydroxy group, a methyl group, an ethyl group, a propyl group, an isopropyl group, a t-butyl group, a hydroxymethyl group, a fluoromethyl group, a difluoromethyl group, a trifluoromethyl group, a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, a trifluoromethoxy group, a phenyl group and a pyridyl group.

Still more preferably, X is a phenyl group, a 2-pyridyl group, a 3-pyridyl group, a 3-pyridazinyl group, a 2-pyrimidinyl group or a 5-pyrimidinyl group that may be substituted with 1 or 2 substituents selected from the substituent group α, and the substituent group α consists of a fluorine atom, a chlorine atom, a bromine atom, a cyano group, a hydroxy group, a methyl group, an ethyl group, a t-butyl group, a trifluoromethyl group, a methoxy group, an ethoxy group, a trifluoromethoxy group, a phenyl group and a pyridyl group.

Even more preferably, X is a phenyl group or a pyridyl group that may be substituted with 1 or 2 substituents selected from the substituent group α, and the substituent group α consists of a fluorine atom, a chlorine atom, a cyano group, a trifluoromethyl group, a methoxy group and a trifluoromethoxy group.

Even more preferably, X is a phenyl group or a 2-pyridyl group that may be substituted with 1 or 2 substituents selected from the substituent group α, and the substituent group α consists of a fluorine atom, a chlorine atom, a trifluoromethyl group,a methoxy group and a trifluoromethoxy group.

Preferable specific examples of X include 2-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 2-chlorophenyl, 4-chlorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 2-bromophenyl, 4-bromophenyl, 2-chloro-4-fluorophenyl, 4-chloro-2-fluorophenyl, 2-bromo-4-fluorophenyl, 4-bromo-2-fluorophenyl, 2-cyanophenyl, 4-cyanophenyl, 2-cyano-4-fluorophenyl, 4-cyano-2-fluorophenyl, 2-hydroxyphenyl, 4-hydroxyphenyl, 2-methylphenyl, 4-methylphenyl, 2-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 2-trifluoromethoxyphenyl, 4-trifluoromethoxyphenyl, 2-biphenyl, 4-biphenyl, 5-fluoropyridin-2-yl, 6-fluoropyridin-3-yl, 5-chloropyridin-2-yl, 6-chloropyridin-3-yl, 6-methoxypyridin-3-yl, 5-cyanopyridin-2-yl, 5-trifluoromethylpyridin-2-yl, 5-trifluoromethoxypyridin-2-yl, 3,5-difluoropyridin-2-yl, 6-methoxypyridazin-3-yl, 6-isopropoxypyridazin-3-yl, 5-fluoropyrimidin-2-yl, 5-chloropyrimidin-2-yl, 5-bromopyrimidin-2-yl, 5-trifluoromethylpyrimidin-2-yl, 5-trifluoromethoxypyrimidin-2-yl or 5-phenylpyrimidin-2-yl.

More preferable specific examples of X include 4-fluorophenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 4-chlorophenyl, 2,4-dichlorophenyl, 4-trifluoromethylphenyl, 4-trifluoromethoxyphenyl, 5-fluoropyridin-2-yl, 5-chloropyridin-2-yl, 5-trifluoromethylpyridin-2-yl or 6-methoxypyridin-3-yl.

Y of compound (i) of the present invention is preferably -CO-, -O- or -NRa-, and Ra is preferably a hydrogen atom, a methyl group or an ethyl group. In the case where Ra in Y is an ethyl group, Ra may also preferably form a 5-membered ring by bonding with atoms that are components of X. More preferably, Y is -O- or -NRa-, and Ra is a hydrogen atom,a methyl group or an ethyl group. Y is even more preferably -O-.

Since compound (i) of the present invention is able to be in the form of a salt by reacting with acid in the case of having a basic group such as an amino group or by reacting with base in the case of having an acidic group such as a sulfonamido group, a "pharmacologically acceptable salt thereof" refers to that salt.

Examples of salts based on basic groups include inorganic acid salts such as hydrogen halides such as hydrofluorides, hydrochlorides, hydrobromides or hydroiodides; nitrates, perchlorates, sulfates or phosphates; organic acid salts such as lower alkanesulfonic acid salts such as methanesulfonates, trifluoromethanesulfonates or ethanesulfonates; arylsulfonic acid salts such as benzenesulfonates or p-toluenesulfonates; acetates, malates, fumarates, succinates, citrates, ascorbates, tartrates, oxalates or maleates; and amino acid salts such as

glycine salts, lysine salts, arginine salts, ornithine salts, glutamates or aspartates.

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, aluminum salts or iron salts; inorganic salts such as ammonium salts, amine salts such as organic salts such as t-octylamine salts, dibenzylamine salts, morpholine salts, glucosamine salts, phenylglycine alkyl ester salts, ethylenediamine salts, N-methylglucamine salts, guanidine salts, diethylamine salts, triethylamine salts, dicyclohexylamine salts, N,N'-dibenzylethylenediamine salts, chloroprocaine salts, procaine salts, diethanolamine salts, N-benzylphenethylamine salts, piperazine salts, tetramethylammonium salts or tris(hydroxymethyl)aminomethane salts; and amino acid salts such as glycine salts, lysine salts, arginine salts, ornithine salts, glutamates or aspartates.

A compound represented by general formula (i) of the present invention or a pharmacologically acceptable salt thereof may absorb moisture and form a hydrate as a result of allowing it to stand in air, and such hydrates are also included in the present invention.

A compound represented by general formula (i) of the present invention or a pharmacologically acceptable salt thereof may form a solvate as a result of allowing it to stand in a solvent, and such solvates are also included in the present invention.

A compound represented by general formula (i) of the present invention or a pharmacologically acceptable salt thereof has optical isomers based on an asymmetric center in a molecule thereof. In compounds of the present invention, these isomers and mixtures of these isomers are all represented by a single formula, namely general formula (i). Thus, the present invention includes all of these isomers and mixtures of these isomers.

Although examples of typical compounds represented by general formula (i) of the present invention include the compounds listed below, the present invention is not limited to these compounds.

Examples of these compounds include:

N-{(1S)-2-[4-(2-fluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,

N-{(1S)-2-[4-(3-fluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,

N-{(1S)-2-[4-(4-fluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-

hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(4-chlorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-[(1S)-1-methyl-2-oxo-2-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}ethyl]quinoxaline-2-carboxamide,
N-{(1S)-2-[4-(4-cyanophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(2,4-difluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(3,4-difluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2-{4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}-1-methyl-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2-{4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}-1-methyl-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-[(1S)-1-methyl-2-oxo-2-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)ethyl]quinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(2-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(3-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-chlorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-[(1S)-1-({4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-cyanophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(2,4-difluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(3,4-difluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-{(1S)-1-[(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(2-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-

3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(3-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-chlorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-[(1S)-2-methyl-1-({4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-cyanophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(2,4-difluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(3,4-difluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-{(1S)-2-methyl-1-[(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide,
3-hydroxy-N-[(1S)-1-({4-[(6-methoxypyridin-3-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]quinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(2,4-difluorobenzoyl)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(2,4-difluorophenyl)(hydroxy)methyl]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-hydroxy-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-1-cyclopropyl-2-[4-(2-fluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-1-cyclopropyl-2-[4-(3-fluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-1-cyclopropyl-2-[4-(4-fluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(4-chlorophenoxy)piperidin-1-yl]-1-cyclopropyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-cyclopropyl-2-oxo-2-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}ethyl]-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(4-cyanophenoxy)piperidin-1-yl]-1-cyclopropyl-2-oxoethyl}-3-

hydroxyquinoxaline-2-carboxamide,
N-{(1S)-1-cyclopropyl-2-[4-(2,4-difluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-1-cyclopropyl-2-[4-(3,4-difluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-cyclopropyl-2-{4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2-{4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}-1-cyclopropyl-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-cyclopropyl-2-oxo-2-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)ethyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2,2-dimethyl-1-{[4-(2-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2,2-dimethyl-1-{[4-(3-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2,2-dimethyl-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-chlorophenoxy)piperidin-1-yl]carbonyl}-2,2-dimethylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2,2-dimethyl-1-({4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}carbonyl)propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-cyanophenoxy)piperidin-1-yl]carbonyl}-2,2-dimethyl-propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(2,4-difluorophenoxy)piperidin-1-yl]carbonyl}-2,2-dimethylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(3,4-difluorophenoxy)piperidin-1-yl]carbonyl}-2,2-dimethylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2,2-dimethyl-1-({4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2,2-dimethylpropyl]-3-hydroxyquinoxaline-2-carboxamide, and
N-{(1S)-2,2-dimethyl-1-[(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}-3-hydroxyquinoxaline-2-carboxamide,

Among these compounds, preferred are:
N-{(1S)-2-[4-(2-fluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(3-fluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(4-fluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-

hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(4-chlorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-[(1S)-1-methyl-2-oxo-2-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}ethyl]quinoxaline-2-carboxamide,
N-{(1S)-2-[4-(4-cyanophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(2,4-difluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(3,4-difluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2-{4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}-1-methyl-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2-{4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}-1-methyl-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-[(1S)-1-methyl-2-oxo-2-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)ethyl]quinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(2-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(3-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-chlorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-[(1S)-1-({4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-cyanophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(2,4-difluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(3,4-difluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-{(1S)-1-[(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(2-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-

3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(3-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-chlorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-[(1S)-2-methyl-1-({4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-cyanophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(2,4-difluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(3,4-difluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-{(1S)-2-methyl-1-[(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide,
N-{(1S)-1-cyclopropyl-2-[4-(2-fluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-1-cyclopropyl-2-[4-(3-fluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-1-cyclopropyl-2-[4-(4-fluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(4-chlorophenoxy)piperidin-1-yl]-1-cyclopropyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-cyclopropyl-2-oxo-2-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}ethyl]-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(4-cyanophenoxy)piperidin-1-yl]-1-cyclopropyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-1-cyclopropyl-2-[4-(2,4-difluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-1-cyclopropyl-2-[4-(3,4-difluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-cyclopropyl-2-{4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2-{4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}-1-cyclopropyl-2-

oxoethyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-cyclopropyl-2-oxo-2-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)ethyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2,2-dimethyl-1-{[4-(2-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2,2-dimethyl-1-{[4-(3-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2,2-dimethyl-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-chlorophenoxy)piperidin-1-yl]carbonyl}-2,2-dimethylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2,2-dimethyl-1-({4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}carbonyl)propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-cyanophenoxy)piperidin-1-yl]carbonyl}-2,2-dimethylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(2,4-difluorophenoxy)piperidin-1-yl]carbonyl}-2,2-dimethylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(3,4-difluorophenoxy)piperidin-1-yl]carbonyl}-2,2-dimethylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2,2-dimethyl-1-({4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2,2-dimethylpropyl]-3-hydroxyquinoxaline-2-carboxamide, and
N-{(1S)-2,2-dimethyl-1-[(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}-3-hydroxyquinoxaline-2-carboxamide,

Among these compounds, more preferred are:
N-{(1S)-2-[4-(4-chlorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(2,4-difluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(3,4-difluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2-{4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}-1-methyl-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2-{4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}-1-methyl-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-[(1S)-1-methyl-2-oxo-2-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)ethyl]quinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-chlorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-

hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-{(1S)-1-[(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-[(1S)-2-methyl-1-({4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-{(1S)-2-methyl-1-[(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide, and
N-{(1S)-1-cyclopropyl-2-[4-(4-fluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide.

[Effect of the Invention]

A compound represented by general formula (i) of the present invention or a pharmacologically acceptable salt thereof has superior anticoagulant action. Accordingly, it is useful as an active ingredient of a preventive and/or therapeutic preparation for blood coagulation disorders (such as a preventive and/or therapeutic agent for thromboembolisms, congenital anticoagulant factor deficiencies or plasminogen abnormalities, or preventive agents for thrombogenesis following artificial valve replacement surgery, or thrombogenesis caused by nonvalvular atrial fibrillation or atrial fibrillation accompanying valvular heart disease.

BEST MODE FOR CARRYING OUT THE INVENTION

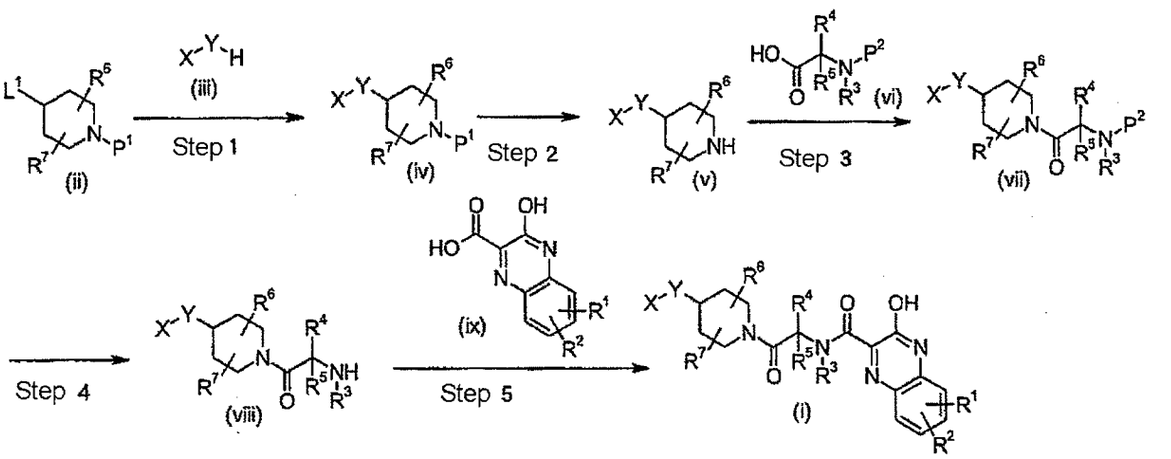
A compound represented by general formula (i) of the present invention can be manufactured in accordance with a manufacturing method indicated in <Manufacturing Method 1> to <Manufacturing Method 5>.

<Manufacturing Method 1>

This manufacturing method is a method for obtaining a compound of

the present invention represented by general formula (i) from a compound represented by general formula (ii).

(Scheme 1)



In the above formulae, R^1, R^2, R^3, R^4, R^5, R^6, R^7, X and Y are the same as previously defined.

L^1 represents a leaving group. Examples of leaving groups (L^1) include halogen atoms such as a chloro group or a bromo group, and sulfonyloxy groups such as a methanesulfonyloxy group, a p-toluenesulfonyloxy group or a trifluoromethanesulfonyloxy group.

P^1 and P^2 represent protecting groups of an amino group. Examples of protecting groups (P^1 and P^2) include alkoxycarbonyl groups such as a methoxycarbonyl group, an ethoxycarbonyl group, a t-butoxycarbonyl group or an allyloxycarbonyl group, an aryloxycarbonyl groups such as a benzyloxycarbonyl group or a para-methoxybenzyloxycarbonyl group; and arylmethyl groups such as a benzyl group or a triphenylmethyl group.

Step 1

This step is a step for synthesizing a compound represented by general formula (iv) by reacting a piperidine derivative represented by general formula (ii), having a leaving group (L^1) at the 4 position, and in which the amino group is protected by a protecting group (P^1), and a compound represented by general formula (iii) in an inert solvent in the presence of a base.

Examples of inert solvents include halogen-based solvents such as methylene chloride, chloroform, dichloroethane or carbon tetrachloride, ether-based solvents such as tetrahydrofuran, 1,2-dimethoxyethane or dioxane, aromatic-based solvents such as benzene or toluene, and amide-based solvents such as N,N-dimethylformamide or N-methylpyrrolidone.

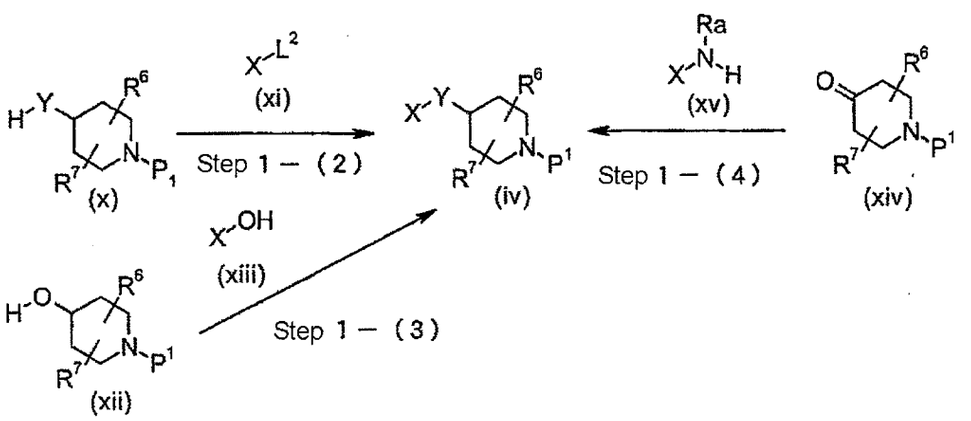
Examples of bases include organic bases such as pyridine, triethylamine, N,N-diisopropylethylamine, 4-(dimethylamino)pyridine, N-methylmorpholine, 2,6-lutidine or collidine, and carbonates, alkoxides

and hydroxides of alkaline metals or alkaline earth metals such as sodium carbonate, potassium carbonate, cesium carbonate, cerium fluoride, sodium hydrogen carbonate, sodium ethoxide, potassium butoxide or sodium hydroxide.

The reaction temperature is from cooling to reflux heating (the temperature at which the solvent is heated and refluxed varies depending on the solvent), and specifically is 0 to 200°C and preferably 0 to 150°C.

The reaction time varies depending on the reaction temperature, raw material compounds, reaction reagents, solvent used in the reaction and the like. It is normally 30 minutes to 48 hours and preferably 1 to 8 hours.

A compound represented by general formula (iv) obtained in this step can be synthesized using a different method as indicated below. (Scheme 2)



In the above formulae, R^6, R^7, Ra, P^1, X and Y are the same as previously defined.

L^2 represents a leaving group. Examples of leaving groups (L^2) include halogen atoms such as a chloro group or a bromo group, and a methanesulfonyloxy group, a p-toluenesulfonyloxy group or a trifluoromethanesulfonyloxy group.

Step 1-(2)

This step is a step for synthesizing a compound represented by the above formula (iv) from a compound represented by general formula (x) and a compound represented by general formula (xi).

This reaction can be achieved by a method that complies with the reaction conditions used in Step 1.

Step 1-(3)

Among the compounds represented by formula (iv), a compound in which Y represents an oxygen atom can be synthesized from a compound represented by the above general formula (xii) using a Mitsunobu reaction carried out in a solvent.

Examples of solvents used in this reaction include solvents that are inert in the reaction, including aromatic-based solvents such as benzene, toluene or xylene, and ether-based solvents such as diethyl ether, tetrahydrofuran or dioxane.

Examples of reaction reagents include organic phosphorous reagents such as triphenylphosphine and diazo reagents such as diethyl azodicarboxylate, diisopropyl azodicarboxylate or dipiperidineamide azodicarboxylate, and preferably triphenylphosphine and diisopropyl azodicarboxylate are used .

The reaction temperature is from cooling to reflux heating (the temperature at which the solvent is heated and refluxed varies depending on the solvent), and specifically is 0 to 200°C and preferably 0 to 150°C.

The reaction time varies depending on the reaction temperature, raw material compounds, reaction reagents, solvent used in the reaction and the like. It is normally 30 minutes to 48 hours and preferably 1 to 8 hours.

Step 1-(4)

Among the compounds represented by formula (iv), a compound in which Y represents a nitrogen atom can be synthesized from a 4-piperidinone derivative represented by the above formula (xiv), in which the amino group is protected with a protecting group (P^1), using a reductive amination method carried out in a solvent.

Examples of solvents used in this reaction include solvents that are inert in the reaction, including aromatic-based solvents such as benzene, toluene or xylene, ether-based solvents such as diethyl ether, tetrahydrofuran or dioxane, and alcohols such as methanol, ethanol or isopropanol.

As the reaction reagents, reducing agents such as sodium borohydride, sodium cyanoborohydride or sodium triacetoxyborohydride are used, and preferably sodium cyanoborohydride is used .

The reaction temperature is from cooling to reflux heating (the temperature at which the solvent is heated and refluxed varies depending on the solvent), and specifically is 0 to 200°C and preferably 0 to 150°C.

Although the reaction time varies depending on the reaction temperature, raw material compounds, reaction reagents, solvent used in the reaction and the like, it is normally 30 minutes to 48 hours and preferably 1 to 8 hours.

Step 2

This step is a step for obtaining a compound represented by general formula (v), or a salt thereof, by removing a protecting group (P^1) of a

compound represented by general formula (iv) by a suitable method.

The method used to remove the protecting group varies depending on the chemical properties of the protecting group used, and in the case of an acyl-type protecting group such as an alkanoyl group, alkoxycarbonyl group or aroyl group, the protecting group can be removed by hydrolysis by using a base such as an alkali metal hydroxide such as lithium hydroxide, sodium hydroxide or potassium hydroxide.

In addition, in the case of a substituted methoxycarbonyl-type protecting group such as a t-butylcarbonyl group or para-methoxybenzyloxycarbonyl group, the protecting group can be removed by a suitable acid such as acetic acid, hydrochloric acid, sulfuric acid, hydrobromic acid, phosphoric acid, trifluoroacetic acid, trifluoromethanesulfonic acid or a combination thereof.

In addition, an arylmethoxycarbonyl group such as a benzyloxycarbonyl group, a para-methoxybenzyloxycarbonyl group or a para-nitrobenzyloxycarbonyl group, and an arylmethyl group such as a benzyl group can be removed by hydrolysis using a palladium-carbon catalyst.

A triphenylmethyl group can be removed with, for example, formic acid, acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid, trifluoromethanesulfonic acid or a combination thereof, and can be removed by hydrolysis using a palladium-carbon catalyst.

This step is preferably carried out in water, a suitable organic solvent or a mixed solvent thereof, and examples of suitable organic solvents used include solvents that are inert in the reaction including halogen-based solvents such as methylene chloride, chloroform, dichloroethane or carbon tetrachloride, ethers such as tetrahydrofuran, 1,2-dimethoxyethane or dioxane, and alcohols such as methanol or ethanol.

The reaction temperature is from cooling to reflux heating (the temperature at which the solvent is heated and refluxed varies depending on the solvent), and specifically is 0 to 200°C and preferably 0 to 150°C.

Although the reaction time varies depending on the reaction temperature, raw material compounds, reaction reagents, solvent used in the reaction and the like, it is normally 30 minutes to 48 hours and preferably 1 to 8 hours.

Step 3

This step is a step for obtaining compounds represented by general formula (vii) by reacting compounds represented by general formula (v), or a salt thereof, with amino acid derivatives represented by general formula (vi).

In this reaction, after converting the amino acid derivative represented by general formula (vi) to an activating compound, the amino acid derivative is condensed with a compound represented by general formula (v). While examples of activating compounds include acid halides produced using an acid halide such as thionyl chloride, active esters obtained by reacting with a phenol such as para-nitrophenol, active amides obtained by reacting with, for example, 1,1-carbonyldiimidazole, and reaction products with 1-benzotriazolyloxy-pyrrolidino-phosphonium hexafluorophosphite or N,N-dicyclohexylcarbodiimide hydrochloride which are usually used in peptide synthesis from amino acids. Reaction products with N,N-dicyclohexylcarbodiimide hydrochloride are preferably used. In this reaction, 1-hydroxybenzotriazole and the like can also be added as necessary.

A compound represented by general formula (vii) can be obtained by reacting an activating compound of an amino acid derivative obtained in this manner and a compound represented by general formula (v), or a salt thereof, in an inert solvent, and normally in the presence of a base.

Examples of inert solvents used include solvents that are inert in the reaction, including halogen-based solvents such as methylene chloride, chloroform, dichloroethane or carbon tetrachloride, ether-based solvents such as tetrahydrofuran, 1,2-dimethoxyethane or dioxane, aromatic-based solvents such as benzene or toluene, and amide-based solvents such as N,N-dimethylformamide or N-methylpyrrolidone.

Examples of bases used include organic bases such as pyridine, triethylamine, N,N-diisopropylethylamine, 4-(dimethylamino)pyridine, N-methylmorpholine, 2,6-lutidine or collidine, and carbonates, alkoxides and hydroxides of alkaline metals or alkaline earth metals such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate, sodium ethoxide, potassium butoxide, sodium hydroxide or potassium hydride. Triethylamine and N-methylmorpholine are preferably used.

The reaction temperature is from cooling to reflux heating (the temperature at which the solvent is heated and refluxed varies depending on the solvent), and specifically is 0 to 200°C and preferably 0 to 150°C.

The reaction time varies depending on the reaction temperature, raw material compounds, reaction reagents, solvent used in the reaction and the like. It is normally 30 minutes to 48 hours and preferably 1 to 8 hours.

Step 4

This step is a step for obtaining a compound represented by general formula (viii), or a salt thereof, by removing a protecting group (P^2) of

an amino group of a compound represented by general formula (vii).

This reaction can be achieved by a method that complies with the reaction conditions used in Step 2.

Step 5

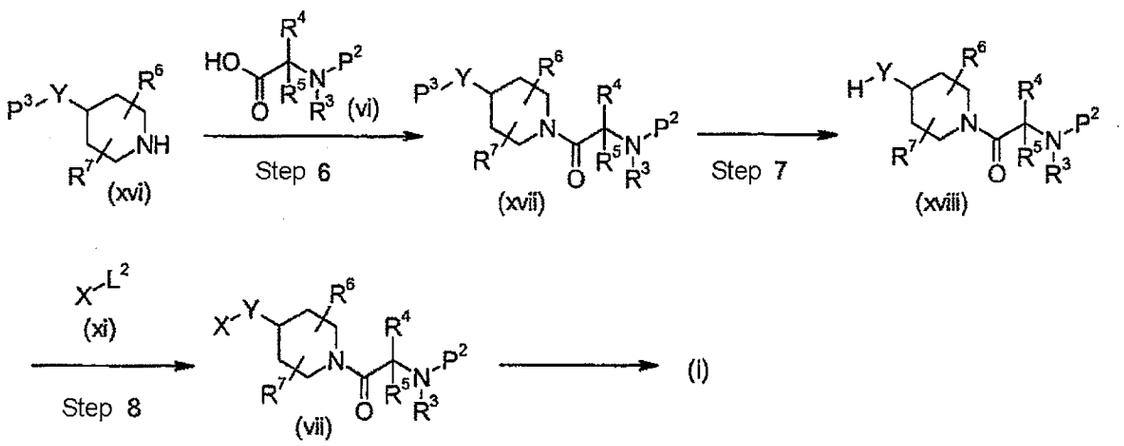
This step is a step for obtaining a compound represented by general formula (i) by carrying out a condensation reaction between an amine represented by general formula (viii), or a salt thereof, and a carboxylic acid represented by general formula (ix).

This reaction can be achieved by a method that complies with the reaction conditions used in Step 3.

<Manufacturing Method 2>

This manufacturing method is a method for obtaining a compound of the present invention represented by general formula (i) by synthesizing a compound represented by general formula (vii) from a compound represented by general formula (xvi).

(Scheme 3)



In the above formulae, R^3, R^4, R^5, R^6, R^7, P^2, L^2, X and Y are the same as previously defined.

P^3 represents an amino group or a protecting group of a hydroxy group. As examples of protecting groups, P^2 and P^3 are both protecting groups of an amino group in the case where Y is represented by formula NRa. In other cases these protecting groups indicate different groups from each other, and groups for which P^3 is stable under conditions for removing P^2 are respectively selected.

In the case where Y is an oxygen atom, examples of protecting groups include acyl-type protecting groups such as an acetyl group, an alkanoyl group or a benzoyl group, arylmethyl groups such as a benzyl group, silyl ether groups such as a t-butyldiphenylsilyl group or a t-butyldimethylsilyl group, a methoxymethyl group and a tetrahydropyranyl group, and preferably a t-butyldiphenylsilyl group is used.

Step 6

This step is a step for obtaining a compound represented by the aforementioned formula (xvii) by a reaction of a piperidine derivative represented by the aforementioned formula (xvi) and an amino acid represented by the aforementioned formula (vi).

This reaction can be achieved by a method that complies with the reaction conditions used in Step 3.

Step 7

This step is a step for obtaining a compound represented by the aforementioned formula (xviii), or a salt thereof, by removing a protecting group (P^3) of a compound represented by the aforementioned formula (xvii).

In the case where Y in formula (xvii) is a group represented by formula NRa, this step can be achieved by a method that complies with the reaction conditions used in Step 2.

In the case where Y in formula (xvii) is an oxygen atom, the method used to remove the protecting group (P^3) varies depending on the chemical properties of the protecting group used, and for example, an acyl group such as an alkanoyl group or aroyl group can be removed by hydrolysis with a suitable base such as an alkali metal hydroxide such as lithium hydroxide, sodium hydroxide or potassium hydroxide. In the case of an arylmethyl group, the protecting group can be removed by hydrolysis using a palladium-carbon catalyst. A silyl group such as a t-butyldimethylsilyl group or a t-butyldiphenylsilyl group can be removed by a hydrofluoride such as tetrabutylammonium fluoride. In addition, a methoxymethyl group or a tetrahydropyranyl group can be removed by acetic acid or hydrochloric acid and the like.

Examples of solvents used in this reaction include solvents that are inert in the reaction, including halogen-based solvents such as methylene chloride, chloroform, dichloroethane or carbon tetrachloride, ether-based solvents such as tetrahydrofuran, 1,2-dimethoxyethane or dioxane, aromatic-based solvents such as benzene or toluene, alcohol-based solvents such as methanol, ethanol or isopropanol, and amide-based solvents such as N,N-dimethylformamide and N-methylpyrrolidone.

The reaction temperature is from cooling to reflux heating (the temperature at which the solvent is heated and refluxed varies depending on the solvent), and specifically is 0 to 200°C and preferably 0 to 150°C.

Although the reaction time varies depending on the reaction temperature, raw material compounds, reaction reagents, solvent used in the reaction and the like, it is normally 30 minutes to 48 hours and

preferably 1 to 8 hours.

Step 8

This step is a step for synthesizing a compound represented by the aforementioned formula (vii) by reacting a compound represented by the aforementioned formula (xviii), or a salt thereof, with a compound represented by the aforementioned formula (xi).

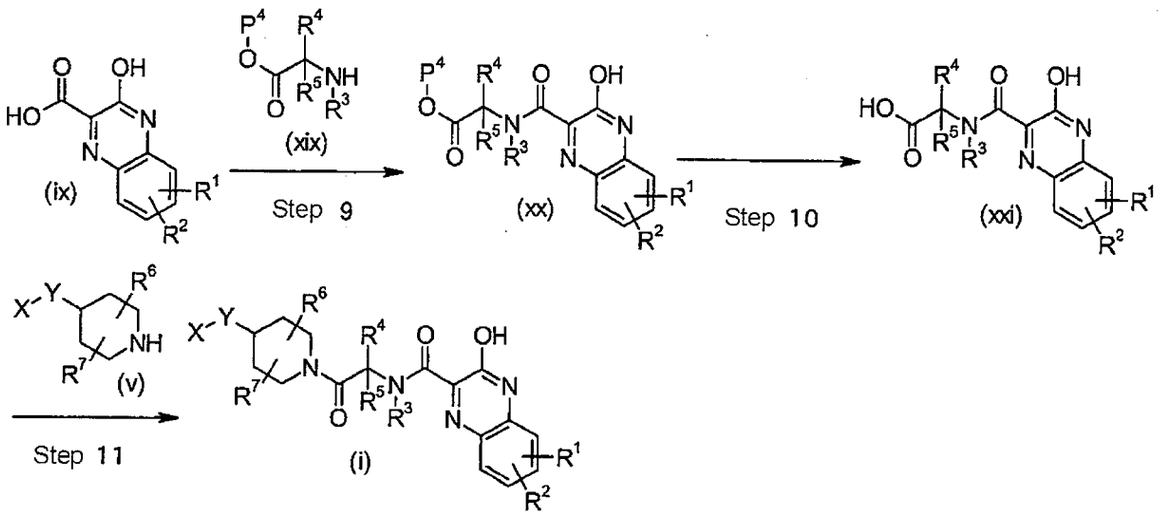
This reaction can be achieved by a method that complies with the reaction conditions used in Step 1.

The compound represented by formula (vii) can be converted to a compound of the present invention represented by formula (i) by a method that complies with the scheme used in Manufacturing Method 1.

<Manufacturing Method 3>

This manufacturing method is a method for obtaining a compound of the present invention represented by formula (i) by synthesizing a carboxylic acid represented by general formula (xxi) from a carboxylic acid derivative represented by general formula (ix), and reacting with a piperidine derivative represented by general formula (v), or a salt thereof.

(Scheme 4)



In the above formulae, R^1, R^2, R^3, R^4, R^5, R^6, R^7, X and Y are the same as previously defined. P^4 represents a protecting group of a carboxylic acid. Examples of protecting groups (P^4) include a methyl group, an ethyl group, a t-butyl group and a benzyl group.

Step 9

This step is a step for obtaining a compound represented by general formula (xx) by reacting a carboxylic acid represented by general formula (ix) with an amino acid represented by general formula (xix).

This reaction can be achieved by a method that complies with the reaction conditions used in Step 3.

Step 10

This step is a step for obtaining a carboxylic acid derivative represented by general formula (xxi) by removing a protecting group (P^4) of a compound represented by the aforementioned formula (xx) in a solvent.

The conditions of this reaction for removing the protecting group varies depending on the chemical properties of the protecting group used, and in the case of, for example, a methyl group or ethyl group, the protecting group can be removed by hydrolysis by using a suitable base such as an alkali metal hydroxide such as lithium hydroxide, sodium hydroxide or potassium hydroxide.

In the case of a t-butyl group, the protecting group can be removed by treating with trifluoroacetic acid or hydrochloric acid.

In addition, in the case of an arylmethyl group such as a benzyl group, the protecting group can be removed by hydrolysis using a palladium-carbon catalyst.

Examples of solvents used in this reaction include solvents that are inert in the reaction, including halogen-based solvents such as methylene chloride, chloroform, dichloroethane or carbon tetrachloride, ether-based solvents such as tetrahydrofuran, 1,2-dimethoxyethane or dioxane, aromatic-based solvents such as benzene or toluene, alcohol-based solvents such as methanol, ethanol or isopropanol, and amide-based solvents such as N,N-dimethylformamide or N-methylpyrrolidone.

The reaction temperature is from cooling to reflux heating (the temperature at which the solvent is heated and refluxed varies depending on the solvent), and specifically is 0 to 200°C and preferably 0 to 150°C.

Although the reaction time varies depending on the reaction temperature, raw material compounds, reaction reagents, solvent used in the reaction and the like, it is normally 30 minutes to 48 hours and preferably 1 to 8 hours.

Step 11

This step is a step for obtaining a compound represented by general formula (i) by a condensation reaction between a carboxylic acid derivative represented by the aforementioned formula (xxi) and a piperidine derivative represented by the aforementioned formula (v), or a salt thereof.

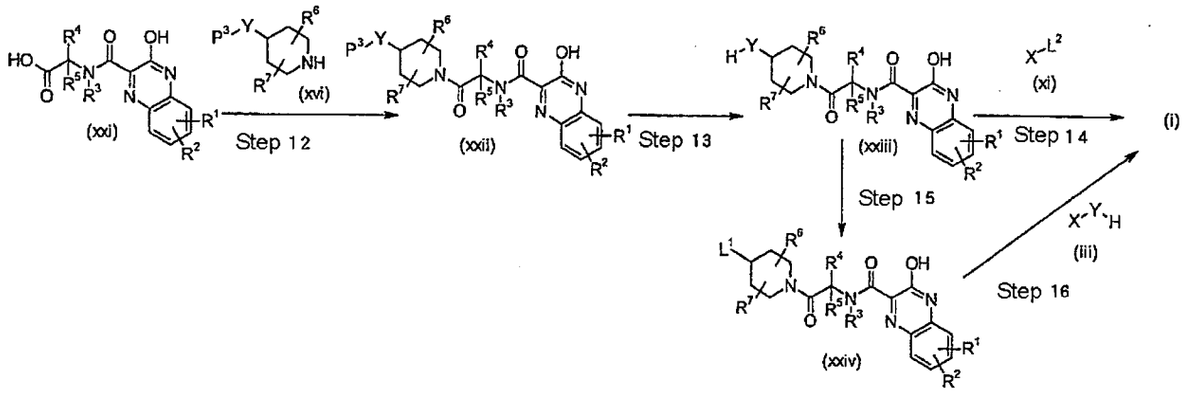
This reaction can be achieved by a method that complies with the reaction conditions used in Step 3.

<Manufacturing Method 4>

This manufacturing method is a method for obtaining a compound of

the present invention represented by general formula (i) from a compound represented by general formula (xxi) by going through an intermediate represented by general formula (xxiv).

(Scheme 5)



In the above formulae, R^1, R^2, R^3, R^4, R^5, R^6, R^7, L^1, L^2, P^3, X and Y are the same as previously defined.

Step 12

This step is a step for obtaining a compound represented by general formula (xxii) from a carboxylic acid derivative represented by the aforementioned formula (xxi) and a piperidine derivative represented by the aforementioned formula (xvi).

This reaction can be achieved by a method that complies with the reaction conditions used in Step 3.

Step 13

This step is a step for obtaining a compound represented by general formula (xxiii), or a salt thereof, by removing a protecting group (P^3) of a compound represented by the aforementioned general formula (xxii).

This reaction can be achieved by a method that complies with the reaction conditions used in Step 7.

Step 14

This step is a step for obtaining a compound represented by general formula (i) by reacting a compound represented by the aforementioned formula (xi) with a compound represented by the aforementioned formula (xxiii), or a salt thereof.

This reaction can be achieved by a method that complies with the reaction conditions used in Step 1.

Step 15

This step is a step for obtaining a compound represented by the aforementioned formula (xxiv) by converting a hydroxy group of a compound represented by the aforementioned formula (xxiii) in which Y represents an oxygen atom to a leaving group (L^1 group).

Examples of leaving groups (L^1) used include a halogen atom such as

a chloro group or a bromo group, and a methanesulfonyloxy group, a p-toluenesulfonyloxy group and a trifluoromethanesulfonyloxy group, and preferably a methanesulfonyloxy group is used.

In the case where a methanesulfonyloxy group is selected for the leaving group, for example, this reaction can be carried out by using methanesulfonyl chloride as a reagent and reacting the reaction reagent with a compound represented by the aforementioned formula (xxiii) in a solvent and in the presence of a base.

Although examples of bases include organic bases such as pyridine, triethylamine, N,N-diisopropylethylamine, 4-(dimethylamino)pyridine, N-methylmorpholine, 2,6-lutidine or collidine, and carbonates, alkoxides and hydroxides of alkali metals or alkaline earth metals such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate, sodium ethoxide, potassium butoxide, sodium hydroxide or potassium hydride, preferably triethylamine and N,N-diisopropylethylamine are used.

Examples of solvents used include solvents that are inert in the reaction, including halogen-based solvents such as methylene chloride, chloroform, dichloroethane or carbon tetrachloride, ether-based solvents such as tetrahydrofuran, 1,2-dimethoxyethane or dioxane, aromatic-based solvents such as benzene or toluene, and amide-based solvents such as N,N-dimethylformamide or N-methylpyrrolidone.

The reaction temperature is from cooling to reflux heating (the temperature at which the solvent is heated and refluxed varies depending on the solvent), and specifically is 0 to 200°C and preferably 0 to 150°C.

Although the reaction time varies depending on the reaction temperature, raw material compounds, reaction reagents, solvent used in the reaction and the like, it is normally 30 minutes to 48 hours and preferably 1 to 8 hours.

Step 16

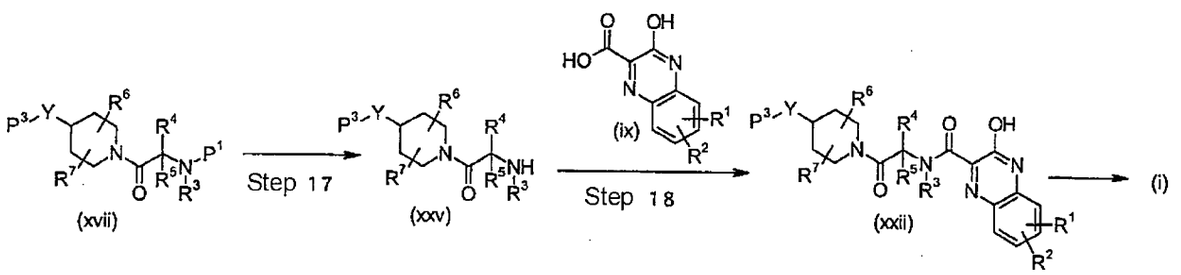
This step is a step for obtaining a compound of the present invention represented by general formula (i) from a compound represented by the aforementioned formula (xxiv) and a compound represented by the aforementioned formula (iii).

This reaction can be achieved by a method that complies with the reaction conditions used in Step 1.

<Manufacturing Method 5>

This manufacturing method is a method for obtaining a compound of the present invention represented by general formula (i) by synthesizing a compound represented by general formula (xxii) from a compound represented by the aforementioned formula (xvii).

(Scheme 6)



In the above formulae, R^1, R^2, R^3, R^4, R^5, R^6, R^7, P^2, P^3 and Y are the same as previously defined.

Although P^2 and P^3 are both amino group protecting groups in the case where Y represents a group represented by formula NRa, these protecting groups indicate respective and separate groups, and groups for which P^3 is stable under conditions for removing P^2 are respectively selected.

Step 17

This step is a step for obtaining a compound represented by the aforementioned formula (xxv), or a salt thereof, by removing a protecting group (P^2) of a compound represented by the aforementioned formula (xvii).

This reaction can be achieved by a method that complies with the reaction conditions used in Step 2.

Step 18

This step is a step for obtaining a compound represented by the aforementioned formula (xxii) from an amine derivative represented by the aforementioned formula (xxv), or a salt thereof, and a carboxylic acid derivative represented by the aforementioned formula (ix).

This reaction can be achieved by a method that complies with the reaction conditions used in Step 5.

The compound represented by the aforementioned formula (xxii) can be converted to a compound of the present invention represented by general formula (i) by a method that complies with the scheme used in Manufacturing Method 4.

Following completion of each of the above reactions, the desired compound can be recovered from the reaction mixture in accordance with ordinary methods.

For example, after suitably neutralizing the reaction mixture or after removing insoluble matter by filtering in the case where insoluble matter is present, mutually immiscible solvents such as water and ethyl acetate are added followed by fractionating the organic layer, washing with water and the like, and separating the organic layer containing the

desired compound. The desired compound is then obtained by drying with anhydrous magnesium sulfate and the like and distilling off the solvent.

The resulting desired compound can be separated and purified if necessary by suitably combining ordinary methods, such as recrystallization, reprecipitation, or methods commonly used to separate and purify organic compounds, examples of which include adsorption column chromatography using a carrier such as silica gel, alumina or magnesium-silica gel-based Florisil; a method using a synthetic adsorbent such as partition column chromatography using a carrier such as Sephadex LH-20 (Pharmacia), Amberlite XAD-11 (Rohm and Haas Chemical) or Diaion HP-20 (Mitsubishi Chemical), a method using ion exchange chromatography or forward phase-reverse phase column chromatography using a silica gel or alkylated silica gel (and preferably, high-performance liquid chromatography), followed by eluting with a suitable eluent.

Furthermore, each of the compounds (ii), (iii), (vi), (ix), (x), (xi), (xii), (xiii), (xiv), (xv), (xvi) and (xix) used as starting raw materials or auxiliary materials in the manufacturing methods of manufacturing methods 1 to 5 are either themselves known compounds or are compounds that are easily obtained from known compounds by treating in compliance with known methods.

Since the hydroxyquinoxalinecarboxamide derivatives of the present invention have superior anticoagulant action, they are useful as pharmaceuticals and particularly as preventive and/or therapeutic agents for blood coagulation disorders. The specific examples include preventive and/or therapeutic agents for blood coagulation disorders such as thromboembolism, congenital anticoagulant factor deficiency or plasminogen abnormality, and preventive agents for thrombogenesis following artificial valve replacement surgery, or thrombogenesis caused by nonvalvular atrial fibrillation or atrial fibrillation accompanying valvular heart disease.

Examples of administration forms of a compound of the present invention represented by general formula (i), or a pharmacologically acceptable salt thereof, include oral administration forms such as tablets, capsules, granules, powders or syrups, and parenteral administration forms such as injection preparations or suppositories. These preparations are produced by commonly known methods using additives such as vehicles, lubricants, binders, disintegrating agents, stabilizers, correctives or diluents.

In the case of administering a pharmaceutical composition having as the primary agent thereof a compound of the present invention represented

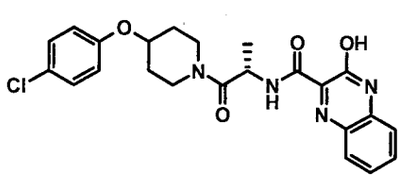
by general formula (i), or a pharmacologically acceptable salt thereof, administration can be carried out systemically or locally and orally or parenterally. Examples of drug forms used for oral administration include tablets, pills, powders, granules, capsules, solutions, suspensions, emulsions, syrups and elixirs. Examples of drug forms used for parenteral administration include injection preparations, ointments, gels, creams, poultices, medicated patches, aerosols, inhalants, sprays, eye drops, nose drops, suppositories and inhalants. These drug forms can be prepared in accordance with ordinary methods using additives suitably selected as necessary from pharmaceutically acceptable additives such as diluents, vehicles, binders, stabilizers, antiseptics, colorants, solubilizers, suspending agents, buffers or wetting agents.

Although the amount used varies depending on the symptoms, body weight, age and administration method of the subject receiving administration (warm-blooded animal such as a human), in the case of oral administration, for example, the amount used has a lower limit of 0.001 mg/kg of body weight (and preferably 0.01 mg/kg of body weight) per administration and an upper limit of 500 mg/kg of body weight (and preferably 50 mg/kg of body weight) per administration, while in the case of intravenous administration, the amount used has a lower limit of 0.005 mg/kg of body weight (and preferably 0.05 mg/kg of body weight) per administration, and an upper limit of 50 mg/kg of body weight (and preferably 5 mg/kg of body weight) per administration, and administration is preferably carried out one to several times per day corresponding to symptoms.

[Examples]

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

Example 1



N-{(1S)-2-[4-(4-Chlorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide

Example 1-1

t-Butyl [(1S)-2-(4-hydroxypiperidin-1-yl)-1-methyl-2-oxoethyl]carbamate

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (2.30

g, 12.0 mmol) and 1-hydroxybenzotriazole monohydrate (1.84 g, 12.0 mmol)were added to a methylene chloride solution (50 ml) of 4-hydroxypiperidine (1.00 g, 10.0 mmol) and N-(t-butoxycarbonyl)-L-alanine (1.89 g, 10.0 mmol), at 0°C, under nitrogen stream, followed by further addition of triethylamine (1.21 ml, 12.0 mmol), and stirring was carried out at room temperature overnight. The reaction solution was diluted with methylene chloride, followed by sequential washing with a saturated aqueous sodium hydrogencarbonate solution, a saturated aqueous ammonium chloride solution, water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., NH, 40+M) to afford t-butyl [(1S)-2-(4-hydroxypiperidin-1-yl)-1-methyl-2-oxoethyl]carbamate (2.02 g, yield 74%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 5.57 (1H, d, J=7.5 Hz), 4.64 (1H, m), 4.15-3.66 (3H, m), 3.40-3.14 (2H, m), 1.99-1.84 (2H, m), 1.71-1.49 (2H, m), 1.44 (9H, s), 1.31 and 1.30 (3H, d, J=7.0 Hz).

MS (FAB, m/z): 273 $(M+H)^+$.

Example 1-2

t-Butyl {(1S)-2-[4-(4-chlorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}carbamate

A 40% toluene solution of diisopropyl azodicarboxylate (2.80 ml, 5.21 mmol) was added to a toluene solution (18 ml) of t-butyl [(1S)-2-(4-hydroxypiperidin-1-yl)-1-methyl-2-oxoethyl]carbamate (1.29 g, 4.74 mmol), 4-chlorophenol (670 mg, 5.21 mmol) and triphenylphosphine (1.37 g, 5.21 mmol), at room temperature, under nitrogen stream, and stirring was carried out at 90°C overnight. The reaction solution was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., 40+M) to afford t-butyl {(1S)-2-[4-(4-chlorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}carbamate (700 mg, yield 34%) as a pale yellow amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.25 (2H, d, J=9.0 Hz), 6.85 (2H, d, J=9.0 Hz), 5.55 (1H, d, J=7.8 Hz), 4.65 (1H, m), 4.52 (1H, m), 3.88-3.36 (4H, m), 2.01-1.76 (4H, m), 1.44 (9H, s), 1.31 (3H, d, J=7.0 Hz).

MS (ESI, m/z): 383 $(M+H)^+$.

Example 1-3

N-{(1S)-2-[4-(4-Chlorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide

A 4N-hydrochloric acid 1,4-dioxane solution (5 ml) was added to a 1,4-dioxane solution (5 ml) of t-butyl {(1S)-2-[4-(4-chlorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}carbamate (701 mg, 1.83 mmol), under nitrogen stream, and the mixture was allowed to react at room temperature overnight. The reaction solution was concentrated to afford (2S)-1-[4-(4-chlorophenoxy)piperidin-1-yl]-1-oxopropane-2-amine hydrochloride (558 mg) as a white solid.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (115 mg, 0.600 mmol) and 1-hydroxybenzotriazole monohydrate (91.0 mg, 0.600 mmol) were added to a methylene chloride solution (5.0 ml) of the resulting compound (160 mg, 0.500 mmol) and 3-hydroxyquinoxaline-2-carboxylic acid (98.0 mg, 0.500 mmol), at room temperature, under nitrogen stream, followed by further addition of N-methylmorpholine (0.270 ml, 2.50 mmol), and stirring was carried out at room temperature overnight. The reaction solution was diluted with methylene chloride, followed by sequential washing with a saturated aqueous sodium hydrogencarbonate solution, a saturated aqueous ammonium chloride solution, water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. After the organic layer was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., 25+M), the residue resulting from concentration was suspended in a mixed solvent of methylene chloride-ethyl acetate, and the solid substance was collected by filtration to afford the desired title compound (130 mg, yield 57%) as a pale yellow solid.

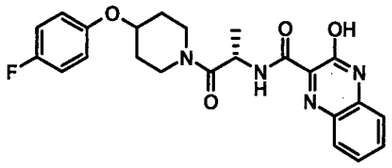
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.86 (1H, brs), 9.71 (1H, brs), 7.88 (1H, dd, J=7.4 Hz, 6.8Hz), 7.65 (1H, dd, J=7.8 Hz, 7.4 Hz), 7.40 (1H, d, J=6.8 Hz), 7.38 (1H, d, J=7.8 Hz), 7.34 (2H, d, J=7.4 Hz), 7.04 (2H, m), 5.03 (1H, m), 4.66 (1H, m), 4.06-3.16 (4H, m), 2.08-1.87 (2H, m), 1.73-1.45 (2H, m), 1.31 (3H, d, J=6.6 Hz).

IR (KBr) cm^{-1}: 2945, 1690, 1640, 1500, 1240.

MS (ESI, m/z): 455 $(M+H)^+$.

HRMS (ESI, m/z): 455.1478 (Calcd for $C_{23}H_{24}ClN_4O_4$: 455.1486).

Example 2



N-{(1S)-2-[4-(4-Fluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide

Example 2-1

t-Butyl {(1S)-2-[4-(4-fluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}carbamate

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (460 mg, 2.40 mmol) and 1-hydroxybenzotriazole monohydrate (367 mg, 2.40 mmol) were added to a methylene chloride solution (20 ml) of 4-(4-fluorophenoxy)piperidine hydrochloride (463 mg, 2.00 mmol) and N-(t-butoxycarbonyl)-L-alanine (416 mg, 2.20 mmol), at room temperature, under nitrogen stream, followed by further addition of N-methylmorpholine (1.10 ml, 10.0 mmol), and stirring was carried out at room temperature overnight. The reaction solution was poured into a 2N aqueous hydrochloric acid solution, followed by extraction with methylene chloride and sequential washing with water, a saturated aqueous sodium hydrogencarbonate solution, water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., 25+M) to afford t-butyl {(1S)-2-[4-(4-fluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}carbamate (683 mg, yield 93%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.99 (2H, dd, J=8.6 Hz, 8.6 Hz), 6.87 (2H, m), 5.56(1H, d, J=6.6 Hz), 4.65 (1H, m), 4.48 (1H, m), 4.09-3.36 (4H, m), 2.00-1.74 (4H, m), 1.44 (9H, s), 1.31 (3H, d, J=7.0 Hz).

MS (FAB, m/z): 367 $(M+H)^+$.

Example 2-2

N-{(1S)-2-[4-(4-Fluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide

Concentrated hydrochloric acid (0.5 ml) was added to an ethanol solution (2.0 ml) of t-butyl {(1S)-2-[4-(4-fluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}carbamate (111 mg, 0.300 mmol), under nitrogen stream, and stirring was carried out at room temperature overnight. The reaction solution was concentrated to afford (2S)-1-[4-(4-fluorophenoxy)piperidin-1-yl]-1-oxopropane-2-amine hydrochloride (100 mg) as a white solid.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (69.6 mg, 0.360 mmol) and 1-hydroxybenzotriazole monohydrate (55.6 mg, 0.360 mmol) were added to a methylene chloride solution (3.0 ml) of the resulting compound (100 mg, 0.300 mmol) and 3-hydroxyquinoxaline-2-carboxylic acid (57.5 mg, 0.300 mmol), at room temperature, under nitrogen stream, followed by further addition of N-methylmorpholine (0.170 ml, 1.50 mmol), and stirring was carried out at room temperature overnight. The reaction solution was poured into a 2N aqueous hydrochloric acid solution, followed by extraction with ethyl acetate and sequential washing with water, a saturated aqueous sodium hydrogencarbonate solution, water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. After the organic layer was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., 25+M), the residue resulting from concentration was suspended in a mixed solvent of methylene chloride-diethyl ether, and the solid substance was collected by filtration to afford the desired title compound (59.1 mg, yield 44%) as a pale yellow solid.

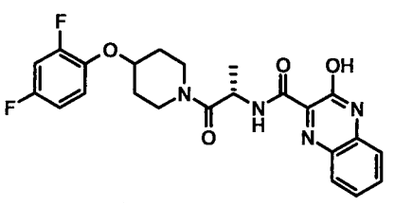
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.9 (1H, brs), 9.70 (1H, brs), 7.88 (1H, dd, J=7.8 Hz, 4.6 Hz), 7.65 (1H, dt, J=7.8 Hz, 1.0 Hz), 7.40 (1H, d, J=7.8 Hz), 7.38(1H, d, J=7.8 Hz), 7.13 (2H, m), 7.03 (2H, m), 5.02 (1H, m), 4.60 (1H, m), 4.02-3.19 (4H, m), 2.06-1.85 (2H, m), 1.72-1.44 (2H, m), 1.31 (3H, d, J=6.6 Hz).

IR (KBr) cm^{-1}: 2935, 1685, 1640, 1505, 1205.

MS (ESI, m/z): 439 $(M+H)^+$.

HRMS (ESI, m/z): 439.1791 (Calcd for $C_{23}H_{24}FN_4O_4$: 439.1782).

Example 3



N-{(1S)-2-[4-(2,4-Difluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide

Example 3-1

t-Butyl {(1S)-2-[4-(2,4-difluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}carbamate

Analogously to Example 1-2, t-butyl {(1S)-2-[4-(2,4-difluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}carbamate (700 mg,

yield 41%) was obtained from t-butyl [(1S)-2-(4-hydroxypiperidin-1-yl)-1-methyl-2-oxoethyl]carbamate (1.21 g, 4.44 mmol) and 2,4-difluorophenol (640 mg, 4.89 mmol as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.02-6.94 (1H, m), 6.92-6.84 (1H, m), 6.84-6.76 (1H, m), 5.55 (1H, d, J=7.4 Hz), 4.65 (1H, m), 4.42 (1H, m), 3.90-3.35 (4H, m), 2.00-1.77 (4H, m), 1.44 (9H, s), 1.32 and 1.31 (3H, d, J=7.0 Hz).

MS (ESI, m/z): 385 $(M+H)^+$.

Example 3-2

N-{(1S)-2-[4-(2,4-Difluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 1-3, (2S)-1-[4-(2,4-difluorophenoxy)piperidin-1-yl]-1-oxopropane-2-amine hydrochloride (476 mg, yield 82%) was obtained from t-butyl {(1S)-2-[4-(2,4-difluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}carbamate (700 mg, 1.82 mmol). The resulting compound (160 mg, 0.500 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (98.0 mg, 0.500 mmol) to afford the desired title compound (164 mg, yield 67%) as a pale yellow solid.

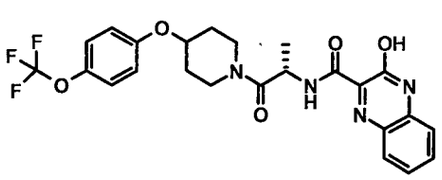
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.86 (1H, brs), 9.77 (1H, brs), 7.87 (1H, d, J=7.4 Hz), 7.64 (1H, dd, J=7.8 Hz, 7.8 Hz), 7.37 (1H, dd, J=7.8 Hz, 7.4 Hz), 7.38 (1H, d, J=7.8 Hz), 7.35-7.27 (2H, m), 7.07-6.99 (1H, m), 5.02 (1H, m), 4.59 (1H, m), 4.11-3.65 (2H, m), 3.57-3.11 (2H, m), 2.10-1.85 (2H, m), 1.80-1.46 (2H, m), 1.32 and 1.31 (3H, d, J=6.6 Hz).

IR (KBr) cm^{-1}: 2950, 1685, 1640, 1630, 1500.

MS (ESI, m/z): 457 $(M+H)^+$.

HRMS (ESI, m/z): 457.1709 (Calcd for $C_{23}H_{23}F_2N_4O_4$: 457.1687).

Example 4



3-Hydroxy-N-[(1S)-1-methyl-2-oxo-2-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}ethyl]quinoxaline-2-carboxamide

Example 4-1

t-Butyl [(1S)-1-methyl-2-oxo-2-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}ethyl]carbamate

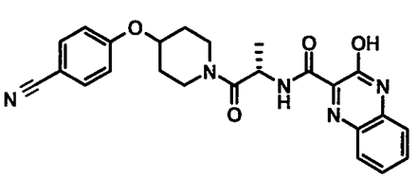
Analogously to Example 1-2, t-butyl [(1S)-1-methyl-2-oxo-2-{4-[4-

(trifluoromethoxy)phenoxy]piperidin-1-yl}ethyl]carbamate (824 mg, yield 39%) was obtained from t-butyl {(1S)-2-[(4-hydroxypiperidin-1-yl)carbonyl]-1-methyl-2-oxoethyl}carbamate (1.32 g, 4.85 mmol) and 4-(trifluoromethoxy)phenol (950 mg, 5.33 mmol) as a pale yellow oil.
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.16 (2H, d, J=9.0 Hz), 6.90 (2H, d, J=9.0 Hz), 5.55 (1H, d, J=7.6 Hz), 4.65 (1H, m), 4.55 (1H, m), 3.88-3.38 (4H, m), 2.28-1.44 (4H, m), 1.44 (9H, s), 1.31 and 1.27 (3H, d, J=6.6 Hz).
MS (ESI, m/z): 433 $(M+H)^+$.

Example 4-2
3-Hydroxy-N-[(1S)-1-methyl-2-oxo-2-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}ethyl]quinoxaline-2-carboxamide

Analogously to Example 1-3, (2S)-1-oxo-1-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}propane-2-amine hydrochloride was obtained from t-butyl [(1S)-1-methyl-2-oxo-2-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}ethyl]carbamate. The resulting compound (184 mg, 0.500 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (98.0 mg, 0.500 mmol) to afford the desired title compound (115 mg, 46%) as a pale yellow solid.
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.85 (1H, brs), 9.71 (1H, brs), 7.88 (1H, dd, J=7.8 Hz, 7.4 Hz), 7.65 (1H, dd, J=7.8 Hz, 7.8 Hz), 7.40 (1H, d, J=7.4 Hz), 7.38 (1H, d, J=7.8 Hz), 7.30 (2H, d, J=9.0 Hz), 7.11 (2H, dd, J=9.0 Hz, 3.8 Hz), 5.03 (1H, m), 4.69 (1H, m), 4.04-3.72 (2H, m), 3.56-3.19 (2H, m), 2.08-1.86 (2H, m), 1.75-1.48 (2H, m), 1.32 (3H, d, J=6.6 Hz).
IR (KBr) cm^{-1}: 2945, 1685, 1640, 1620, 1505, 1240.
MS (ESI, m/z): 505 $(M+H)^+$.
HRMS (ESI, m/z): 505.1686 (Calcd for $C_{24}H_{24}F_3N_4O_5$: 505.1699).

Example 5



N-{(1S)-2-[4-(4-Cyanophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide

Example 5-1
t-Butyl {(1S)-2-[4-(4-cyanophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}carbamate

Analogously to Example 2-1, t-butyl {(1S)-2-[4-(4-

cyanophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}carbamate (190 mg, yield 78%) was obtained from 4-[(piperidin-4-yl)oxy]benzonitrile hydrochloride (155 mg, 0.650 mmol) and N-(t-butoxycarbonyl)-L-alanine (123 mg, 0.650mmol) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.60 (2H, d, J=9.0 Hz), 6.96 (2H, d, J=9.0 Hz), 5.52 (1H, d, J=7.8 Hz), 4.70-4.59 (2H, m), 4.90-4.30 (4H, m), 2.05-1.78 (4H, m), 1.44 (9H, s), 1.31 (3H, d, J=7.0 Hz).

MS (FAB, m/z): 374 $(M+H)^+$.

Example 5-2

N-{(1S)-2-[4-(4-Cyanophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 1-3, 4-[(1-L-alanylpiperidin-4-yl)oxy]benzonitrile hydrochloride (133 mg, yield 84%) was obtained from t-butyl {(1S)-2-[4-(4-cyanophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}carbamate (190 mg, 0.510 mmol). The resulting compound (108 mg, 0.350 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (68.6 mg, 0.350 mmol) to afford the desired title compound (107 mg, yield 68%) as a pale yellow solid.

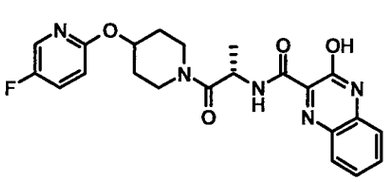
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.87 (1H, brs), 9.70 (1H, brs), 7.88 (1H, dd, J=7.8 Hz, 7.4 Hz), 7.78 (2H, d, J=9.0 Hz), 7.65 (1H, dd, J=7.8 Hz, 7.8 Hz), 7.40 (1H, d, J=7.8 Hz), 7.38 (1H, d, J=7.4 Hz), 7.19 (2H, dd, J=9.0 Hz, 2.6 Hz), 5.03 (1H, m), 4.83 (1H, m), 4.07-3.73 (2H, m), 3.57-3.17 (2H, m), 2.12-1.89 (2H, m), 1.78-1.47 (2H, m), 1.31 (3H, d, J=7.0 Hz).

IR (KBr) cm^{-1}: 2945, 2220, 1685, 1640, 1605, 1505, 1255.

MS (ESI, m/z): 446 $(M+H)^+$.

HRMS (ESI, m/z): 446.1851 (Calcd for $C_{24}H_{24}N_5O_4$: 446.1828).

Example 6



N-[(1S)-2-{4-[(5-Fluoropyridin-2-yl)oxy]piperidin-1-yl}-1-methyl-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide

Example 6-1

t-Butyl [(1S)-2-{4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}-1-methyl-2-oxoethyl]carbamate

Analogously to Example 2-1, t-butyl [(1S)-2-{4-[(5-fluoropyridin-2-

yl)oxy]piperidin-1-yl}-1-methyl-2-oxoethyl]carbamate (316 mg, yield 86%) was obtained from 5-fluoro-2-[(piperidin-4-yl)oxy]pyridine dihydrochloride (269 mg, 1.00 mmol) and N-(t-butoxycarbonyl)-L-alanine (189 mg, 1.00 mmol) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.98-7.94 (1H, m), 7.38-7.31 (1H, m), 6.70 (1H, dd, J=9.0 Hz, 3.4 Hz), 5.58 (1H, d, J=8.2 Hz), 5.23 (1H, m), 4.66 (1H, m), 4.01-3.34 (4H, m), 2.11-1.92 (2H, m), 1.89-1.72 (2H, m), 1.45 (9H, s), 1.32 (3H, d, J=7.0 Hz).

MS (FAB, m/z): 368 $(M+H)^+$.

Example 6-2

N-[(1S)-2-{4-[(5-Fluoropyridin-2-yl)oxy]piperidin-1-yl}-1-methyl-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 1-3, (2S)-1-{4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}-1-oxopropane-2-amine dihydrochloride (283 mg, yield 100%) was obtained from t-butyl [(1S)-2-{4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}-1-methyl-2-oxoethyl]carbamate (306 mg, 0.831 mmol). From the resulting compound (119 mg, 0.350 mmol), through condensation with 3-hydroxyquinoxaline-2-carboxylic acid (68.6 mg, 0.350 mmol), the desired title compound (87.8 mg, yield 57%) was afforded as a yellow solid.

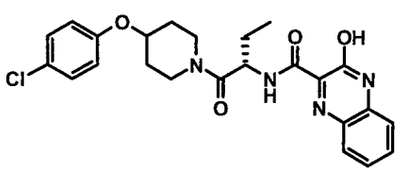
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.88 (1H, brs), 9.75 (1H, brs), 8.16 (1H, d, J=3.0 Hz), 7.88 (1H, dd, J=7.6 Hz, 4.2 Hz), 7.74-7.62 (2H, m), 7.40 (1H, d, J=7.6 Hz), 7.38 (1H, d, J=7.6 Hz), 6.92-6.83 (1H, m), 5.18 (1H, m), 5.03 (1H, m), 4.10-3.73 (2H, m), 3.56-3.16 (2H, m), 2.14-1.91 (2H, m), 1.79-1.46 (2H, m), 1.32 and 1.31(3H, d, J=6.6 Hz).

IR (KBr) cm^{-1}: 2950, 1690, 1630, 1480, 1220.

MS (ESI, m/z): 440 $(M+H)^+$.

HRMS (ESI, m/z): 440.1736 (Calcd for $C_{23}H_{24}FN_5O_4$: 440.1734).

Example 7



N-[(1S)-1-{[4-(4-Chlorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide

Example 7-1

t-Butyl {(1S)-1-[(4-hydroxypiperidin-1-yl)carbonyl]propyl}carbamate

Analogously to Example 1-1, t-butyl {(1S)-1-[(4-hydroxypiperidin-1-

yl)carbonyl]propyl}carbamate (5.95 g, yield 42%) was obtained from 4-hydroxypiperidine (5.06 g, 50.0 mmol) and (S)-2-(t-butoxycarbonylamino)butyric acid (10.1 g, 50.0 mmol) as a pale yellow amorphous subsutance.

^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 5.48 (1H, d, J=7.4Hz), 4.58 (1H, m), 4.32-3.70 (3H, m), 3.39-3.18 (2H, m), 2.00-1.82 (2H, m), 1.82-1.63 (2H, m), 1.63-1.48 (3H, m), 1.43 (9H, s), 1.01-0.88 (3H, m).

MS (FAB/z): 287 $(M+H)^+$.

Example 7-2

t-Butyl [(1S)-1-{[4-(4-chlorophenoxy)piperidin-1-yl]carbonyl}propyl]carbamate

Analogously to Example 1-2, a mixture (1.01 g) containing t-butyl [(1S)-1-{[4-(4-chlorophenoxy)piperidin-1-yl]carbonyl}propyl]carbamate was obtained from t-butyl {(1S)-1-[(4-hydroxypiperidin-1-yl)carbonyl]propyl}carbamate (1.00 g, 3.50 mmol) and 4-chlorophenol (490 mg, 3.85 mmol). The mixture was used as it is in the next reaction without further purificaiton.

MS (FAB, m/z): 397 $(M+H)^+$.

Example 7-3

N-[(1S)-1-{[4-(4-Chlorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 1-3, (2S)-1-[4-(4-chlorophenoxy)piperidin-1-yl]-1-oxobutan-2-amine hydrochloride (131 mg) was obtained from t-butyl [(1S)-1-{[4-(4-chlorophenoxy)piperidin-1-yl]carbonyl}propyl]carbamate (1.39 g, 3.50 mmol). From the resulting compound (117 mg, 0.350 mmol), through condensation with 3-hydroxyquinoxaline-2-carboxylic acid (68.6 mg, 0.350 mmol), the desired title compound (55.0 mg, yield 34%) was afforded as a pale yellow solid.

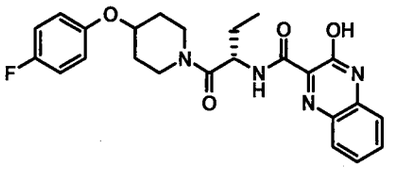
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.82 (1H, brs), 9.63 (1H, brs), 7.85 (1H, dd, J=7.4 Hz, 7.4 Hz), 7.63 (1H, dd, J=7.8 Hz, 7.4 Hz), 7.37 (1H, d, J=7.4 Hz), 7.36 (1H, d, J=7.8 Hz), 7.33 (2H, d, J=9.0 Hz), 7.04 and 7.03 (2H, d, J=9.0 Hz), 4.98 (1H, m), 4.66 (1H, m), 4.02-3.78 (2H, m), 3.56-3.19 (2H, m), 2.07-1.45 (6H, m), 0.91 (3H, t, J=7.4 Hz).

IR (KBr) cm^{-1}: 2935, 1690, 1640, 1490, 1240.

MS (ESI, m/z): 469 $(M+H)^+$.

HRMS (ESI, m/z): 469.1650 (Calcd for $C_{24}H_{26}ClN_4O_4$: 469.1643).

Example 8



N-[(1S)-1-{[4-(4-Fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide

Example 8-1

t-Butyl N-[(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]carbamate

Analogously to Example 2-1, t-butyl N-[(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]carbamate (703 mg, yield 92%) was obtained from 4-(4-fluorophenoxy)piperidine hydrochloride (463 mg, 2.00 mmol) and (2S)-2-(t-butoxycarbonylamino)butyric acid (407 mg, 2.00 mmol) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.99 (2H, d, J=8.6 Hz), 6.87 (2H, m), 5.44 (1H, d, J=8.6 Hz), 4.59 (1H, m), 4.47 (1H, m), 3.83-3.38 (4H, m), 1.70-1.63 (4H, m), 1.63-1.50 (2H, m), 1.44 (9H, s), 0.94 (3H, t, J=7.4 Hz).

MS (ESI, m/z): 381 $(M+H)^+$.

Example 8-2

N-[(1S)-1-{[4-(4-Fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 2-2, (2S)-1-[4-(4-fluorophenoxy)piperidin-1-yl]-1-oxobutan-2-amine hydrochloride (535 mg) was obtained from t-butyl [(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]carbamate (703 mg, 1.80 mmol) as a white solid. The resulting compound (317 mg, 1.00 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (190 mg, 1.00 mmol) to afford the desired title compound (358 mg, yield 79%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.86 (1H, brs), 9.56 (1H, m), 7.88 (1H, dd, J=7.8 Hz, 7.8 Hz), 7.65 (1H, dd, J=7.8 Hz, 7.8 Hz), 7.40 (1H, d, J=7.8 Hz), 7.38 (1H, d, J=7.8 Hz), 7.14 (2H, m), 7.03 (2H, m), 5.00 (1H, m), 4.60 (1H, m), 4.03-3.79 (2H, m), 3.57-3.20 (2H, m), 2.07-1.44 (6H, m), 0.92 (3H, t, J=7.4 Hz).

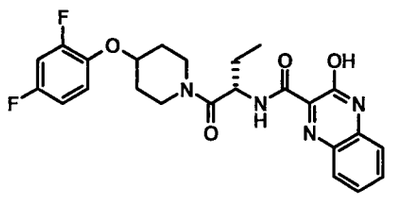
IR (KBr) cm^{-1}: 2965, 1690, 1630, 1505, 1205.

MS (ESI, m/z): 453 $(M+H)^+$.

HRMS (ESI, m/z): 453.1950 (Calcd for $C_{24}H_{26}FN_4O_4$: 453.1938)

Anal. Calcd for $C_{24}H_{25}FN_4O_4$: C, 63.71; H, 5.57; N, 12.38; F, 4.20. Found: C, 63.67; H, 5.46; N, 12.42; F, 4.09.

Example 9



N-[(1S)-1-{[4-(2,4-Difluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 1-2, a mixture (1.88 g) containing t-butyl [(1S)-1-{[4-(2,4-difluorophenoxy)piperidin-1-yl]carbonyl}propyl]carbamate was obtained from t-butyl {(1S)-2-[(4-hydroxypiperidin-1-yl)carbonyl]propyl}carbamate (1.18 g, 4.13 mmol) and 2,4-difluorophenol (590 mg, 4.54 mmol). The mixture was used as it is in the next reaction without further purification.

Analogously to Example 1-3, (2S)-1-[4-(2,4-difluorophenoxy)piperidin-1-yl]-1-oxobutan-2-amine hydrochloride (629 mg) was obtained from the resulting mixture (1.65 g, 4.13 mmol). The resulting compound (228 mg, 0.682 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (133 mg, 0.682 mmol) to afford the desired title compound (174 mg, yield 52%) as a pale yellow solid.

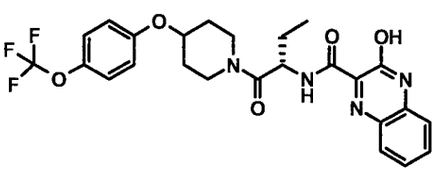
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.84 (1H, brs), 9.54 (1H, brs), 7.90-7.83 (1H, m), 7.65 (1H, dd, J=8.6 Hz, 8.2 Hz), 7.40 (1H, d, J=7.4 Hz), 7.38 (1H, d, J=8.6 Hz), 7.35-7.27 (2H, m), 7.27-7.07 (1H, m), 4.99 (1H, m), 4.59 (1H, m), 4.02-3.78 (2H, m), 3.57-3.20 (2H, m), 2.09-1.49 (6H, m), 0.92 (3H, t, J=7.0 Hz).

IR (KBr) cm^{-1}: 2940, 1685, 1640, 1505, 1210.

MS (ESI, m/z): 471 $(M+H)^+$.

HRMS (ESI, m/z): 471.1848 (Calcd for $C_{24}H_{25}F_2N_4O_4$: 471.1844).

Example 10



3-Hydroxy-N-[(1S)-1-({4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Example 10-1

t-Butyl [(1S)-1-({4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}carbonyl)propyl]carbamate

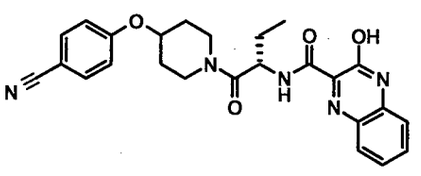
Analogously to Example 1-2, a mixture (1.58 g) containing t-butyl

[(1S)-1-({4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}carbonyl)propyl]carbamate was obtained from t-butyl {(1S)-1-[(4-hydroxypiperidin-1-yl)carbonyl}propyl}carbamate (1.13 g, 4.13 mmol) and 4-(trifluoromethoxy)phenol (590 mg, 4.54 mmol). The mixture was used as it is in the next reaction without further purification.
MS (FAB, m/z): 447 $(M+H)^+$.

Example 10-2
3-Hydroxy-N-[(1S)-1-({4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Analogously to Example 1-3, (2S)-1-oxo-1-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}butan-2-amine hydrochloride (310 mg) was obtained from t-butyl [(1S)-1-({4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}carbonyl)propyl]carbamate (1.84 g, 4.12 mmol). The resulting compound (184 mg, 0.530 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (104 mg, 0.530 mmol) to afford the desired title compound (134 mg, yield 49%) as a pale yellow solid.
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.84 (1H, brs), 9.56 (1H, m), 7.87 (1H, dd, J=7.8 Hz, 7.8 Hz), 7.65 (1H, dd, J=7.8 Hz, 7.8 Hz), 7.40 (1H, d, J=7.8 Hz), 7.38 (1H, d, J=7.8 Hz), 7.30 (2H, d, J=8.6 Hz), 7.11 (2H, dd, J=8.6 Hz, 5.0 Hz), 5.00 (1H, m), 4.69 (1H, m), 4.08-3.79 (2H, m), 3.58-3.20 (2H, m), 2.10-1.46 (6H, m), 0.92 (3H, t, J=7.4 Hz).
IR (KBr) cm^{-1}: 2945, 1685, 1640, 1505, 1240.
MS (ESI, m/z): 519 $(M+H)^+$.
HRMS (ESI, m/z): 519.1850 (Calcd for $C_{25}H_{26}F_3N_4O_5$: 519.1855).

Example 11



N-[(1S)-1-{[4-(4-Cyanophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide
Example 11-1
t-Butyl [(1S)-1-{[4-(4-cyanophenoxy)piperidin-1-yl]carbonyl}propyl]carbamate

Analogously to Example 2-1, t-butyl [(1S)-1-{[4-(4-cyanophenoxy)piperidin-1-yl]carbonyl}propyl]carbamate (226 mg, yield 90%) was obtained from 4-[(piperidin-4-yl)oxy]benzonitrile hydrochloride (155

mg, 0.650 mmol) and (2S)-2-(t-butoxycarbonylamino)butyric acid (132 mg, 0.650 mmol) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.60 (2H, d, J=9.0 Hz), 6.96 (2H, d, J=9.0 Hz), 5.41 (1H, d, J=8.6 Hz), 4.70-4.55 (2H, m), 3.90-3.41 (4H, m), 2.07-1.70 (4H, m), 1.44 (9H, s), 1.57 (2H, q, J=7.4 Hz), 0.94 (3H, t, J=7.4 Hz).

MS (FAB, m/z): 388 $(M+H)^+$.

Example 11-2

N-[(1S)-1-{[4-(4-Cyanophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 1-3, 4-({1-[(2S)-2-aminobutanoyl]piperidin-4-yl}oxy)benzonitrile hydrochloride (133 mg, yield 84%) was obtained from t-butyl [(1S)-1-{[4-(4-cyanophenoxy)piperidin-1-yl]carbonyl}propyl]carbamate (226 mg, 0.583 mmol). The resulting compound (113 mg, 0.350 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (68.6 mg, 0.350 mmol) to afford the desired title compound (107 mg, yield 66%) as a yellow solid.

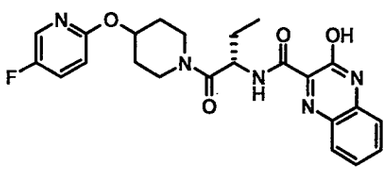
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.85 (1H, brs), 9.56 (1H, m), 7.87 (1H, dd, J=8.2 Hz, 7.8 Hz), 7.78 (2H, d, J=9.0 Hz), 7.65 (1H, dd, J=7.8 Hz, 7.4 Hz), 7.40 (1H, d, J=7.4 Hz), 7.38 (1H, d, J=8.2 Hz), 7.19 (2H, dd, J=9.0 Hz, 4.2 Hz), 5.00 (1H, m), 4.83 (1H, m), 4.07-3.81 (2H, m), 3.61-3.16 (2H, m), 2.14-1.46 (6H, m), 0.92 (3H, t, J=7.4 Hz).

IR (KBr) cm^{-1}: 2965, 2220, 1685, 1630, 1505, 1250.

MS (ESI, m/z): 460 $(M+H)^+$.

HRMS (ESI, m/z): 460.1973 (Calcd for $C_{25}H_{26}N_5O_4$: 460.1984).

Example 12



N-[(1S)-1-({4-[(5-Fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]-3-hydroxyquinoxaline-2-carboxamide

Example 12-1

t-Butyl [(1S)-1-({4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate

Analogously to Example 2-1, t-butyl [(1S)-1-({4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate (317 mg, yield 83%) was obtained from 5-fluoro-2-[(piperidin-4-yl)oxy]pyridine dihydrochloride (269 mg, 1.00 mmol) and (2S)-2-(t-butoxycarbonylamino)butyric acid (203

mg, 1.00mmol) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.96 (1H, dd, J=3.0 Hz, 3.0 Hz), 7.39-7.32 (1H, m), 6.70 (1H, dd, J=9.0 Hz, 3.4 Hz), 5.47 (1H, d, J=8.6 Hz), 5.23 (1H, m), 4.60 (1H, m), 3.99-3.38 (4H, m), 2.10-1.91 (2H, m), 1.88-1.70 (2H, m), 1.64-1.50 (2H, m), 1.44 (9H, s), 0.94 (3H, t, J=7.4 Hz).

MS (FAB, m/z): 382 $(M+H)^+$.

Example 12-2

N-[(1S)-1-({4-[(5-Fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 1-3, (2S)-1-{4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}-1-oxobutan-2-amine dihydrochloride (285 mg, yield 100%) was obtained from t-butyl [(1S)-1-({4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate (307 mg, 0.805 mmol). The resulting compound (124 mg, 0.350 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (68.6 mg, 0.350 mmol) to afford the desired title compound (74.2 mg, yield 47%) as a yellow solid.

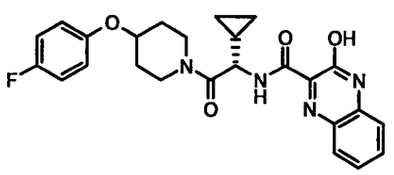
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.85 (1H, brs), 9.58 (1H, d, J=7.0 Hz), 8.16 (1H, d, J=2.6 Hz), 7.88 (1H, dd, J=7.4 Hz, 5.4 Hz), 7.74-7.62 (2H, m), 7.40 (1H, d, J=7.4 Hz), 7.38 (1H, d, J=8.2 Hz), 6.93-6.84 (1H, m), 5.19 (1H, m), 5.00 (1H, m), 4.08-3.81 (2H, m), 3.58-3.16 (2H, m), 2.15-1.92 (2H, m), 1.88-1.48 (4H, m), 0.92 (3H, t, J=7.4 Hz).

IR (KBr) cm^{-1}: 2950, 1690, 1630, 1480, 1215.

MS (ESI, m/z): 454 $(M+H)^+$.

HRMS (ESI, m/z): 454.1890 (Calcd for $C_{23}H_{25}FN_5O_4$: 454.1891).

Example 13



N-{(1S)-1-Cyclopropyl-2-[4-(4-fluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide

Example 13-1

t-Butyl {(1S)-1-cyclopropyl-2-[4-(4-fluorophenoxy)piperidin-1-yl)-2-oxoethyl}carbamate

Analogously to Example 2-1, t-butyl {(1S)-1-cyclopropyl-2-[4-(4-fluorophenoxy)piperidin-1-yl]-2-oxoethyl}carbamate (3.06 g, yield 90%) was obtained from 4-(4-fluorophenoxy)piperidine hydrochloride (2.00 g, 8.63 mmol) and (2S)-2-(t-butoxycarbonylamino)cyclopropylacetic acid (1.86

g, 8.63 mmol) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.99 (2H, dd, J=8.6 Hz, 8.6 Hz), 6.87 (2H, dd, J=8.6Hz, 4.6 Hz), 5.46 (1H, d, J=7.8 Hz), 4.54-4.42 (2H, m), 3.84-3.44 (4H, m), 2.08-1.74 (4H, m), 1.44 (9H, s), 1.16-1.03 (1H, m), 0.58-0.31 (4H, m).

MS (ESI, m/z): 393 $(M+H)^+$.

Example 13-2

N-{(1S)-1-Cyclopropyl-2-[4-(4-fluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide

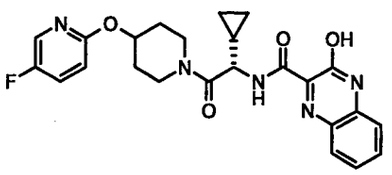
Analogously to Example 2-2, (1S)-1-cyclopropyl-2-[4-(4-fluorophenoxy)piperidin-1-yl]-2-oxoethanamine hydrochloride (2.00 g, yield 88%) was obtained from t-butyl {(1S)-1-cyclopropyl-2-[4-(4-fluorophenoxy)piperidin-1-yl]-2-oxoethyl}carbamate (3.06 g, 7.80 mmol) as a colorless oil. The resulting compound (2.00 g, 6.84 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (1.48 g, 7.80 mmol) under nitrogen stream to afford the desired title compound (2.71 g, yield 85%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.88 (1H, s), 9.62 (1H, d, J=6.0 Hz), 7.87 (1H, dd, J=7.6 Hz, 2.0 Hz), 7.65 (1H, dt, J=7.6 Hz, 2.0 Hz), 7.40 (1H, dt, J=7.6 Hz, 2.0 Hz), 7.37 (1H, d, J=7.6 Hz), 7.12 (2H, m), 7.02 (2H, m), 4.76 (1H, q, J=8.4 Hz), 4.61 (1H, m), 4.12-3.80 (2H, m), 3.60-3.20 (2H, m), 2.08-1.88 (2H, m), 1.75-1.45 (2H, m), 1.23 (1H, dd, J=6.4 Hz), 0.53-0.38 (4H, m).

MS (ESI, m/z): 465 $(M+H)^+$.

Anal. Calcd for $C_{25}H_{25}FN_4O_4$: C, 64.64; H, 5.42; N, 12.06. Found: C, 64.27; H, 5.30; N, 12.01.

Example 14



N-[(1S)-1-Cyclopropyl-2-{4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide

Example 14-1

t-Butyl [(1S)-1-cyclopropyl-2-{4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}-2-oxoethyl]carbamate

Analogously to Example 2-1, t-butyl [(1S)-1-cyclopropyl-2-{4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}-2-oxoethyl]carbamate (276 mg,

yield 70%) was obtained from 5-fluoro-2-[(piperidin-4-yl)oxy]pyridine dihydrochloride (269 mg, 1.00 mmol) and (2S)-2-(t-butoxycarbonylamino)-2-cyclopropylacetic acid (215 mg, 1.00 mmol) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.97 (1H, d, J=2.6 Hz), 7.40-7.32 (1H, m), 6.71 (1H, dd, J=9.0 Hz, 3.4 Hz), 5.47 (1H, d, J=7.8 Hz), 5.24 (1H, m), 4.51 (1H, dd, J=7.4 Hz, 7.4 Hz), 3.99-3.73 (2H, m), 3.66-3.42 (2H, m), 2.12-1.94 (2H, m), 1.91-1.73 (2H, m), 1.44 (9H, s), 1.17-1.06 (1H, m), 0.58-0.34 (4H, m).

MS (FAB, m/z): 394 $(M+H)^+$.

Example 14-2

N-[(1S)-1-Cyclopropyl-2-{4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 1-3, (1S)-1-cyclopropyl-2-{4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}-2-oxoethanamine dihydrochloride (248 mg, yield 100%) was obtained from t-butyl [(1S)-1-cyclopropyl-2-{4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}-2-oxoethyl]carbamate (266 mg, 0.676 mmol). The resulting compound (160 mg, 0.439 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (85.6 mg, 0.439 mmol) to afford the desired title compound (78.3 mg, yield 38%) as a yellow solid.

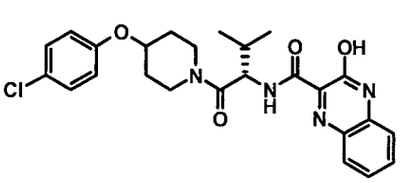
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.87 (1H, brs), 9.67 (1H, brs), 8.16 (1H, d, J=2.6 Hz), 7.88 (1H, m), 7.76-7.62 (2H, m), 7.40 (1H, d, J=7.0 Hz), 7.39 (1H, d, J=8.6 Hz), 6.95-6.83 (1H, m), 5.19 (1H, m), 4.79 (1H, m), 4.10-3.82 (2H, m), 3.59-3.14 (2H, m), 2.17-1.45 (4H, m), 1.28-1.17 (1H, m), 0.53-0.36 (4H, m).

IR (KBr) cm^{-1}: 2960, 1690, 1630, 1530, 1480.

MS (ESI, m/z): 466$(M+H)^+$.

HRMS (ESI, m/z): 466.1882 (Calcd for $C_{24}H_{25}FN_5O_4$: 466.1891).

Example 15



N-[(1S)-1-{[4-(4-Chlorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 15-1

t-Butyl N-[(1S)-1-{[4-(4-chlorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (844

mg, 4.40 mmol) and 1-hydroxybenzotriazole monohydrate (595 mg, 4.40 mmol) were added to a methylene chloride solution (30 ml) of 4-(4-chlorophenoxy)piperidine hydrochloride (910 mg, 3.67 mmol) and N-(t-butoxycarbonyl)-L-valine (876 mg, 4.03 mmol), at room temperature, under nitrogen stream, followed by further addition of N-methylmorpholine (0.888 ml, 8.07 mmol), and stirring was carried out at room temperature overnight. The reaction solution was poured into a 2N aqueous hydrochloric acid solution, followed by extraction with methylene chloride and sequential washing with water, a saturated aqueous sodium hydrogencarbonate solution, water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., 25+M) to afford t-butyl [(1S)-1-{[4-(4-chlorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate (1.38 g, yield 92%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.41-7.23 (2H, m), 7.07-6.83 (2H, m), 5.34 (1H, d, J=8.3 Hz), 4.53-4.48 (2H, m), 3.80-3.46 (4H, m), 2.00-1.78 (5H, m), 1.48-1.40 (9H, m), 0.97 (3H, d, J=6.8 Hz), 0.89 (3H, d, J=6.8 Hz).

MS (FAB, m/z): 411 $(M+H)^+$.

Example 15-2

N-[(1S)-1-{[4-(4-Chlorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Concentrated hydrochloric acid (6.0 ml) was added to an ethanol solution (12 ml) of t-butyl [(1S)-1-{[4-(4-chlorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate (1.38 g, 3.36 mmol), under nitrogen stream, and the mixture was allowed to react at room temperature overnight. The reaction solution was concentrated to afford (2S)-1-[4-(4-chlorophenoxy)piperidin-1-yl]-3-methyl-1-oxobutan-2-amine hydrochloride (1.17 g) as a white solid.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (149 mg, 0.777 mmol) and 1-hydroxybenzotriazole monohydrate (105 mg, 0.777 mmol), were added to a methylene chloride solution (5.0 ml) of the resulting compound (180 mg, 0.518 mmol) and 3-hydroxyquinoxaline-2-carboxylic acid (148 mg, 0.777 mmol), at room temperature, under nitrogen stream, followed by further addition of triethylamine (0.289 ml, 2.07 mmol), and stirring was carried out at room temperature overnight. The reaction solution was poured into a 2N aqueous hydrochloric acid solution, followed by extraction with ethyl acetate and sequential

washing with water, a saturated aqueous sodium hydrogencarbonate solution, water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. After the organic layer was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., 25+M), the residue resulting from concentration was suspended in a mixed solvent of methylene chloride-diethyl ether, and the solid substance was collected by filtration to afford the desired title compound (113 mg, yield 45%) as a pale yellow solid.

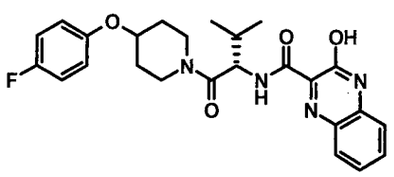
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.86 (1H, s), 10.19 (1H, s), 7.97 (1H, t, J=7.0 Hz), 7.61 (1H, s), 7.53 (1H, s), 7.36 (1H, s), 7.26 (2H, t, J=7.0 Hz), 6.86 (2H, t, J=7.0 Hz), 5.09-5.07 (1H, m), 4.57-4.55 (1H, m), 4.01-3.68 (4H, m), 2.21-2.02 (5H, m), 1.14-1.11 (6H, m).

IR (KBr) cm^{-1}: 2960, 1690, 1640, 1490, 1240, 1150.

MS (FAB, m/z): 483 $(M+H)^+$.

HRMS (ESI, m/z): 483.1797 (Calcd for $C_{25}H_{28}ClN_4O_4$: 483.1799).

Example 16



N-[(1S)-1-{[4-(4-Fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 16-1

t-Butyl [(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate

Analogously to Example 2-1, t-butyl [(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate (745 mg, yield 86%) was obtained from 4-(4-fluorophenoxy)piperidine hydrochloride (510 mg, 2.20 mmol) and N-(t-butoxycarbonyl)-L-valine (478 mg, 2.20 mmol) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.01-6.95 (2H, m), 6.89-6.84 (2H, m), 5.34 (1H, d, J=8.8 Hz), 4.52-4.45 (2H, m), 3.82-3.45 (4H, m), 2.05-1.76 (5H, m), 1.44 (9H, s), 0.97 (3H, d, J=6.8 Hz), 0.89 (3H, d, J=6.8 Hz).

MS (ESI, m/z): 395 $(M+H)^+$.

Example 16-2

N-[(1S)-1-{[4-(4-Fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 2-2, (2S)-1-[4-(4-fluorophenoxy)piperidin-1-yl]-3-methyl-1-oxobutan-2-amine hydrochloride (550 mg, 70%) was obtained from t-butyl [(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate (745 mg, 1.89 mmol) as a colorless oil. The resulting compound (150 mg, 0.450 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (95.0 mg, 0.500 mmol) under nitrogen stream to afford the desired title compound (101 mg, yield 48%) as a pale yellow solid.

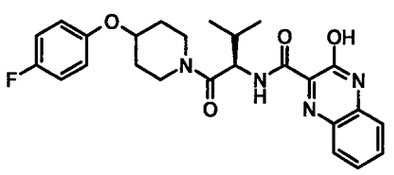
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.51 (1H, brs), 10.14 (1H, brs), 8.05-7.96 (1H, m), 7.70-7.32 (3H, m), 7.04-6.84 (4H, m), 5.08 (1H, dd, J=7.6 Hz, 7.1 Hz), 4.53-4.46 (1H, m), 4.00-3.68 (4H, m), 2.38-2.09 (1H, m), 2.02-1.85 (4H, m), 1.17-1.07 (6H, m).

IR (ATR) cm^{-1}, 1685, 1630, 1500, 1450, 1275, 1245.

MS (ESI, m/z): 467 $(M+H)^+$.

Anal. Calcd for $C_{25}H_{27}FN_4O_4$: C, 64.37; H, 5.83; F, 4.07; N, 12.01. Found: C, 64.01; H, 5.81; F, 3.85; N, 11.69.

Example 17



N-[(1R)-1-{[4-(4-Fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 17-1

t-Butyl [(1R)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate

Analogously to Example 2-1, t-butyl [(1R)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate (326 mg, yield 83%) was obtained from 4-(4-fluorophenoxy)piperidine hydrochloride (232 mg, 1.00 mmol) and N-(t-butoxycarbonyl)-D-valine (217 mg, 1.00 mmol) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 8.72 (2H, dd, J=8.8 Hz, 8.0 Hz), 8.57 (2H, dd, J=8.8 Hz, 4.4 Hz), 5.34 (1H, d, J=8.8 Hz), 4.54-4.43 (2H, m), 3.82-3.40 (4H, m), 2.00-1.80 (5H, m), 1.44 (9H, s), 0.97 and 0.89 (6H, d, J=6.8 Hz).

MS (ESI, m/z): 395 $(M+H)^+$.

Example 17-2

N-[(1R)-1-{[4-(4-Fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-

3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 2-2, (2R)-1-[4-(4-fluorophenoxy)piperidin-1-yl]-3-methyl-1-oxobutan-2-amine hydrochloride (113 mg, yield 46%) was obtained from t-butyl [(1R)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate (326 mg, 0.828 mmol). The resulting compound (113 mg, 0.382 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (72.7 mg, 0.382 mmol) to afford the desired title compound (92.8 mg, yield 51%) as a yellow solid.

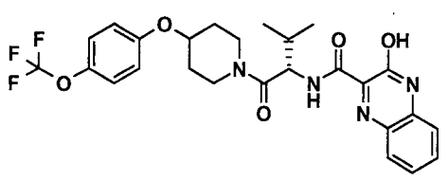
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.67 (1H, brs), 10.17 (1H, brs), 8.05-7.96 (1H, m), 7.70-7.32 (3H, m), 7.04-6.84 (4H, m), 5.08 (1H, dd, J=7.6 Hz, 7.1 Hz), 4.53-4.46 (1H, m), 4.00-3.68 (4H, m), 2.38-2.09 (1H, m), 2.02-1.85 (4H, m), 1.17-1.07 (6H, m).

IR (KBr) cm^{-1}: 2960, 1690, 1630, 1505, 1210.

MS (ESI, m/z): 467 $(M+H)^+$.

HRMS (ESI, m/z): 467.2170 (Calcd for $C_{25}H_{28}FN_4O_4$: 467.2095).

Example 18



3-Hydroxy-N-[(1S)-2-methyl-1-({4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Example 18-1

t-Butyl [(1S)-2-methyl-1-({4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}carbonyl)propyl]carbamate

Analogously to Example 1-2, t-butyl N-[(1S)-2-methyl-1-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}carbonyl}propyl]carbamate (2.09 g, yield 76%) was obtained from t-butyl {(1S)-1-[(4-hydroxypiperidin-1-yl)carbonyl]-2-methylpropyl}carbamate (1.80 g, 6.00 mmol) and 4-(trifluoromethoxy)phenol (1.28 g, 7.20 mmol) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.15 (2H, d, J=9.6 Hz), 6.90 (2H, dd, J=9.6 Hz, 2.4 Hz), 5.34 (1H, d, J=9.6 Hz), 4.51 (2H, m), 3.80-3.45 (4H, m), 2.00-1.80 (5H, m), 1.44 (9H, s), 0.97 (3H, d, J=6.4 Hz), 0.89 (3H, d, J=6.4 Hz).

MS (ESI, m/z): 461 $(M+H)^+$.

Example 18-2

3-Hydroxy-N-[(1S)-2-methyl-1-({4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Analogously to Example 1-3, (2S)-3-methyl-1-oxo-1-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}butan-2-amine hydrochloride was obtained from t-butyl [(1S)-2-methyl-1-({4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}carbonyl)propyl]carbamate (2.09g, 4.54 mmol) as a white solid. The resulting compound (940 mg, 2.37 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (540 mg, 2.84 mmol) to afford the desired title compound (680 mg, yield 54%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.83 (1H, brs), 9.55 (1H, brs), 7.86 (1H, m), 7.61 (1H, m), 7.38 (2H, m), 7.28 (1H, m), 7.11 (3H, m), 4.90 (1H, dd, J=7.6 Hz, 7.1 Hz), 4.68 (1H, m), 3.99-3.80 (2H, m), 3.57-3.20 (2H, m), 2.05 (4H, m), 1.68 (1H, m), 0.94 (6H, d, J=6.4 Hz).

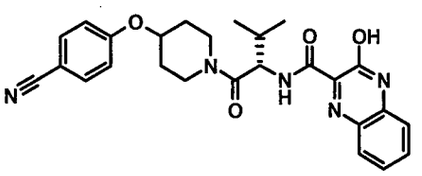
IR (KBr) cm^{-1}: 2960, 1690, 1640, 1505, 1240, 1160.

MS (ESI, m/z): 533 $(M+H)^+$.

HRMS (ESI, m/z): 533.1998 (Calcd for $C_{26}H_{28}F_3N_4O_5$: 533.2012).

Anal. Calcd for $C_{26}H_{27}F_3N_4O_5$: C, 58.64; H, 5.11; N, 10.52. Found: C, 58.28; H, 5.12; N, 10.51.

Example 19



N-[(1S)-1-{[4-(4-Cyanophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 19-1

t-Butyl 4-(4-cyanophenoxy)piperidine-1-carboxylate

Analogously to Example 1-2, t-butyl 4-(4-cyanophenoxy)piperidine-1-carboxylate (2.30 g, yield 100%) was obtained from t-butyl 4-hydroxypiperidine-1-carboxylate (1.50 g, 7.45 mmol) and 4-cyanophenol (980 mg, 8.20 mmol) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.60 (2H, d, J=9.6 Hz), 6.95 (2H, d, J=9.6 Hz), 4.55 (1H, m), 3.70-3.60 (2H, m), 3.40-3.32 (2H, m), 2.00-1.90 (2H, m), 1.80-1.70 (2H, m), 1.44 (9H, s).

MS (ESI, m/z): 303 $(M+H)^+$.

Example 19-2

t-Butyl [(1S)-1-{[4-(4-cyanophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate

Analogously to Example 2-2, 4-[(piperidin-4-yl)oxy]benzonitrile

hydrochloride (1.43 g, yield 80%) was obtained from t-butyl 4-(4-cyanophenoxy)piperidine-1-carboxylate (2.25 g, 7.45 mmol) as a colorless oil. The resulting compound (1.43 g, 5.97 mmol) was condensed with N-(t-butoxycarbonyl)-L-valine (1.43 g, 6.56 mmol) to afford t-butyl [(1S)-1-{[4-(4-cyanophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate (2.28 g, yield 95%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.60 (2H, d, J=9.6 Hz), 6.95 (2H, d, J=9.6 Hz), 5.35 (1H, d, J=9.6 Hz), 4.65 (1H, m), 4.45 (1H, m), 3.90-3.50 (4H, m), 2.00-1.80 (5H, m), 1.44 (9H, s), 0.97 (3H, d, J=6.4 Hz), 0.89 (3H, d, J=6.4 Hz).

MS (ESI, m/z): 402 $(M+H)^+$.

Example 19-3

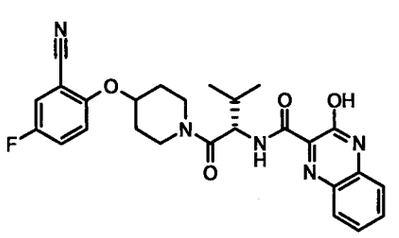
N-[(1S)-1-{[4-(4-Cyanophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 1-3, 4-[(1-valylpiperidin-4-yl)oxy]benzonitrile hydrochloride (1.92 g, yield 100%) was obtained from t-butyl [(1S)-1-{[4-(4-cyanophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate (2.28 g, 5.68 mmol) as a white solid. The resulting compound (301 mg, 1.00 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (228 mg, 1.20 mmol) to afford the desired title compound (255 mg, yield 54%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.82 (1H, brs), 9.48 (1H, brs), 7.86 (1H, t, J=7.2 Hz), 7.78 (2H, d, J=7.2 Hz), 7.64 (1H, t, J=5.6 Hz), 7.38 (2H, m), 7.18 (2H, m), 4.90 (1H, dd, J=12.4 Hz, 6.0 Hz), 4.84 (1H, m), 4.02-3.90 (2H, m), 3.57-3.20 (2H, m), 2.05 (4H, m), 1.55 (1H, m), 0.95 (6H, d, J=4.8 Hz).

LCMS (ESI, m/z): 474 $(M+H)^+$.

Example 20



N-[(1S)-1-{[4-(2-Cyano-4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 20-1

2-Cyano-4-fluorophenol

Pyridine (3.00 ml, 37.5 mmol) was added to an ethanol solution (20

ml) of 5-fluorosalicylaldehyde (1.36 g, 9.71 mmol) and hydroxylamine hydrochloride (2.00 g, 29.1 mmol), at 0°C, under nitrogen stream, and stirring was carried out for 2.5 hours at room temperature. The reaction solution was poured into a 2N aqueous hydrochloric acid solution, followed by extraction with ethyl acetate and sequential washing with water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated to afford 5-fluoro-2-hydroxybenzaldehyde oxime (1.47 g, yield 97%).

Anhydrous trifluoroacetic acid (3.93 ml, 28.4 mmol) was added to a methylene chloride solution (30 ml) of the resulting compound (1.47 g, 9.48 mmol) and triethylamine (3.96 ml, 28.4 mmol), at 0°C, under nitrogen stream, and stirring was carried out for 3 hours at room temperature. Further, potassium carbonate (1.96 g, 14.2 mmol) and methanol (10 ml) were added, and stirring was carried out for 10 minutes at room temperature. The reaction solution was concentrated, followed by pouring into water, extraction with ethyl acetate, and sequential washing with water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by silica gel column chromatography to afford 2-cyano-4-fluorophenol (637 mg, yield 49%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.24-7.18 (2H, m), 6.97 (1H, m), 5.15 (1H, brs).

MS (ESI, m/z): 138 $(M+H)^+$.

Example 20-2

t-Butyl [(1S)-1-{[4-(2-cyano-4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate

Analogously to Example 1-2, t-butyl [(1S)-1-{[4-(2-cyano-4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate (1.33 g, yield 68%) was obtained from t-butyl {(1S)-1-[(4-hydroxypiperidin-1-yl)carbonyl]-2-methylpropyl}carbamate (1.40 g, 4.65 mmol) and 2-cyano-4-fluorophenol (637 mg, 4.65 mmol) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.31-7.24 (2H, m), 6.96 (1H, dd, J=7.2 Hz, 3.2 Hz), 5.33 (1H, m), 4.68 (1H, m), 4.50 (1H, m), 4.02-3.50 (4H, m), 2.00-1.85 (5H, m), 1.44 (9H, s), 0.97 (3H, d, J=6.4 Hz), 0.89 (3H, d, J=6.4 Hz).

MS (ESI, m/z): 420 $(M+H)^+$.

Example 20-3

N-[(1S)-1-{[4-(2-Cyano-4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-

methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 1-3, 5-fluoro-2-[(1-L-valylpiperidin-4-yl)oxy]benzonitrile hydrochloride was obtained from t-butyl [(1S)-1-{[4-(2-cyano-4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate (910 mg, 2.17 mmol) as a white solid.

The resulting compound was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (495 mg, 2.60 mmol) under nitrogen stream to afford the desired title compound (987 mg, yield 93%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.82 (1H, brs), 9.52 (1H, d, J=8.8 Hz), 7.86 (1H, d, J=8.0 Hz), 7.77 (1H, dt, J=5.2 Hz, 2.8 Hz), 7.75-7.55 (2H, m), 7.44-7.40 (3H, m), 4.90 (2H, m), 4.02-3.40 (4H, m), 2.08-1.59 (5H, m), 0.95 (6H, d, J=6.4 Hz).

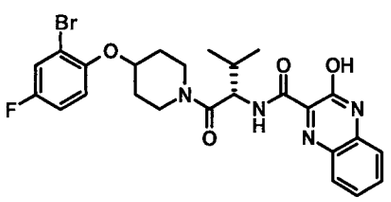
IR (KBr) cm^{-1}: 2965, 2230, 1690, 1640, 1495, 1275, 1210.

MS (ESI, m/z): 492 $(M+H)^+$.

HRMS (ESI, m/z): 514.1860 (Calcd for $C_{26}H_{26}FN_5NaO_4$: 514.1867).

Anal. Calcd for $C_{26}H_{26}FN_5O_4$: C, 63.53; H, 5.33; N, 14.25. Found:: C, 63.53; H, 5.59; N, 14.29.

Example 21



N-[(1S)-1-{[4-(2-Bromo-4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 21-1

t-Butyl [(1S)-1-{[4-(2-bromo-4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate

Analogously to Example 2-1, t-butyl [(1S)-1-{[4-(2-bromo-4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate (997 mg, yield 83%) was obtained from 4-(2-bromo-4-fluorophenoxy)piperidine hydrochloride (786 mg, 2.53 mmol) and N-(t-butoxycarbonyl)-L-valine (550 mg, 2.53 mmol) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.33-7.28 (1H, m), 7.01-6.95 (1H, m), 6.90-6.86 (1H, m), 5.35 (1H, d, J=9.0 Hz), 4.60-4.47 (2H, m), 4.01-3.50 (4H, m), 2.01-1.78 (5H, m), 1.44 (9H, s), 0.98 and 0.89 (6H, d, J=6.6 Hz).

MS (FAB, m/z): 473 $(M+H)^+$.

Example 21-2

N-[(1S)-1-{[4-(2-Bromo-4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 2-2, (2S)-1-[4-(2-bromo-4-fluorophenoxy)piperidin-1-yl]-3-methyl-1-oxobutan-2-amine hydrochloride (737 mg) was obtained from t-butyl [(1S)-1-{[4-(2-bromo-4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate (997 mg, 2.10 mmol). The resulting compound (737 mg, 1.80 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (353 mg, 1.80 mmol) to afford the desired title compound (609 mg, yield 62%) as a pale yellow solid.

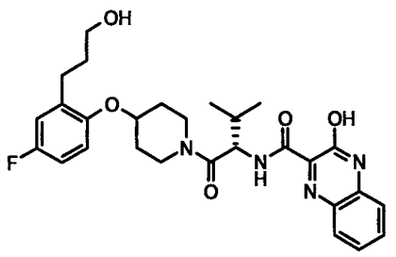
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.83 (1H, brs), 9.50 (1H, d, J=9.0 Hz), 7.90-7.84 (1H, m), 7.69-7.62 (1H, m), 7.60-7.53 (1H, m), 7.41-7.35 (2H, m), 7.33-7.20 (2H, m), 4.91 (1H, m), 4.74 (1H, m), 3.92-3.41 (4H, m), 3.92-3.41 (5H, m), 0.96 and 0.95 (6H, d, J=6.2 Hz).

IR (KBr) cm^{-1}: 2960, 1690, 1630, 1530, 1485, 1190.

MS (ESI, m/z): 545 $(M+H)^+$;

HRMS (ESI, m/z): 545.1210 (Calcd for $C_{25}H_{27}BrFN_4O_4$: 545.1200).

Example 22



N-[(1S)-1-({4-[4-Fluoro-2-(3-hydroxypropyl)phenoxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 22-1

t-Butyl [(1S)-1-({4-[4-fluoro-2-(3-hydroxy-1-propynyl)phenoxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate

Analogously to Example 1-2, t-butyl [(1S)-1-{[4-(2-bromo-4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate (1.58 g, yield 56%) was obtained from t-butyl {(1S)-1-[(4-hydroxypiperidin-1-yl)carbonyl]-2-methylpropyl}carbamate (1.80 g, 6.00 mmol) and 2-bromo-4-fluorophenol (1.38 g, 7.20 mmol) as a colorless oil.

The resulting compound (643 mg, 1.36 mmol) and 2-propyn-1-ol (107 mg, 1.90 mmol) were dissolved in a mixed solvent of N,N-dimethylformamide (3.0 ml) and triethylamine (3.0 ml), under nitrogen stream, and at room temperature bis(triphenylphosphine)palladium dichloride (98.0 mg, 0.140 mmol) and copper iodide (53.0 mg, 0.280 mmol) were added, followed by stirring at 70°C for 9 hours. The reaction solution was poured into

water, followed by extraction with ethyl acetate and sequential washing with water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by silica gel column chromatography to afford t-butyl [(1S)-1-({4-[4-fluoro-2-(3-hydroxy-1-propynyl)phenoxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (82.5 mg, yield 14%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.10 (1H, d, J=7.6 Hz), 6.99 (1H, m), 6.86 (1H, m), 5.33 (1H, m), 4.57 (1H, m), 4.50 and 4.35 (2H, d, J=4.8 Hz), 4.49 (1H, m), 3.90-3.50 (4H, m), 2.00-1.80 (5H, m), 1.44 (9H, s), 0.97 (3H, d, J=6.8 Hz), 0.89 (3H, d, J=6.8 Hz).

MS (ESI, m/z): 449 $(M+H)^+$.

Example 22-2

t-Butyl [(1S)-1-({4-[4-fluoro-2-(3-hydroxypropyl)phenoxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate

The resulting compound (82.5 mg, 0.184 mmol) and 10% palladium carbon catalyst (14.2 mg) were suspended in methanol (4.0 ml), under hydrogen stream, and stirring was carried out at room temperature for 4 hours. The reaction solution was celite filtered, and the mother liquor was concentrated to afford t-butyl [(1S)-1-({4-[4-fluoro-2-(3-hydroxypropyl)phenoxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (77.1 mg, yield 93%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.90 (1H, dd, J=7.2 Hz, 3.2 Hz), 6.84 (1H, m), 6.78 (1H, dd, J=8.4 Hz, 4.8 Hz), 5.34 (1H, d, J=9.2 Hz), 4.50 (2H, m), 3.90-3.50 (4H, m), 3.63 (2H, t, J=5.2 Hz), 2.71 (2H, q, J=8.0 Hz), 2.00-1.80 (5H, m), 1.85 (2H, q, J=8.0 Hz), 1.44 (9H, s), 0.97 (3H, d, J=6.8 Hz), 0.89 (3H, d, J=6.8 Hz).

MS (ESI, m/z): 453 $(M+H)^+$.

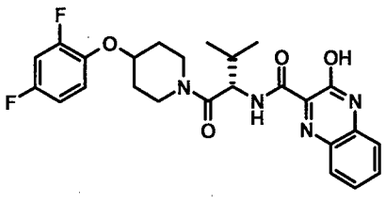
Example 22-3

N-[(1S)-1-({4-[4-Fluoro-2-(3-hydroxypropyl)phenoxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 1-3, 3-{5-fluoro-2-[(1-L-valylpiperidin-4-yl)oxy]phenyl}propan-1-ol hydrochloride was obtained from t-butyl [(1S)-1-({4-[4-fluoro-2-(3-hydroxypropyl)phenoxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (75.6 mg, 0.167 mmol) as a white solid. The resulting compound was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (38.0 mg, 0.200 mmol) to afford the desired title compound (44.6 mg, yield 51%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.82 (1H, brs), 9.56 (1H, brs), 7.85 (1H, t, J=8.0 Hz), 7.63 (1H, dt, J=8.0 Hz, 1.6 Hz), 7.37 (2H, m), 7.04-6.93 (3H, m), 4.90 (1H, t, J=7.6 Hz), 4.61 (1H, m), 3.90-3.40 (4H, m), 3.41 (2H, t, J=5.2 Hz), 2.67 (2H, q, J=8.0 Hz), 2.10 (1H, m), 2.00-1.55 (4H, m), 1.70 (2H, q, J=8.0 Hz), 0.97 (3H, d, J=6.4 Hz), 0.94 (3H, d, J=6.4 Hz).
LCMS (ESI, m/z): 525 $(M+H)^+$.

Example 23



N-[(1S)-1-{[4-(2,4-Difluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 23-1

t-Butyl 4-(2,4-difluorophenoxy)piperidine-1-carboxylate

A 40% toluene solution of diisopropyl azodicarboxylate (4.71 ml, 8.94 mmol) was added to a toluene solution (30 ml) of t-butyl 4-hydroxypiperidine-1-carboxylate (1.50 g, 7.45 mmol), 2,4-difluorophenol (1.07 g, 8.20 mmol) and triphenylphosphine (2.34 g, 8.94 mmol), at room temperature, under nitrogen stream, and stirring was carried out at 90°C overnight. The reaction solution was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., 40+M) to afford t-butyl 4-(2,4-difluorophenoxy)piperidine-1-carboxylate (2.28 g, yield 98%) as a pale yellow oily substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.99-6.75 (3H, m), 4.35-4.30 (1H, m), 3.77-3.71 (2H, m), 3.32-3.28 (2H, m), 1.92-1.88 (2H, m), 1.79-1.68 (2H, m), 1.53-1.38 (9H, m).
MS (FAB, m/z): 314 $(M+H)^+$.

Example 23-2

t-Butyl [(1S)-1-{[4-(2,4-difluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate

A 4N-hydrochloric acid 1,4-dioxane solution (30 ml) was added to a 1,4-dioxane solution (30 ml) of t-butyl 4-(2,4-difluorophenoxy)piperidine-1-carboxylate (2.28 g, 7.28 mmol), under nitrogen stream, and the mixture was allowed to react at room temperature overnight. The reaction solution was concentrated to afford 4-(2,4-

difluorophenoxy)piperidine hydrochloride (1.63 g) as a white solid.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.50 g, 7.84 mmol) and 1-hydroxybenzotriazole monohydrate (1.06 g, 7.84 mmol) were added to a methylene chloride solution (30 ml) of the resulting compound (1.63 g, 6.53 mmol) and N-(t-butoxycarbonyl)-L-valine (1.56 g, 7.18 mmol), at room temperature, under nitrogen stream, followed by further addition of N-methylmorpholine (1.58 ml, 14.4 mmol), and stirring was carried out at room temperature overnight. The reaction solution was poured into a 2N aqueous hydrochloric acid solution, followed by extraction with methylene chloride and sequential washing with water, a saturated aqueous sodium hydrogencarbonate solution, water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., 25+M) to afford t-butyl [(1S)-1-{[4-(2,4-difluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate (2.39 g, yield 89%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 7.00-6.99 (1H, m), 6.91-6.89 (1H, m), 6.83-6.81 (1H, m), 5.37-5.36 (1H, m), 4.52-4.45 (2H, m), 3.85-3.79 (2H, m), 3.64-3.45 (2H, m), 2.02-1.82 (5H, m), 1.51-1.48 (9H, m), 1.00 (3H, t, J=6.8 Hz), 0.92 (3H, t, J=6.8 Hz).

MS (FAB, m/z): 413 $(M+H)^+$.

Example 23-3

N-[(1S)-1-{[4-(2,4-Difluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

A 4N-hydrochloric acid 1,4-dioxane solution (30 ml) was added to a 1,4-dioxane solution (30 ml) of t-butyl [(1S)-1-{[4-(2,4-difluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate (2.39 g, 5.79 mmol), under nitrogen stream, and stirring was carried out at room temperature overnight. The reaction solution was concentrated to afford (2S)-1-[4-(2,4-difluorophenoxy)piperidin-1-yl]-3-methyl-1-oxobutan-2-amine hydrochloride (2.01 g) as a white solid.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (288 mg, 1.50 mmol) and 1-hydroxybenzotriazole monohydrate (203 mg, 1.50 mmol) were added to a methylene chloride solution (5.0 ml) of the resulting compound (350 mg, 1.00 mmol) and 3-hydroxyquinoxaline-2-carboxylic acid (285 mg, 1.50 mmol), at room temperature, under nitrogen stream, followed by further addition of triethylamine (0.558 ml, 4.00 mmol), and stirring was carried out at room temperature overnight. The reaction solution was

diluted with methylene chloride, followed by sequential washing with a saturated aqueous sodium hydrogencarbonate solution, a saturated aqueous ammonium chloride solution, water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. After the organic layer was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., 25+M), the residue resulting from concentration was suspended in a mixed solvent of methylene chloride-ethyl acetate, and the solid substance was collected by filtration to afford the desired title compound (283 mg, yield 58%) as a pale yellow solid.

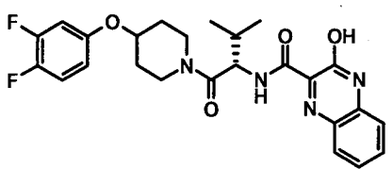
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.83 (1H, s), 9.47 (1H, t, J=4.1 Hz), 7.86 (1H, d, J=8.6 Hz), 7.64 (1H, t, J=8.6 Hz), 7.40-7.27 (4H, m), 7.02 (1H, t, J=8.8 Hz), 4.90 (1H, q, J=8.1 Hz), 4.60 (1H, brs), 3.94-3.90 (2H, m), 3.57-3.22 (2H, m), 2.09-1.91 (3H, m), 1.73-1.52 (2H, m), 0.95 (6H, t, J=6.8 Hz).

IR (KBr) cm^{-1}: 2965, 1685, 1635, 1505, 1210.

MS (FAB, m/z): 485 $(M+H)^+$.

HRMS (ESI, m/z): 485.2007 (Calcd for $C_{25}H_{27}F_2N_4O_4$: 485.2000).

Example 24



N-[(1S)-1-{[4-(3,4-Difluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 24-1

t-Butyl 4-(3,4-difluorophenoxy)piperidine-1-carboxylate

Analogously to Example 1-2, t-butyl 4-(3,4-difluorophenoxy)piperidine-1-carboxylate (1.69 g, yield 89%) was obtained from t-butyl 4-hydroxypiperidine-1-carboxylate (1.22 g, 6.07 mmol) and 3,4-difluorophenol (790 mg, 6.07 mmol) as a pale yellow oily substance.

^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 7.05 (1H, q, J=9.3 Hz), 6.77-6.67 (1H, m), 6.62-6.59 (1H, m), 4.38-4.34 (1H, m), 3.71-3.66 (2H, m), 3.36-3.31 (2H, m), 1.92-1.88 (2H, m), 1.74-1.71 (2H, m), 1.49-1.44 (9H, m).

MS (FAB, m/z): 314 $(M+H)^+$.

Example 24-2

t-Butyl [(1S)-1-{[4-(3,4-difluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate

Analogously to Example 23-2, 4-(3,4-difluorophenoxy)piperidine hydrochloride (1.23 g) was obtained from t-butyl 4-(3,4-difluorophenoxy)piperidine-1-carboxylate (1.69 g, 5.39 mmol) as a white solid.

The resulting compound (1.23 g, 4.93 mmol) was condensed with N-(t-butoxycarbonyl)-L-valine (1.18 g, 5.42 mmol) under nitrogen stream to afford t-butyl [(1S)-1-{[4-(3,4-difluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate (2.03 g, yield 100%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.07 (1H, dd, J=18.0 Hz, 9.4 Hz), 6.75-6.72 (1H, m), 6.64-6.59 (1H, m), 5.34 (1H, d, J=9.0 Hz), 4.51-4.43 (2H, m), 3.80-3.57 (4H, m), 1.97-1.79 (5H, m), 1.43-1.41 (9H, m), 0.97 (3H, d, J=7.0 Hz), 0.88 (3H, d, J=7.0 Hz).

MS (FAB, m/z): 413 $(M+H)^+$.

Example 24-3

N-[(1S)-1-{[4-(3,4-Difluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 1-3, (2S)-1-[4-(3,4-difluorophenoxy)-piperidin-1-yl]-3-methyl-1-oxobutan-2-amine hydrochloride (1.73 g) was obtained from t-butyl [(1S)-1-{[4-(3,4-difluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate (2.03 g, 4.92 mmol) as a white solid. The resulting compound (350 mg, 1.00 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (285 mg, 1.50 mmol) to afford the desired title compound (270 mg, yield 56%) as a pale yellow solid.

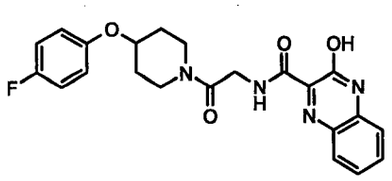
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.83 (1H, s), 9.48 (1H, dd, J=8.8 Hz, 4.9 Hz), 7.87-7.85 (1H, m), 7.66-7.62 (1H, m), 7.38-7.33 (3H, m), 7.21-7.14 (1H, m), 6.84 (1H, s), 4.90 (1H, dd, J=13.9 Hz, 6.8 Hz), 4.65-4.64 (1H, m), 3.95-3.90 (2H, m), 3.56-3.22 (2H, m), 2.02-1.96 (3H, m), 1.69-1.49 (2H, m), 0.95-0.94 (6H, m).

IR (KBr) cm^{-1}: 2965, 1685, 1630, 1515, 1215, 1160.

MS (FAB, m/z): 485 $(M+H)^+$.

HRMS (ESI, m/z): 485.2022 (Calcd for $C_{25}H_{27}F_2N_4O_4$: 485.2000).

Example 25



N-{2-[4-(4-Fluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-

hydroxyquinoxaline-2-carboxamide

Example 25-1

t-Butyl {2-[4-(4-fluorophenoxy)piperidin-1-yl]-2-oxoethyl}carbamate

Analogously to Example 2-1, t-butyl {2-[4-(4-fluorophenoxy)piperidin-1-yl]-2-oxoethyl}carbamate (273 mg, yield 77%) was obtained from 4-(4-fluorophenoxy)piperidine hydrochloride (231 mg, 1.00 mmol) and N-(t-butoxycarbonyl)glycine (175 mg, 1.00 mmol) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.99 (2H, dd, J=9.0 Hz, 8.2 Hz), 6.87 (2H, dd, J=9.0 Hz, 4.2 Hz), 5.54 (1H, brs), 4.48 (1H, m), 3.99 (1H, d, J=4.6 Hz), 3.98 (1H, d, J=4.6 Hz), 3.73 (2H, t, J=5.8 Hz), 3.65-3.57 (1H, m), 3.38-3.30 (1H, m), 1.96-1.75 (4H, m), 1.96 (9H, s).

MS (ESI, m/z): 353 $(M+H)^+$.

Example 25-2

N-[2-{[4-(4-Fluorophenoxy)piperidin-1-yl]carbonyl}-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 2-2, 2-[4-(4-fluorophenoxy)piperidin-1-yl]-2-oxoethanamine hydrochloride (190 mg, yield 85%) was obtained from t-butyl {2-[4-(4-fluorophenoxy)piperidin-1-yl]-2-oxoethyl}carbamate (273 mg, 0.773 mmol). From the resulting compound (144 mg, 0.500 mmol), through condensation with 3-hydroxyquinoxaline-2-carboxylic acid (95.1 mg, 0.500 mmol), a mixture containing the desired title compound was afforded. Repurification by preparative TLC afforded the desired title compound (28.5 mg, yield 13%) as a yellow solid.

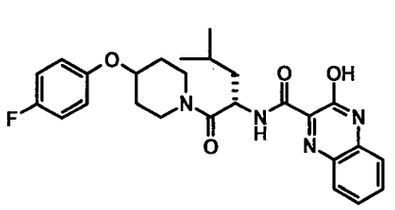
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.85 (1H, brs), 9.79 (1H, brs), 7.88 (1H, d, J=8.2 Hz), 7.68-7.55 (1H, m), 7.41-7.30 (2H, m), 7.17-7.08 (2H, m), 7.07-6.98 (2H, m), 4.59 (1H, m), 4.28 (2H, d, J=4.6 Hz), 4.00-3.20 (4H, m), 2.04-1.85 (2H, m), 1.71-1.48 (2H, m).

IR (KBr) cm^{-1}: 2950, 1695, 1650, 1620, 1505, 1210.

MS (ESI, m/z): 425 $(M+H)^+$.

HRMS (ESI, m/z): 425.1626 (Calcd for $C_{22}H_{22}FN_4O_4$: 425.1625).

Example 26



N-[(1S)-1-{[4-(4-Fluorophenoxy)piperidin-1-yl]carbonyl}-3-methylbutyl]-3-

hydroxyquinoxaline-2-carboxamide

Example 26-1

Benzyl [(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}-3-methylbutyl]carbamate

Analogously to Example 2-1, benzyl [(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}-3-methylbutyl]carbamate (755 mg, yield 85%) was obtained from 4-(4-fluorophenoxy)piperidine hydrochloride (463 mg, 2.00 mmol) and N-(benzyloxycarbonyl)-L-leucine (531 mg, 2.00 mmol) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.38-7.30 (5H, m), 6.99 (2H, dd, J=9.0 Hz, 8.6 Hz), 6.87 (2H, dd, J=9.0 Hz, 4.2 Hz), 5.57 (1H, d, J=8.2 Hz), 5.10 (2H, s), 4.75 (1H, m), 4.47 (1H, m), 3.83-3.39 (4H, m), 2.00-1.64 (5H, m), 1.61-1.47 (1H, m), 1.44-1.34 (1H, m), 1.00 and 0.93 (6H, d, J=6.6 Hz).

Example 26-2

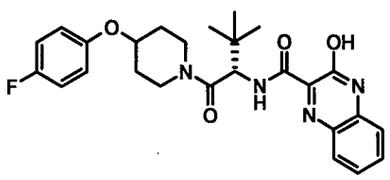
N-[(1S)-1-{[4-(4-Fluorophenoxy)piperidin-1-yl]carbonyl}-3-methylbutyl]-3-hydroxyquinoxaline-2-carboxamide

5% Palladium carbon catalyst (75.0 mg) was added to an ethanol solution (22.5 ml) of benzyl [(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}-3-methylbutyl]carbamate (755 mg, 1.70 mmol), under hydrogen stream, and stirring was carried out at room temperature for 2 hours. After the catalyst was celite filtered and washed with methylene chloride, the mother liquor was concentrated to afford (2S)-1-[4-(4-fluorophenoxy)piperidin-1-yl]-4-methyl-1-oxopentan-2-amine (521 mg) as a colorless oil.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (230 mg, 1.20 mmol) and 1-hydroxybenzotriazole monohydrate (184 mg, 1.20 mmol) were added to a methylene chloride solution (10 ml) of the resulting compound (308 mg, 1.00 mmol) and 3-hydroxyquinoxaline-2-carboxylic acid (190 mg, 1.00 mmol), at room temperature, under nitrogen stream, followed by further addition of N-methylmorpholine (0.550 ml, 5.00 mmol), and stirring was carried out at room temperature overnight. The reaction solution was diluted with methylene chloride, followed by sequential washing with a saturated aqueous sodium hydrogencarbonate solution, a saturated aqueous ammonium chloride solution, water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. After the organic layer was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., 25+M), the residue resulting from concentration was suspended in a mixed solvent of methylene chloride-

ethyl acetate, the solid substance was collected by filtration to afford the desired title compound (126 mg, yield 26%) as a pale yellow solid.
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.83 (1H, brs), 9.52 (1H, d, J=7.8 Hz), 7.86 (1H, dd, J=7.4 Hz, 7.0 Hz), 7.65 (1H, dd, J=7.8 Hz, 7.4 Hz), 7.40 (1H, d, J=7.0 Hz), 7.38 (1H, d, J=7.4 Hz), 7.17-7.09 (2H, m), 7.07-6.99 (2H, m), 5.08 (1H, m), 4.60 (1H, m), 4.02-3.18 (4H, m), 2.11-1.84 (2H, m), 1.76-1.44 (5H, m), 0.96 and 0.92 (6H, d, J=6.6 Hz).
IR (KBr) cm^{-1}: 2955, 1685, 1640, 1505, 1205.
MS (ESI, m/z): 481 $(M+H)^+$.
HRMS (ESI, m/z): 481.2268 (Calcd for $C_{26}H_{30}FN_4O_4$: 481.2251).

Example 27



N-[(1S)-1-{[4-(4-Fluorophenoxy)piperidin-1-yl]carbonyl}-2,2-dimethylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 27-1

t-Butyl [(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}-2,2-dimethylpropyl]carbamate

Analogously to Example 2-1, t-butyl [(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}-2,2-dimethylpropyl]carbamate (619 mg, yield 76%) was obtained from 4-(4-fluorophenoxy)piperidine hydrochloride (463 mg, 2.00 mmol) and (2S)-N-(t-butoxycarbonyl)-2-amino-3,3-dimethylbutyric acid (462 mg, 2.00 mmol) as a colorless oil.
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.02-6.95 (2H, m), 6.95-6.89 (2H, m), 5.36 (1H, d, J=9.8 Hz), 4.56 (1H, d, J=9.8 Hz), 4.51-4.40 (1H, m), 3.93-3.47 (4H, m), 2.00-1.74 (4H, m), 1.43 (9H, s), 0.99 (9H, s).
MS (ESI, m/z): 409 $(M+H)^+$.

Example 27-2

N-[(1S)-1-{[4-(4-Fluorophenoxy)piperidin-1-yl]carbonyl}-2,2-dimethylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 2-2, (2S)-1-[4-(4-fluorophenoxy)piperidin-1-yl]-3,3-dimethyl-1-oxobutan-2-amine hydrochloride (522 mg, yield 100%) was obtained from t-butyl [(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}-2,2-dimethylpropyl]carbamate (619 mg, 1.52 mmol). From the resulting compound, through condensation with 3-hydroxyquinoxaline-2-carboxylic acid (190 mg, 1.00 mmol), the desired title compound (160 mg,

yield 33%) was afforded as a pale yellow solid.

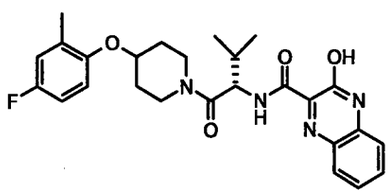
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.86 (1H, brs), 9.71 and 9.68 (1H, d, J=9.0 Hz), 7.89 (1H, d, J=8.2 Hz), 7.66 (1H, dd, J=8.2 Hz, 7.8 Hz), 7.44-7.37 (2H, m), 7.16-7.09 (2H, m), 7.07-6.99 (2H, m), 5.07 and 5.05 (1H, d, J=9.0 Hz), 4.61 (1H, m), 4.11-3.14 (4H, m), 2.07-1.84 (2H, m), 1.74-1.41 (2H, m), 1.03 (9H, s).

IR (KBr) cm^{-1}: 2950, 1690, 1630, 1505, 1205.

MS (ESI, m/z): 481 $(M+H)^+$.

HRMS (ESI, m/z): 481.2280 (Calcd for $C_{26}H_{30}FN_4O_4$: 481.2251).

Example 28



N-[(1S)-1-{[4-(4-Fluoro-2-methylphenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 28-1

t-Butyl [(1S)-1-{[4-(4-fluoro-2-methylphenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate

Analogously to Example 1-2, t-butyl [(1S)-1-{[4-(4-fluoro-2-methylphenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate (480 mg, yield 60%) was obtained from t-butyl {(1S)-1-[(4-hydroxypiperidin-1-yl)carbonyl]-2-methylpropyl}carbamate (601 mg, 2.00 mmol) and 4-fluorocresol (277 mg, 2.20 mmol) as a colorless oil.

^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 6.91-6.86 (1H, m), 6.85-6.78 (1H, m), 6.78-6.73 (1H, m), 5.36 (1H, d, J=9.4 Hz), 4.53-4.44 (2H, m), 3.88-3.45 (4H, m), 2.24 and 2.22 (3H, s), 2.02-1.74 (5H, m), 1.44 (9H, s), 0.98 and 0.90 (6H, d, J=7.0 Hz).

MS (FAB, m/z): 409 $(M+H)^+$.

Example 28-2

N-[(1S)-1-{[4-(4-Fluoro-2-methylphenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 1-3, (2S)-1-[4-(4-fluoro-2-methylphenoxy)piperidin-1-yl]-3-methyl-1-oxobutan-2-amine hydrochloride (388 mg, yield 96%) was obtained from t-butyl [(1S)-1-{[4-(4-fluoro-2-methylphenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate (480 mg, 1.18 mmol). The resulting compound (194mg, 0.564 mmol) was condensed with

3-hydroxyquinoxaline-2-carboxylic acid (110 mg, 0.564 mmol) to afford the desired title compound (89.5 mg, yield 33%) as a pale yellow solid.

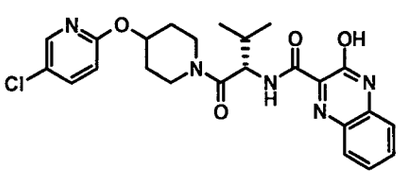
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.82 (1H, brs), 9.52 (1H, brs), 7.90-7.82 (1H, m), 7.69-7.61 (1H, m), 7.43-7.36 (2H, m), 7.08-7.01 (2H, m), 7.00-6.92 (1H, m), 4.96 (1H, m), 4.60 (1H, m), 3.94-3.35 (4H, m), 2.19 and 2.16 (3H, s), 2.10-1.84 (3H, m), 1.76-1.64 (1H, m), 1.62-1.52 (1H, m), 0.98-0.92 (6H, m).

IR (KBr) cm^{-1}: 2965, 1690, 1630, 1495, 1205.

MS (ESI, m/z): 481 $(M+H)^+$.

HRMS (ESI, m/z): 481.2255 (Calcd for $C_{26}H_{30}FN_4O_4$: 481.2251).

Example 29



N-[(1S)-1-({4-[(5-Chloropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 29-1

t-Butyl 4-[(5-chloropyridin-2-yl)oxy]piperidine-1-carboxylate

t-Butyl 4-(methanesulfonyloxy)piperidine-1-carboxylate (3.02 g, 10.8 mmol) and potassium carbonate (2.35 g, 17.0 mmol) were added to a N,N-dimethylformamide solution (77 ml) of 5-chloro-2-hydroxypyridine (1.00 g, 7.72 mmol), at room temperature, and stirring was carried out at 75°C overnight. After the reaction solution was cooled to room temperature, water was added to the residue resulting from concentration, followed by extraction with methylene chloride. The resulting organic layer was dried over anhydrous sodium sulfate, and the residue resulting from concentration was purified by silica gel column chromatography to afford t-butyl 4-[(5-chloropyridin-2-yl)oxy]piperidine-1-carboxylate (1.57 g, yield 65%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.06 (1H, d, J=2.7 Hz), 7.51 (1H, dd, J=8.8 Hz, 2.7 Hz), 6.67 (1H, d, J=8.8 Hz), 5.18-5.13 (1H, m), 3.79-3.73 (2H, m), 3.31-3.24 (2H, m), 1.99-1.93 (2H, m), 1.74-1.66 (2H, m), 1.47 (9H, s).

Example 29-2

t-Butyl [(1S)-1-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate

Concentrated hydrochloric acid (5.0 ml) was added to an ethanol solution (10 ml) of t-butyl 4-[(5-chloropyridin-2-yl)oxy]piperidine-1-

carboxylate (1.57 g, 5.02 mmol), at 0°C, and stirring was carried out at room temperature for 2 days. The reaction solution was concentrated to afford 5-chloro-2-[(piperidin-4-yl)oxy]pyridine dihydrochloride (1.61 g).

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.44 g, 7.53 mmol) was added to a methylene chloride solution (50 ml) of the resulting compound (1.61 g), N-(t-butoxycarbonyl)-L-valine (1.09 g, 5.02 mmol), 1-hydroxybenzotriazole monohydrate (814 mg, 6.02 mmol) and N-methylmorpholine (3.31 ml, 30.1 mmol), at room temperature, and stirring was carried out at room temperature overnight. Water was added to the reaction solution, followed by extraction with methylene chloride and subsequent sequential washing with a saturated aqueous sodium hydrogencarbonate solution, water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by silica gel column chromatography to afford t-butyl [(1S)-1-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (1.94 g, yield 94%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.08-8.06 (1H, m), 7.53 (1H, dd, J=8.8 Hz, 2.8 Hz), 6.68 (1H, dd, J=8.8 Hz, 1.2 Hz), 5.35 (1H, d, J=8.8 Hz), 5.28-5.21 (1H, m), 4.50 (1H, dd, J=8.8 Hz, 5.7 Hz), 3.98-3.43 (4H, m), 2.09-1.73 (5H, m), 1.44 (9H, s), 0.97 (3H, d, J=6.6 Hz), 0.89 (3H, d, J=6.6 Hz).

Example 29-3

(2S)-1-{4-[(5-Chloropyridin-2-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine dihydrochloride

Concentrated hydrochloric acid (5.0 ml) was added to an ethanol solution (10 ml) of t-butyl [(1S)-1-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (1.94 g, 4.71 mmol), at 0°C, and stirring was carried out at room temperature overnight. The reaction solution was concentrated to afford (2S)-1-{4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine dihydrochloride (1.93 g, yield 100%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.43 (2H, brs), 8.13-8.12 (1H, m), 7.69 (1H, brs), 6.92 (1H, brs), 5.36 (1H, brs), 4.51 (1H, brs), 3.88-3.46 (4H, m), 2.28-1.86 (5H, m), 1.20-1.11 (6H, m).

MS (ESI, m/z): 312 $(M+H)^+$.

Example 29-4

N-[(1S)-1-({4-[(5-Chloropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (150 mg, 0.780 mmol), was added to a methylene chloride solution (5.2 ml) of (2S)-1-{4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine dihydrochloride (200 mg, 0.520 mmol), 3-hydroxyquinoxaline-2-carboxylic acid (102 mg, 0.520 mmol), 1-hydroxybenzotriazole monohydrate (84.3 mg, 0.620 mmol) and N-methylmorpholine (0.343 ml, 3.12 mmol), at room temperature, and stirring was carried out at room temperature for 3 days. Water was added to the reaction solution, followed by extraction with methylene chloride and subsequent sequential washing with a saturated aqueous sodium hydrogencarbonate solution, water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. After the organic layer was concentrated and the resulting residue was purified by silica gel column chromatography, the residue resulting from concentration was suspended in a mixed solvent of ethanol-diethyl ether, and the solid substance was collected by filtration to afford the desired title compound (190 mg, yield 76%) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 12.44 (1H, brs), 10.15 (1H, brs), 8.08 (1H, dd, J=6.3 Hz, 2.7 Hz), 8.02-8.00 (1H, m), 7.61-7.37 (4H, m), 6.70 (1H, t, J=9.2 Hz), 5.32-5.27 (1H, m), 5.09 (1H, t, J=7.4 Hz), 4.06-3.59 (4H, m), 2.34-1.82 (5H, m), 1.14-1.10 (6H, m).

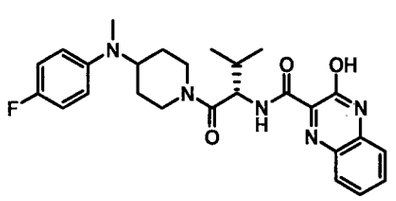
IR (KBr) cm^{-1}: 2965, 1690, 1630, 1525, 1465.

MS (ESI, m/z): 484 $(M+H)^+$.

HRMS (ESI, m/z): 484.1765 (Calcd for $C_{24}H_{27}ClN_5O_4$: 484.1752).

Anal. Calcd for $C_{24}H_{26}ClN_5O_4$: C, 59.56; H, 5.42; N, 14.47; Cl, 7.33. Found: C, 59.48; H, 5.50; N, 14.49; Cl, 7.16.

Example 30



N-[(1S)-1-({4-[(4-Fluorophenyl)(methyl)amino]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 30-1

t-Butyl 4-[(4-fluorophenyl)amino]piperidine-1-carboxylate

Sodium cyanoborohydride (661 mg, 10.0 mmol) was added to a methylene chloride solution (30 ml) of t-butyl 4-oxopiperidine-1-carboxylate (2.66 g, 13.1 mmol), 4-fluoroaniline (1.46 g, 13.1 mmol) and

acetic acid (0.750 ml, 13.1 mmol), at 0°C, and stirring was carried out at room temperature for 15 hours. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, followed by extraction with ethyl acetate, and the extract was washed sequentially with water and saline, and dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was washed with diisopropyl ether, followed by drying to afford t-butyl 4-[(4-fluorophenyl)amino]piperidine-1-carboxylate (3.09 g, yield 80%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.91-6.84 (2H, m), 6.56-6.51 (2H, m), 4.12-3.97 (2H, m), 3.36-3.32 (2H, m),2.95-2.87 (1H, m), 2.06-1.98 (2H, m), 1.47 (9H, s), 1.36-1.24 (2H, m).

Example 30-2

N-(4-Fluorophenyl)-N-methylpiperidin-4-amine dihydrochloride

Sodium cyanoborohydride (641 mg, 10.2 mmol) was added to an acetic acid solution (14 ml) of t-butyl 4-[(4-fluorophenyl)amino]piperidine-1-carboxylate (1.50 g, 5.10 mmol) and formaldehyde (2.07 ml, 25.5 mmol), at 0°C, and stirring was carried out at room temperature for 31 hours. The reaction solution was concentrated under reduced pressure, and a saturated aqueous sodium hydrogencarbonate solution was added to the residue, followed by extraction with ethyl acetate. The extract was washed sequentially with water and saline, and dried over anhydrous sodium sulfate. After the organic layer was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Yamazen Corporation, W-Prep 2XY), the residue resulting from concentration was dissolved in ethanol (24 ml), and then concentrated hydrochloric acid (10 ml) was added under ice cooling, followed by stirring at room temperature for 12 hours. The reaction solution was concentrated under reduced pressure to afford N-(4-fluorophenyl)-N-methylpiperidin-4-amine dihydrochloride (1.28 g, yield 89%) as an amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.84-7.79 (2H, m), 7.43-7.37 (2H, m), 4.14-4.05 (1H, m), 3.61-3.49 (2H, m), 3.33 (3H, s), 3.17-3.04 (2H, m), 2.38-1.94 (4H, m).

Example 30-3

1-[(2S)-2-Amino-3-methylbutanoyl]-N-(4-fluorophenyl)-N-methylpiperidin-4-amine dihydrochloride

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (364

mg, 1.90 mmol) was added to a methylene chloride solution (30 ml) of N-(4-fluorophenyl)-N-methylpiperidin-4-amine dihydrochloride (445 mg, 1.58 mmol), N-(t-butoxycarbonyl)-L-valine (343 mg, 1.48 mmol), 1-hydroxybenzotriazole monohydrate (257 mg, 1.90 mmol) and N-methylmorpholine (0.556 ml, 5.06 mmol), at room temperature, and stirring was carried out under room temperature for 4 hours. The reaction solution was concentrated under reduced pressure, and water was added to the residue, followed by extraction with ethyl acetate. The extract was washed sequentially with water, a saturated aqueous sodium hydrogencarbonate solution and saturated saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Yamazen Corporation, W-Prep 2XY), and the resulting residue was dissolved in ethanol (10 ml). To this was added concentrated hydrochloric acid (5.0 ml) under ice cooling, and stirring was carried out at room temperature for 12 hours. The reaction solution was concentrated under reduced pressure to afford the desired title compound (528 mg, yield 88%) as an amorphous substance.

^{1}H-NMR (CD_3OD, 400 MHz) δ: 7.84-7.72 (2H, m), 7.42-7.30 (2H, m), 4.74-4.63 (1H, m), 4.42-4.29 (1H, m), 4.16-3.08 (2H, m), 3.28 (3H, s), 3.27-3.18 (1H, m), 2.80-2.69 (1H, m), 2.26-1.60 (5H, m), 1.12-0.98 (6H, m).

Example 30-4

N-[(1S)-1-({4-[(4-Fluorophenyl)(methyl)amino]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (113 mg, 0.590 mmol) was added to a methylene chloride solution (5.0 ml) of 1-[(2S)-2-amino-3-methylbutanoyl]-N-(4-fluorophenyl)-N-methylpiperidin-4-amine dihydrochloride (150 mg, 0.390 mmol), 3-hydroxyquinoxaline-2-carboxylic acid (77.3 mg, 0.390 mmol), 1-hydroxybenzotriazole monohydrate (64.0 mg, 0.470 mmol) and N-methylmorpholine (0.217 ml, 1.97 mmol), at room temperature, and stirring was carried out at room temperature overnight. Water was added to the reaction solution, followed by extraction with methylene chloride and subsequent sequential washing with a saturated aqueous sodium hydrogencarbonate solution, water and saline, and the resulting organic layer was dried over anhydrous sodium sulfate. After the organic layer was concentrated and the resulting residue was purified by silica gel column chromatography, the residue resulting from concentration was suspended in a mixed solvent of ethanol-diethyl ether,

and the solid substance was collected by filtration to afford the desired title compound (135 mg, yield 71%) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 12.20 (1H, brs), 10.16 (1H, brs), 8.06-8.02 (1H, m), 7.64-7.40 (3H, m), 6.99-6.93 (2H, m), 6.80 (2H, dq, J=16.0 Hz, 3.6 Hz), 5.14-5.06 (1H, m), 4.84 (1H, s), 4.35 (1H, s), 3.67 (1H, s), 3.29-3.18 (1H, m), 2.75-2.69 (4H, m), 2.27 (1H, m), 1.96-1.62 (4H, m), 1.10 (6H, dd, J=13.2 Hz, 5.2 Hz).

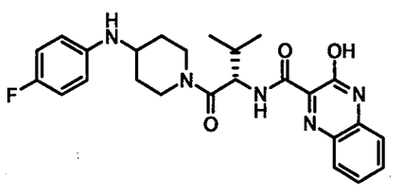
IR (KBr) cm^{-1}: 2960, 1685, 1640, 1510.

MS (ESI, m/z): 480 $(M+H)^+$.

HRMS (ESI, m/z): 480.2414 (Calcd for $C_{26}H_{31}FN_5O_3$: 480.2411).

Anal. Calcd for $C_{26}H_{30}FN_5O_3$: C, 65.12; H, 6.31; N, 14.60; F, 3.96. Found: C, 64.97; H, 6.32; N, 14.34; F, 3.94.

Example 31



N-[(1S)-1-({4-[(4-Fluorophenyl)amino]piperidin-1-yl}carbonyl]-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Concentrated hydrochloric acid (5.0 ml) was added to an ethanol solution (10 ml) of t-butyl 4-[(4-fluorophenyl)amino]piperidine-1-carboxylate (1.00 g, 3.40 mmol), under ice cooling, and stirring was carried out at room temperature for 12 hours. The reaction solution was concentrated under reduced pressure, and the resulting residue was washed with diethyl ether and □-hexane to afford 1-[(2S)-2-amino-3-methylbutanoyl]-N-(4-fluorophenyl)piperidin-4-amine dihydrochloride (768 mg, yield 84%) as an orange oil.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (118 mg, 0.610 mmol) was added to a methylene chloride solution (5.0 ml) of 1-[(2S)-2-amino-3-methylbutanoyl]-N-(4-fluorophenyl)piperidin-4-amine dihydrochloride (150 mg, 0.410 mmol), 3-hydroxyquinoxaline-2-carboxylic acid (80.3 mg, 0.410 mmol), 1-hydroxybenzotriazole monohydrate (66.4 mg, 0.490 mmol) and N-methylmorpholine (0.225 ml, 2.05 mmol), at room temperature, and stirring was carried out at room temperature overnight. Water was added to the reaction solution, followed by extraction with methylene chloride and subsequent sequential washing with a saturated aqueous sodium hydrogencarbonate solution, water and saline, and the resulting organic layer was dried over anhydrous sodium sulfate. After the organic layer was concentrated and the resulting residue was purified

by silica gel column chromatography, the residue resulting from concentration was suspended in a mixed solvent of ethanol-diethyl ether, and the solid substance was collected by filtration to afford the desired title compound (121 mg, yield 64%) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 12.19 (1H, brs), 10.11 (1H, brs), 8.00 (1H, m), 7.62 (1H, m), 7.44-7.26 (2H, m), 6.90 (2H, q, J=7.2 Hz), 6.59-6.54 (2H, m), 5.08-5.05 (1H, m), 4.67-4.51 (1H, m), 4.24 (1H, brs), 3.51-3.30 (3H, m), 3.07-2.90 (1H, m), 2.32-2.12 (3H, m), 1.48-1.35 (2H, m), 1.13-1.09 (6H, m).

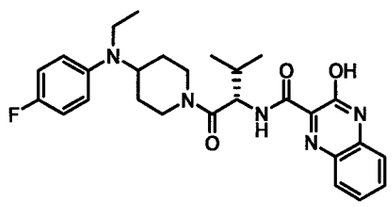
IR (KBr) cm^{-1}: 2960, 1685, 1630, 1510, 1215.

MS (FAB, m/z): 466 $(M+H)^+$.

HRMS (FAB, m/z): 466.2242 (Calcd for $C_{25}H_{29}FN_5O_3$: 466.2255).

Anal. Calcd for $C_{25}H_{28}FN_5O_3$: C, 64.50; H, 6.06; N, 15.04; F, 4.08. Found: C, 64.18; H, 5.77; N, 14.93; F, 4.02.

Example 32



N-[(1S)-1-({4-[(Ethyl)(4-fluorophenyl)amino]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 32-1

t-Butyl 4-[(ethyl)(4-fluorophenyl)amino]piperidine-1-carboxylate

Sodium cyanoborohydride (661 mg, 10.0 mmol) was added to an acetonitrile solution (5.0 ml) of t-butyl 4-[(4-fluorophenyl)amino]piperidine-1-carboxylate (1.47 g, 5.00 mmol), acetaldehyde (0.559 ml, 5.00 mmol) and acetic acid (0.0570 ml, 1.00 mmol), at 0°C, and stirring was carried out at room temperature for 3 hours. Further acetic acid (2.0 ml) was added, and stirring was carried out for 30 minutes. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, followed by extraction with ethyl acetate and subsequent sequential washing with water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by silica gel column chromatography to afford t-butyl 4-[(ethyl)(4-fluorophenyl)amino]piperidine-1-carboxylate (1.27 g, yield 79%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.94 (2H, t, J=8.8 Hz), 6.74 (2H, dd, J=8.8 Hz,

4.5 Hz), 4.20 (2H, brs), 3.48 (1H, tt, J=11.6 Hz, 3.6 Hz), 3.18 (2H, q, J=7.0 Hz), 2.78-2.72 (2H, m), 1.78 (2H, d, J=12.1 Hz), 1.62-1.46 (2H, m), 1.46 (9H, s), 1.08 (3H, t, J=7.0 Hz).
MS (ESI, m/z): 323 $(M+H)^+$.

Example 32-2
t-Butyl [(1S)-1-({4-[(ethyl)(4-fluorophenyl)amino]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate

Analogously to Example 29-2, t-butyl [(1S)-1-({4-[(ethyl)(4-fluorophenyl)amino]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (1.36 g, yield 82%) was obtained from t-butyl 4-[(ethyl)(4-fluorophenyl)amino]piperidine-1-carboxylate (1.27 g, 3.94 mmol) as a colorless amorphous substance.
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.97-6.92 (2H, m), 6.80-6.73 (2H, m), 5.34 (1H, d, J=6.6 Hz), 4.68 (1H, t, J=13.2 Hz), 4.50-4.47 (1H, m), 4.08-4.00 (1H, m), 3.59-3.51 (1H, m), 3.17-3.07 (3H, m), 2.68-2.61 (1H, m), 1.93-1.84 (3H, m), 1.68-1.43 (11H, m), 1.08-1.05 (3H, m), 0.97 (3H, dd, J=12.4 Hz, 5.2 Hz), 0.89 (3H, dd, J=8.4 Hz, 5.2 Hz).

Example 32-3
1-[(2S)-2-Amino-3-methylbutanoyl]-N-ethyl-N-(4-fluorophenyl)piperidin-4-amine dihydrochloride

Analogously to Example 29-3, 1-[(2S)-2-amino-3-methylbutanoyl]-N-ethyl-N-(4-fluorophenyl)piperidin-4-amine dihydrochloride (1.37 g, yield 100%) was obtained from t-butyl [(1S)-1-({4-[ethyl(4-fluorophenyl)amino]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (1.36 g, 3.23 mmol) as a colorless amorphous substance.
^{1}H-NMR (CD_3OD, 400 MHz) δ: 7.78-7.72 (2H, m), 7.44-7.39 (2H, m), 4.69-3.13 (8H, m), 2.74-1.73 (5H, m), 1.12-1.06 (6H, m), 0.99 (3H, t, J=7.6 Hz).
MS (ESI, m/z): 322 $(M+H)^+$.

Example 32-4
N-[(1S)-1-({4-[Ethyl(4-fluorophenyl)amino]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 29-4, the desired title compound (179 mg, yield 72%) was obtained from 1-[(2S)-2-amino-3-methylbutanoyl]-N-ethyl-N-(4-fluorophenyl)piperidin-4-amine dihydrochloride (200 mg, 0.510 mmol) as a yellow solid.
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 12.33 (1H, brs), 10.14 (1H, brs), 8.04 (1H, t, J=9.2 Hz), 7.65-7.26 (3H, m), 6.99-6.91 (2H, m), 6.84-6.74 (2H, m), 5.14-

5.06 (1H, m), 4.82-4.74 (1H, m), 4.32 (1H, brs), 3.64-3.55 (1H, m), 3.24-3.12 (3H, m), 2.78-2.71 (1H, m), 2.28 (1H, brs), 2.03-1.55 (4H, m), 1.11-1.03 (9H, m).

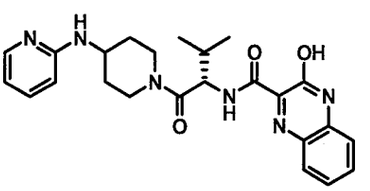
IR (KBr) cm^{-1}: 2965, 1690, 1635, 1510, 1450.

MS (ESI, m/z): 494 $(M+H)^+$, 516 $(M+Na)^+$.

HRMS (ESI, m/z): 516.2399 (Calcd for $C_{27}H_{32}FN_5NaO_3$: 516.2387).

Anal. Calcd for $C_{27}H_{32}FN_5O_3$: C, 65.70; H, 6.53; N, 14.19; F, 3.85. Found: C, 65.34; H, 6.48; N, 14.02; F, 3.79.

Example 33



N-[(1S)-2-Methyl-1-{[4-(pyridin-2-ylamino)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide

Example 33-1

t-Butyl [(1S)-2-methyl-1-({4-[(pyridin-2-ylamino)piperidin-1-yl]carbonyl}propyl]carbamate

Sodium triacetoxy borohydride (1.41 g, 6.31 mmol) was added to a methylene chloride solution (53 ml) of 2-aminopyridine (500 mg, 5.26 mmol), t-butyl 4-oxopiperidine-1-carboxylate (1.06 g, 5.26 mmol) and acetic acid (0.301 ml, 5.26 mmol), at room temperature, and stirring was carried out at room temperature overnight. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, followed by extraction with methylene chloride. The extract was concentrated and the resulting residue was purified by silica gel column chromatography to afford t-butyl 4-[(pyridin-2-ylamino)piperidine-1-carboxylate (335 mg).

Concentrated hydrochloric acid (3.5 ml) was added to an ethanol solution (7.0 ml) of the resulting compound (335 mg), at 0°C, and stirring was carried out at room temperature for 7 hours. The reaction solution was concentrated to afford N-(piperidin-4-yl)-2-aminopyridine trihydrochloride.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (347 mg, 1.81 mmol) was added to a methylene chloride solution (12 ml) of the resulting compound, N-(t-butoxycarbonyl)-L-valine (262 mg, 1.21 mmol), 1-hydroxybenzotriazole monohydrate (196 mg, 1.45 mmol) and N-methylmorpholine (0.797 ml, 7.25 mmol), at room temperature, and stirring was carried out at room temperature overnight. Water was added to the

reaction solution, followed by extraction with methylene chloride and subsequent sequential washing with a saturated aqueous sodium hydrogencarbonate solution, water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by silica gel column chromatography to afford t-butyl [(1S)-2-methyl-1-{[4-(pyridin-2-ylamino)piperidin-1-yl]carbonyl)propyl]carbamate (316 mg, yield 16%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.09 (1H, d, J=5.1 Hz), 7.43-7.38 (1H, m), 6.60-6.56 (1H, m), 6.37 (1H, d, J=7.8 Hz), 5.36-5.34 (1H, m), 4.54-4.45 (2H, m), 4.32-4.18 (1H, m), 3.99-3.91 (2H, m), 3.32-3.21 (1H, m), 2.98-2.86 (1H, m), 2.23-2.08 (2H, m), 1.96-1.89 (1H, m), 1.44 (9H, s), 1.42-1.24 (2H, m), 0.99-0.87 (6H, m).

MS (ESI, m/z): 377 $(M+H)^+$.

Example 33-2

N-[(1S)-2-Methyl-1-{[4-(pyridin-2-ylamino)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide

Concentrated hydrochloric acid (3.0 ml) was added to an ethanol solution (5.0 ml) of t-butyl [(1S)-2-methyl-1-({4-[(pyridin-2-yl)amino]piperidin-1-yl}carbonyl)propyl]carbamate (316 mg, 0.840 mmol), at 0°C, and stirring was carried out at room temperature overnight. The organic layer was concentrated to afford N-{1-[(2S)-2-amino-3-methylbutanoyl]piperidin-4-yl}pyridin-2-amine trihydrochloride as a colorless amorphous substance.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (241 mg, 1.26 mmol)was added to a methylene chloride solution (10 ml) of the resulting compound, 3-hydroxyquinoxaline-2-carboxylic acid (165 mg, 0.840 mmol), 1-hydroxybenzotriazole monohydrate (136 mg, 1.01 mmol) and N-methylmorpholine (0.646 ml, 5.88 mmol), at room temperature, and stirring was carried out at room temperature overnight. Water was added to the reaction solution, followed by extraction with methylene chloride and subsequent sequential washing with a saturated aqueous sodium hydrogencarbonate solution, water and saline, and the resulting organic layer was dried over anhydrous sodium sulfate. After the organic layer was concentrated and the resulting residue was purified by silica gel column chromatography, the residue resulting from concentration was suspended in a mixed solvent of ethanol-diethyl ether, and the solid substance was collected by filtration to afford the desired title compound (248 mg, yield 66%) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 10.11-9.94 (2H, m), 8.12-8.10 (1H, m), 8.01 (1H, d, J=8.0 Hz), 7.64-7.37 (4H, m), 6.60 (1H, q, J=6.2 Hz), 6.43-6.39 (1H, m), 5.12-4.52 (3H, m), 4.23-4.17 (1H, m), 4.00-3.94 (1H, m), 3.49-3.32 (1H, m), 3.12-3.00 (1H, m), 2.36-2.17 (3H, m), 1.68-1.44 (2H, m), 1.12-1.08 (6H, m).

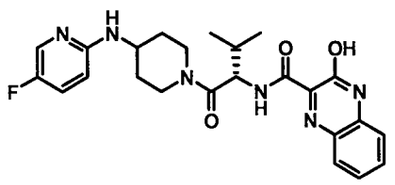
IR (KBr) cm^{-1}: 2960, 1685, 1635, 1605, 1520.

MS (ESI, m/z): 449 $(M+H)^+$.

HRMS (ESI, m/z): 449.2299 (Calcd for $C_{24}H_{29}N_6O_3$: 449.2301).

Anal. Calcd for $C_{24}H_{28}N_6O_3 \cdot 0.5H_2O$: C, 63.00; H, 6.39; N, 18.37. Found: C, 63.17; H, 6.48; N, 18.44.

Example 34



N-[(1S)-1-({4-[(5-Fluoropyridin-2-yl)amino]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 34-1

t-Butyl 4-[(5-fluoropyridin-2-yl)amino]piperidine-1-carboxylate

Sodium triacetoxy borohydride (4.78 g, 21.4 mmol) was added to a methylene chloride solution (90 ml) of 2-amino-5-fluoropyridine (2.00 g, 17.8 mmol), t-butyl 4-oxopiperidine-1-carboxylate (3.59 g, 17.8 mmol) and acetic acid (1.02 ml, 17.8 mmol), at 0°C, and stirring was carried out at room temperature for 4 days. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, followed by extraction with methylene chloride. The organic layer was concentrated to afford t-butyl 4-[(5-fluoropyridin-2-yl)amino]piperidine-1-carboxylate (2.53 g, yield 48%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.94 (1H, d, J=2.4 Hz), 7.18 (1H, td, J=6.8 Hz, 2.4 Hz), 6.32 (1H, dd, J=6.8 Hz, 2.8 Hz), 4.22 (1H, d, J=6.3 Hz), 4.05 (2H, brs), 3.77-3.72 (1H, m), 2.96-2.92 (2H, m), 2.04-2.01 (2H, m), 1.46 (9H, s), 1.38-1.31 (2H, m).

MS (ESI, m/z): 196 $(M-Boc+H)^+$.

Example 34-2

t-Butyl [(1S)-1-({4-[(5-fluoropyridin-2-yl)amino]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate

Analogously to Example 29-2, t-butyl [(1S)-1-({4-[(5-fluoropyridin-2-yl)amino]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (1.29 g,

yield 97%) was obtained from t-butyl 4-[(5-fluoropyridin-2-yl)amino]piperidine-1-carboxylate (1.00 g, 3.39 mmol) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.95-7.94 (1H, m), 7.21-7.16 (1H, m), 6.34-6.32 (1H, m), 5.36-5.34 (1H, m), 4.54-4.46 (2H, m), 4.22 (1H, dd, J=12.8 Hz, 6.2 Hz), 3.99-3.87 (2H, m), 3.30-3.20 (1H, m), 2.96-2.84 (1H, m), 2.21-2.07 (2H, m), 1.96-1.90 (1H, m), 1.44 (9H, s), 1.43-1.31 (2H, m), 0.98-0.87 (6H, m).

MS (ESI, m/z): 295 $(M-Boc+H)^+$.

Example 34-3

N-{1-[(2S)-2-Amino-3-methylbutanoyl]piperidin-4-yl}-5-fluoropyridin-2-amine trihydrochloride

Analogously to Example 29-3, N-{1-[(2S)-2-amino-3-methylbutanoyl]piperidin-4-yl}-5-fluoropyridin-2-amine trihydrochloride (1.25 g, yield 95%) was obtained from t-butyl [(1S)-1-({4-[(5-fluoropyridin-2-yl)amino]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (1.29 g, 3.27 mmol) as a colorless amorphous substance.

^{1}H-NMR (CD_3OD, 400 MHz) δ: 7.96-7.93 (2H, m), 7.17-7.13 (1H, m), 4.60-4.35 (2H, m), 4.08-3.90 (2H, m), 3.44-3.25 (1H, m), 3.12-2.94 (1H, m), 2.24-2.09 (3H, m), 1.71-1.48 (2H, m), 1.12 (3H, dd, J=10.2 Hz, 6.8 Hz), 1.03 (3H, dd, J=12.0 Hz, 6.8 Hz).

MS (ESI, m/z): 295 $(M+H)^+$.

Example 34-4

N-[(1S)-1-({4-[(5-Fluoropyridin-2-yl)amino]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 29-4, the desired title compound (173 mg, yield 75%) was obtained from N-{1-[(2S)-2-amino-3-methylbutanoyl]piperidin-4-yl}-5-fluoropyridin-2-amine trihydrochloride (200 mg, 0.510 mmol) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 12.59 (1H, brs), 10.10 (1H, brs), 8.01-7.95 (2H, m), 7.63-7.39 (3H, m), 7.24-7.17 (1H, m), 6.36 (1H, td, J=7.6 Hz, 2.8 Hz), 5.08 (1H, t, J=5.6 Hz), 4.68-4.35 (2H, m), 4.23 (1H, d, J=10.6 Hz), 4.01-3.90 (1H, m), 3.47-3.32 (1H, m), 3.08-2.93 (1H, m), 2.36-2.14 (3H, m), 1.52-1.39 (2H, m), 1.12-1.09 (6H, m).

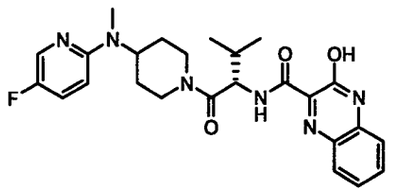
IR (KBr) cm^{-1}: 2965, 1685, 1635, 1525, 1495.

MS (ESI, m/z): 467 $(M+H)^+$, 489 $(M+Na)^+$.

HRMS (ESI, m/z): 489.2013 (Calcd for $C_{24}H_{27}FN_6NaO_3$: 489.2026).

Anal. Calcd for $C_{24}H_{27}FN_6O_3 \cdot 0.25H_2O$: C, 61.20; H, 5.88; N, 17.84; F, 4.03. Found: C, 61.24; H, 5.68; N, 17.86; F, 4.04.

Example 35



N-[(1S)-1-({4-[(5-Fluoropyridin-2-yl)(methyl)amino]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 35-1

t-Butyl 4-[N-(5-fluoropyridin-2-yl)(methyl)amino]piperidine-1-carboxylate

Sodium cyanoborohydride (685 mg, 10.4 mmol) was added to an acetonitrile solution (52 ml) of t-butyl 4-[(5-fluoropyridin-2-yl)amino]piperidine-1-carboxylate (1.53 g, 5.18 mmol), formaldehyde (1.93 ml, 25.9 mmol) and acetic acid (0.297 ml, 5.18 mmol), at 0°C, and stirring was carried out at room temperature for 4 hours. Further acetic acid (1.0 ml) was added, and stirring was carried out overnight. Ethanol (26 ml) was added to the reaction solution, and stirring was carried out overnight. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the organic layer was concentrated, followed by extraction with methylene chloride. The resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by silica gel column chromatography to afford t-butyl 4-[N-(5-fluoropyridin-2-yl)(methyl)amino]piperidine-1-carboxylate (332 mg, yield 22%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.01 (1H, d, J=2.4 Hz), 7.25-7.21 (1H, m), 6.43 (1H, dd, J=7.2 Hz, 2.4 Hz), 4.65-4.59 (1H, m), 4.24 (2H, brs), 2.86-2.81 (2H, m), 2.81 (3H, s), 1.66-1.60 (4H, m), 1.48 (9H, s).

MS (ESI, m/z): 210 $(M-Boc+H)^+$.

Example 35-2

t-Butyl [(1S)-1-({4-[(5-fluoropyridin-2-yl)(methyl)amino]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate

Analogously to Example 29-2, t-butyl [(1S)-1-({4-[(5-fluoropyridin-2-yl)(methyl)amino]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (368 mg, yield 84%) was obtained from t-butyl 4-[(5-fluoropyridin-2-yl)(methyl)amino]piperidine-1-carboxylate (332 mg, 1.07 mmol) as a

colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.01 (1H, dd, J=4.4 Hz, 2.4 Hz), 7.26-7.22 (1H, m), 6.45-6.41 (1H, m), 5.37 (1H, d, J=7.4 Hz), 4.85-4.74 (2H, m), 4.53-4.50 (1H, m), 4.08-4.05 (1H, m), 3.25-3.17 (1H, m), 2.79 (3H, d, J=9.0 Hz), 2.70 (1H, t, J=10.4 Hz), 1.98-1.90 (1H, m), 1.84-1.58 (4H, m), 1.45-1.44 (9H, m), 1.02-0.88 (6H, m).

MS (ESI, m/z): 309 $(M-Boc+H)^+$.

Example 35-3

N-{1-[(2S)-2-Amino-3-methylbutanoyl]piperidin-4-yl}-5-fluoro-N-methylpyridin-2-amine trihydrochloride

Analogously to Example 29-3, N-{1-[(2S)-2-amino-3-methylbutanoyl]piperidin-4-yl}-5-fluoro-N-methylpyridin-2-amine trihydrochloride (370 mg, yield 98%) was obtained from t-butyl [(1S)-1-({4-[(5-fluoropyridin-2-yl)(methyl)amino]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (368 mg, 0.900 mmol) as a colorless amorphous substance.

^{1}H-NMR (CD_3OD, 400 MHz) δ: 8.08-8.03 (2H, m), 7.56-7.53 (1H, m), 4.71 (1H, d, J=14.0 Hz), 4.42-4.35 (2H, m), 4.14-4.08 (1H, m), 3.43-3.34 (1H, m), 3.11 (3H, s), 2.95-2.87 (1H, m), 2.27-2.15 (1H, m), 2.06-1.79 (4H, m), 1.17-1.02 (6H, m).

MS (ESI, m/z): 309 $(M+H)^+$.

Example 35-4

N-[(1S)-1-({4-[(5-Fluoropyridin-2-yl)(methyl)amino]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 29-4, the desired title compound (171 mg, yield 82%) was obtained from N-{1-[(2S)-2-amino-3-methylbutanoyl]piperidin-4-yl}-5-fluoro-N-methylpyridin-2-amine trihydrochloride (181 mg, 0.430 mmol), as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 12.59 (1H, brs), 10.21 (1H, brs), 8.05-8.01 (2H, m), 7.61-7.45 (3H, m), 7.28-7.23 (1H, m), 6.48-6.42 (1H, m), 5.17-5.09 (1H, m), 4.89-4.80 (2H, m), 4.44-4.33 (1H, m), 3.37-3.28 (1H, m), 2.86-2.78 (4H, m), 2.39-2.29 (1H, m), 1.92-1.63 (4H, m), 1.12 (6H, dd, J=16.2 Hz, 5.3 Hz).

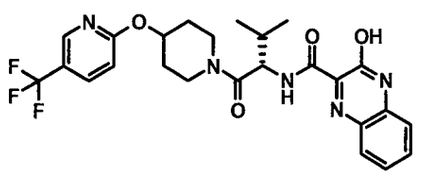
IR (KBr) cm^{-1}: 3460, 2960, 1685, 1640, 1490.

MS (ESI, m/z): 481 $(M+H)^+$.

HRMS (ESI, m/z): 503.2200 (Calcd for $C_{25}H_{29}FN_6NaO_3$: 503.2183).

Anal. Calcd for $C_{25}H_{29}FN_6O_3$: C, 62.49; H, 6.08; N, 17.49; F, 3.95. Found: C, 62.10; H, 6.25; N, 17.19; F, 4.00.

Example 36



3-Hydroxy-N-{(1S)-2-methyl-1-[(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide

Example 36-1

t-Butyl 4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidine-1-carboxylate

Analogously to Example 29-1, t-butyl 4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidine-1-carboxylate (1.26 g, yield 61%) was obtained from 5-trifluoromethyl-2-pyridinol (1.00 g, 5.95 mmol) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.41 (1H, m), 7.76 (1H, dd, J=8.6 Hz, 2.4 Hz), 6.79 (1H, d, J=8.6 Hz), 5.32-5.26 (1H, m), 3.81-3.75 (2H, m), 3.33-3.26 (2H, m), 2.02-1.96 (2H, m), 1.78-1.69 (2H, m), 1.48 (9H, s).

Example 36-2

t-Butyl {(1S)-2-methyl-1-[(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}carbamate

Analogously to Example 29-2, t-butyl {(1S)-2-methyl-1-[(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}carbamate (1.57 g, yield 97%) was obtained from t-butyl 4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidine-1-carboxylate (1.26 g, 3.64 mmol) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.41 (1H, s), 7.78 (1H, dd, J=9.0 Hz, 2.4 Hz), 6.80 (1H, d, J=8.6 Hz), 5.39-5.30 (2H, m), 4.51 (1H, dd, J=9.0 Hz, 5.6 Hz), 4.01-3.44 (4H, m), 2.12-1.74 (5H, m), 1.44 (9H, s), 0.98 (3H, d, J=6.8 Hz), 0.90 (3H, d, J=6.8 Hz).

MS (ESI, m/z): 446 $(M+H)^+$.

Example 36-3

(2S)-3-Methyl-1-oxo-1-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)butan-2-amine dihydrochloride

Analogously to Example 29-3, (2S)-3-methyl-1-oxo-1-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)butan-2-amine dihydrochloride (1.51 g, yield 100%) was obtained from t-butyl {(1S)-2-methyl-1-[(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}carbamate (1.57 g, 3.52 mmol) as a colorless amorphous

substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.44 (5H, brs), 7.90 (1H, brs), 7.00 (1H, brs), 5.46 (1H, brs), 4.54 (1H, brs), 4.13-3.48 (4H, m), 2.31-1.89 (5H, m), 1.28-1.14 (6H, m).

MS (ESI, m/z): 346 $(M+H)^+$.

Example 36-4

3-Hydroxy-N-{(1S)-2-methyl-1-[(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide

Analogously to Example 29-4, the desired title compound (214 mg, yield 87%) was obtained from (2S)-3-methyl-1-oxo-1-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)butan-2-amine dihydrochloride (200 mg, 0.480 mmol) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 12.12 (1H, brs), 10.12 (1H, brs), 8.44-8.42 (1H, m), 8.04-8.01 (1H, m), 7.81-7.37 (4H, m), 6.82 (1H, t, J=9.2 Hz), 5.45-5.39 (1H, m), 5.11-5.08 (1H, m), 4.08-3.57 (4H, m), 2.34-1.89 (5H, m), 1.11 (6H, d, J=7.0 Hz).

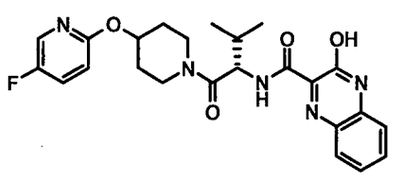
IR (KBr) cm^{-1}: 2965, 1690, 1630, 1615, 1525, 1325.

MS (ESI, m/z): 518 $(M+H)^+$.

HRMS (ESI, m/z): 518.1993 (Calcd for $C_{25}H_{27}F_3N_5O_4$: 518.2015).

Anal. Calcd for $C_{25}H_{26}F_3N_5O_4$: C, 58.02; H, 5.06; N, 13.53; F, 11.01. Found: C, 57.80; H, 5.00; N, 13.51; F, 11.01.

Example 37



N-[(1S)-1-({4-[(5-Fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 37-1

t-Butyl 4-{(5-fluoropyridin-2-yl)oxy}piperidine-1-carboxylate

Analogously to Example 29-1, t-butyl 4-[(5-fluoropyridin-2-yl)oxy]piperidine-1-carboxylate (1.46 g, yield 48%) was obtained from 5-fluoro-2-hydroxypyridine (1.00 g, 8.84 mmol) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.95 (1H, d, J=3.2 Hz), 7.35-7.30 (1H, m), 6.68 (1H, dd, J=9.2 Hz, 3.6 Hz), 5.16-5.10 (1H, m), 3.80-3.74 (2H, m), 3.30-3.24 (2H, m), 1.99-1.94 (2H, m), 1.74-1.66 (2H, m), 1.47 (9H, s).

MS (ESI, m/z): 241 $(M-tBu+H)^+$.

Example 37-2

t-Butyl [(1S)-1-({4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate

Analogously to Example 29-2, t-butyl [(1S)-1-({4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (1.92 g, yield 99%) was obtained from t-butyl 4-[(5-fluoropyridin-2-yl)oxy]piperidine-1-carboxylate (1.46 g, 4.93 mmol) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.97-7.95 (1H, m), 7.34 (1H, ddd, J=9.0 Hz, 7.4 Hz, 3.1 Hz), 6.69 (1H, ddd, J=9.0 Hz, 3.1 Hz, 2.0 Hz), 5.36 (1H, d, J=9.0 Hz), 5.24-5.19 (1H, m), 4.51 (1H, dd, J=8.6 Hz, 5.6 Hz), 3.98-3.42 (4H, m), 2.09-1.71 (5H, m), 1.44 (9H, s), 0.98 (3H, d, J=6.6 Hz), 0.89 (3H, d, J=6.6 Hz).

MS (ESI, m/z): 396 $(M+H)^+$.

Example 37-3

(2S)-1-{4-[(5-Fluoropyridin-2-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine dihydrochloride

Analogously to Example 29-3, (2S)-1-{4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine dihydrochloride (1.93 g, yield 100%) was obtained from t-butyl [(1S)-1-({4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (1.92 g, 4.85 mmol) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.42 (4H, brs), 7.99 (1H, brs), 7.46 (1H, brs), 7.24 (1H, brs), 5.33 (1H, brs), 4.48 (1H, brs), 4.09-3.41 (4H, m), 2.26-1.83 (5H, m), 1.18-1.10 (6H, m).

MS (ESI, m/z): 296 $(M+H)^+$.

Example 37-4

N-[(1S)-1-({4-[(5-Fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 29-4, the desired title compound (200 mg, yield 79%) was obtained from (2S)-1-{4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine dihydrochloride (200 mg, 0.540 mmol) as a yellow solid.

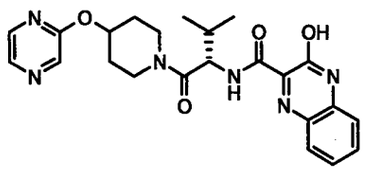
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 12.32 (1H, brs), 10.13 (1H, brs), 8.02-7.96 (2H, m), 7.62-7.32 (4H, m), 6.71 (1H, td, J=9.2 Hz, 3.6 Hz), 5.29-5.24 (1H, m), 5.11-5.08 (1H, m), 4.04-3.59 (4H, m), 2.33-1.85 (5H, m), 1.11 (6H, d, J=6.6 Hz).

IR (KBr) cm^{-1}: 2965, 1685, 1640, 1530, 1480.

MS (ESI, m/z): 468 $(M+H)^+$.

HRMS (ESI, m/z): 468.2042 (Calcd for $C_{24}H_{27}FN_5O_4$: 468.2047).

Example 38



3-Hydroxy-N-[(1S)-2-methyl-1-({4-[(pyrazin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Example 38-1

t-Butyl 4-[pyrazin-2-yl)oxy]piperidine-1-carboxylate

t-Butyl 4-hydroxypiperidine-1-carboxylate (3.73 g, 18.0 mmol) was added to a N,N-dimethylformamide suspension (10 ml) of 60% sodium hydride (533 mg, 14.0 mmol), at 0°C, and stirring was carried out at room temperature for 30 minutes. Chloropyrazine (1.15 g, 10.0 mmol) was further added at room temperature, and stirring was carried out for 1.5 hours. Water was added to the reaction solution, followed by extraction with ethyl acetate and subsequent sequential washing with water and saline, and the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by silica gel column chromatography to afford t-butyl 4-[(pyrazin-2-yl)oxy]piperidine-1-carboxylate (2.79 g, yield 100%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.20 (1H, s), 8.10 (1H, d, J=2.8 Hz), 8.05 (1H, dd, J=2.8 Hz, 1.2 Hz), 5.24-5.18 (1H, m), 3.82-3.76 (2H, m), 3.33-3.27 (2H, m), 2.02-1.97 (2H, m), 1.79-1.70 (2H, m), 1.48 (9H, s).

MS (ESI, m/z): 224 $(M-tBu+H)^+$.

Example 38-2

2-[(Piperidin-4-yl)oxy]pyrazine dihydrochloride

Concentrated hydrochloric acid (10 ml) was added to an ethanol solution (20 ml) of t-butyl 4-[(pyrazin-2-yl)oxy]piperidine-1-carboxylate (2.79 g, 10.0 mmol), at 0°C, and stirring was carried out under room temperature overnight. The organic layer was concentrated to afford 2-[(piperidin-4-yl)oxy]pyrazine dihydrochloride (2.50 g, yield 99%) as a white solid.

^{1}H-NMR (CD_3OD, 400 MHz) δ: 8.27-8.17 (3H, m), 5.39 (1H, brs), 3.48-3.23 (4H, m), 2.24 (2H, s), 2.12 (2H, s).

MS (ESI, m/z): 180 $(M+H)^+$.

Example 38-3

t-Butyl [(1S)-2-methyl-1-({4-[(pyrazin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.44 g, 7.50 mmol) was added to a methylene chloride solution (50 ml) of 2-[(piperidin-4-yl)oxy]pyrazine dihydrochloride (1.26 g, 5.00 mmol), N-(t-butoxycarbonyl)-L-valine (1.09 g, 5.00 mmol), 1-hydroxybenzotriazole monohydrate (811 mg, 6.00 mmol) and N-methylmorpholine (3.30 ml, 30.0 mmol), at room temperature, and stirring was carried out at room temperature overnight. Water was added to the reaction solution, followed by extraction with methylene chloride and subsequent sequential washing with a saturated aqueous sodium hydrogencarbonate solution, water and saline, and the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by silica gel column chromatography to afford t-butyl [(1S)-2-methyl-1-({4-[(pyrazin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate (1.82 g, yield 96%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.22 (1H, d, J=1.2 Hz), 8.13 (1H, d, J=2.8 Hz), 8.07-8.05 (1H, m), 5.36-5.26 (2H, m), 4.53-4.49 (1H, m), 3.98-3.49 (4H, m), 2.11-1.77 (5H, m), 1.44 (9H, s), 0.98 (3H, d, J=7.0 Hz), 0.90 (3H, d, J=6.6 Hz).

MS (ESI, m/z): 379 $(M+H)^+$.

Example 38-4

(2S)-3-Methyl-1-oxo-1-{4-[(pyrazin-2-yl)oxy]piperidin-1-yl}butan-2-amine dihydrochloride

Analogously to Example 29-3, 2S)-3-methyl-1-oxo-1-{4-[(pyrazin-2-yl)oxy]piperidin-1-yl}butan-2-amine dihydrochloride (1.85 g, yield 100%) was obtained from t-butyl [(1S)-2-methyl-1-({4-[(pyrazin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate (1.82 g, 4.81 mmol) (as a colorless amorphous substance.

^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.30 (1H, d, J=3.9 Hz), 8.22-8.17 (6H, m), 5.32-5.22 (1H, m), 4.31-4.28 (1H, m), 4.11-3.75 (2H, m), 3.56-3.20 (2H, m), 2.11-1.97 (3H, m), 1.78-1.57 (2H, m), 1.00-0.92 (6H, m).

MS (ESI, m/z): 279 $(M+H)^+$.

Example 38-5

3-Hydroxy-N-[(1S)-2-methyl-1-({4-[(pyrazin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Analogously to Example 29-4, the desired title compound (232 mg,

yield 91%) was obtained from (2S)-3-methyl-1-oxo-1-{4-[(pyrazin-2-yl)oxy]piperidin-1-yl}butan-2-amine dihydrochloride (200 mg, 0.570 mmol) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 12.37 (1H, brs), 10.16 (1H, brs), 8.25-8.21 (1H, m), 8.15-8.13 (1H, m), 8.09-8.00 (2H, m), 7.63-7.26 (3H, m), 5.38-5.30 (1H, m), 5.12-5.07 (1H, m), 4.09-3.58 (4H, m), 2.36-1.85 (5H, m), 1.11 (6H, d, J=6.6 Hz).

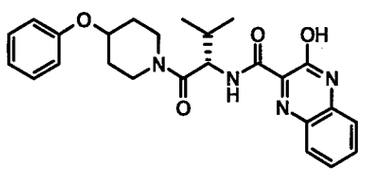
IR (KBr) cm^{-1}: 2960, 1685, 1640, 1525, 1410.

MS (ESI, m/z): 451 $(M+H)^+$, 473 $(M+Na)^+$.

HRMS (ESI, m/z): 473.1929 (Calcd for $C_{23}H_{26}N_6NaO_4$: 473.1913).

Anal. Calcd for $C_{23}H_{26}N_6O_4$: C, 61.32; H, 5.82; N, 18.66. Found: C, 61.23; H, 5.83; N, 18.60.

Example 39



3-Hydroxy-N-{(1S)-2-methyl-1-[(4-phenoxypiperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide

Example 39-1

(2S)-3-Methyl-1-oxo-1-(4-phenoxypiperidin-1-yl)butan-2-amine hydrochloride

A 40% toluene solution of diisopropyl azodicarboxylate (2.10 ml, 3.99 mmol) was added to a toluene solution (15 ml) of t-butyl {(1S)-1-[(4-hydroxypiperidin-1-yl)carbonyl]-2-methylpropyl}carbamate (1.00 g, 3.33 mmol), phenol (344 mg, 3.33 mmol) and triphenylphosphine (1.05 g, 3.99 mmol), at room temperature, and stirring was carried out at room temperature overnight. The reaction solution was concentrated and the resulting residue was diluted with ethyl acetate, followed by sequential washing with a 1N aqueous sodium hydroxide solution, water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by silica gel column chromatography to afford t-butyl N-{(1S)-2-methyl-1-[(4-phenoxypiperidin-1-yl)carbonyl]propyl}carbamate (1.04 g) as a colorless oil. Concentrated hydrochloric acid (2.8 ml) was added to an ethanol solution (5.6 ml) of the resulting compound (1.04 g), at 0°C, and stirring was carried out under room temperature overnight. The reaction solution was concentrated to afford (2S)-3-methyl-1-oxo-1-(4-phenoxypiperidin-1-yl)butan-2-amine hydrochloride (880 mg, yield 84%) as

a colorless amorphous substance.

^{1}H-NMR (CD_3OD, 400 MHz) δ: 7.30-7.25 (2H, m), 6.98-6.92 (3H, m), 4.71-4.62 (1H, m), 4.34 (1H, d, J=5.1 Hz), 4.02-3.46 (4H, m), 2.24-1.70 (5H, m), 1.11 (3H, d, J=7.0 Hz), 1.02 (3H, d, J=7.0 Hz).

MS (ESI, m/z): 277 $(M+H)^+$.

Example 39-2

3-Hydroxy-N-{(1S)-2-methyl-1-[(4-phenoxypiperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide

Analogously to Example 29-4, the desired title compound (174 mg, yield 61%) was obtained from (2S)-3-methyl-1-oxo-1-(4-phenoxypiperidin-1-yl)butan-2-amine hydrochloride (200 mg, 0.640 mmol) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 12.69 (1H, brs), 10.16 (1H, brs), 8.00-7.97 (1H, m), 7.61-7.26 (5H, m), 7.00-6.92 (3H, m), 5.11-5.06 (1H, m), 4.65-4.59 (1H, m), 4.00-3.71 (4H, m), 2.35-1.88 (5H, m), 1.14-1.10 (6H, m).

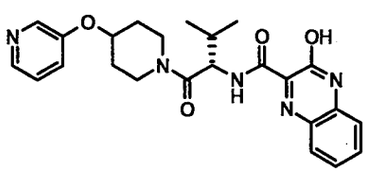
IR (KBr) cm^{-1}: 2960, 1685, 1640, 1530, 1455.

MS (ESI, m/z): 448 $(M+H)^+$.

HRMS (ESI, m/z): 471.2004 (Calcd for $C_{25}H_{28}N_4NaO_4$: 471.2008).

Anal. Calcd for $C_{25}H_{28}N_4O_4 \cdot 0.25H_2O$: C, 66.28; H, 6.34; N, 12.37. Found: C, 66.34; H, 6.32; N, 12.32.

Example 40



3-Hydroxy-N-[(1S)-2-methyl-1-({4-[(pyridin-3-yl)oxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Example 40-1

t-Butyl [(1S)-2-methyl-1-({4-[(pyridin-3-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate

A 40% toluene solution of diisopropyl azodicarboxylate (2.10 ml, 3.99 mmol) was added to a toluene solution (15 ml) of t-butyl 4-hydroxypiperidine-1-carboxylate (1.00 g, 3.33 mmol), 3-hydroxypyridine (348 mg, 3.66 mmol) and triphenylphosphine (1.05 g, 3.99 mmol), at room temperature, and stirring was carried out at room temperature for 4 days. The reaction solution was concentrated and the resulting residue was diluted with ethyl acetate, followed by sequential washing with a 1N aqueous sodium hydroxide solution, water and saline. The resulting organic layer was extracted with a 1N hydrochloric acid, and a 1N aqueous

sodium hydroxide solution was added to the aqueous layer to make it alkaline. The aqueous layer was extracted with ethyl acetate, and the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated to afford t-butyl [(1S)-2-methyl-1-({4-[(pyridin-3-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate (767 mg, yield 61%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) : 8.33 (1H, brs), 8.24 (1H, brs), 7.26-7.22 (2H, m), 5.34-5.30 (1H, m), 4.61 (1H, brs), 4.49 (1H, brs), 3.83-3.47 (4H, m), 2.05-1.82 (5H, m), 1.44 (9H, s), 0.97 (3H, d, J=6.6 Hz), 0.90 (3H, d, J=6.3 Hz).

MS (ESI, m/z): 378 $(M+H)^+$.

Example 40-2

(2S)-3-Methyl-1-oxo-1-{4-[(pyridin-3-yl)oxy]piperidin-1-yl}butan-2-amine dihydrochloride

Concentrated hydrochloric acid (2.0 ml) was added to an ethanol solution (4.0 ml) of t-butyl [(1S)-2-methyl-1-({4-[(pyridin-3-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate (767 mg, 2.03 mmol), at 0°C, and stirring was carried out at room temperature overnight. The organic layer was concentrated to afford (2S)-3-methyl-1-oxo-1-{4-[(pyridin-3-yl)oxy]piperidin-1-yl}butan-2-amine dihydrochloride (786 mg, yield 100%) as a colorless amorphous substance.

^{1}H-NMR (CD_3OD, 400 MHz) δ: 8.71-8.70 (1H, m), 8.48 (1H, d, J=5.6 Hz), 8.35-8.33 (1H, m), 8.05 (1H, dd, J=8.8 Hz, 5.6 Hz), 5.06-4.95 (1H, m), 4.39 (1H, d, J=5.2 Hz), 4.14-3.45 (4H, m), 2.25-1.77 (5H, m), 1.12 (3H, d, J=6.6 Hz), 1.03 (3H, d, J=6.6 Hz).

MS (ESI, m/z): 278 $(M+H)^+$.

Example 40-3

3-Hydroxy-N-[(1S)-2-methyl-1-({4-[(pyridin-3-yl)oxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Analogously to Example 29-4, the desired title compound (148 mg, yield 58%) was obtained from (2S)-3-methyl-1-oxo-1-{4-[(pyridin-3-yl)oxy]piperidin-1-yl}butan-2-amine dihydrochloride (200 mg, 0.570 mmol) as a yellow solid.

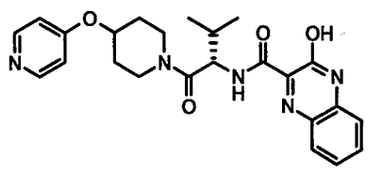
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.37-8.34 (1H, m), 8.26-8.25 (1H, m), 8.04-8.01 (1H, m), 7.65-7.24 (5H, m), 5.10-5.06 (1H, m), 4.67 (1H, brs), 4.03-3.68 (4H, m), 2.33-1.88 (5H, m), 1.13-1.10 (6H, m).

IR (KBr) cm^{-1}: 2965, 1685, 1630, 1525, 1475.

MS (ESI, m/z): 472 $(M+Na)^+$.

HRMS (ESI, m/z): 472.1971 (Calcd for $C_{24}H_{27}N_5NaO_4$: 472.1961).
Anal. Calcd for $C_{24}H_{27}N_5O_4 \cdot 0.25H_2O$: C, 63.49; H, 6.11; N, 15.43. Found:: C, 63.41; H, 5.90; N, 15.39.

Example 41



3-Hydroxy-N-[(1S)-2-methyl-1-({4-[(pyridin-4-yl)oxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Example 41-1

t-Butyl [(1S)-2-methyl-1-({4-[(pyridin-4-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate

Analogously to Example 2-1, t-butyl [(1S)-2-methyl-1-({4-[(pyridin-4-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate (940 mg, yield 100%) was obtained from 4-[(piperidin-4-yl)oxy]pyridine dihydrochloride (580 mg, 2.30 mmol) and N-(t-butoxycarbonyl)-L-valine (500 mg, 2.30 mmol) as a colorless oil.

^{1}H-NMR ($CDCl_3$ 400 MHz) δ: 8.44 (2H, dd, J=6.3 Hz, 1.5 Hz), 6.81 (2H, dd, J=6.3 Hz, 1.5 Hz), 5.33 (1H, d, J=9.5 Hz), 4.72-4.40 (1H, m), 4.49 (1H, dd, J=8.3 Hz, 6.1 Hz), 3.88-3.50 (4H, m), 2.15-1.80 (5H, m), 1.44 (9H, s), 0.97 (3H, d, J=6.8 Hz), 0.90 (3H, d, J=6.8 Hz).
IR (ATR) cm^{-1}: 2965, 1700, 1635, 1590, 1500, 1440, 1365, 1280.
MS (ESI, m/z): 378 $(M+H)^+$.

Example 41-2

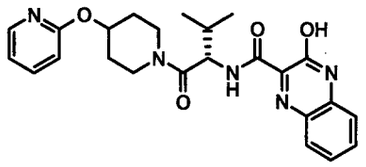
3-Hydroxy-N-[(1S)-2-methyl-1-({4-[(pyridin-4-yl)oxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Analogously to Example 2-2, (2S)-3-methyl-1-oxo-1-{4-[(pyridin-4-yl)oxy]piperidin-1-yl}butan-2-amine dihydrochloride was obtained from N-(t-butoxycarbonyl)-L-valine (500 mg, 2.30 mmol) and from t-butyl [(1S)-2-methyl-1-({4-[(pyridin-4-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate (940 mg, 2.49 mmol) as an amorphous substance. The resulting compound (150 mg, 0.430 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (81.0 mg, 0.430 mmol) to afford the desired title compound (104 mg, yield 63%) as a white solid.

^{1}H-NMR ($CDCl_3$ 400 MHz) δ: 10.16 (1H, s), 8.47 (2H, dt, J=4.6 Hz, 1.2 Hz), 7.98 (1H, dd, J=7.3 Hz, 6.4 Hz), 7.59 (1H, dd, J=7.5 Hz, 7.1 Hz), 7.53 (1H, d, J=8.3 Hz), 7.36 (1H, t, J=7.5 Hz), 6.84 (2H, t, J=6.4 Hz), 5.08

(1H, t, J=7.3 Hz), 4.78-4.68 (1H, m), 4.08-3.99 (1H, m), 3.97-3.63 (3H, m), 2.40-1.86 (5H, m), 1.13 (3H, d, J=6.8 Hz), 1.10 (3H, d, J=6.8 Hz).
IR (ATR) cm^{-1}: 1685, 1630, 1590, 1525, 1495, 1470, 1450, 1275.
MS (ESI, m/z): 450 $(M+H)^+$.
Anal. Calcd for $C_{24}H_{27}N_5O_3 \cdot 0.25H_2O$: C, 63.49; H, 6.11; N, 15.43. Found: C, 63.10; H, 6.13; N, 15.34.

Example 42



3-Hydroxy-N-[(1S)-2-methyl-1-({4-[(pyridin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Example 42-1

t-Butyl [(1S)-2-methyl-1-({4-[(pyridin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate

Analogously to Example 2-1, t-butyl [(1S)-2-methyl-1-({4-[(pyridin-2-yl)oxy]piperidin-1-yl]carbonyl}propyl)carbamate (948 mg, yield 100%) was obtained from 2-[(piperidin-4-yl)oxy]pyridine dihydrochloride (580 mg, 2.30 mmol) and N-(t-butoxycarbonyl)-L-valine (500 mg, 2.30 mmol) as a colorless oil.

^{1}H-NMR ($CDCl_3$ 400 MHz) δ: 8.14-8.11 (1H, m), 7.57 (1H, dt, J=7.1 Hz, 2.0 Hz), 6.86 (1H, dd, J=6.8 Hz, 6.1 Hz), 6.72 (1H, d, J=8.3 Hz), 5.37 (1H, d, J=9.1 Hz), 5.34-5.28 (1H, m), 4.51 (1H, dd, J=8.5 Hz, 5.9 Hz), 3.98-3.73 (2H, m), 3.62-3.42 (2H, m), 2.10-1.73 (5H, m), 1.44 (9H, s), 0.98 (3H, d, J=6.6 Hz), 0.89 (3H, d, J=6.6 Hz).
IR (ATR) cm^{-1}: 2965, 1700, 1635, 1595, 1470, 1430, 1365, 1305.
MS (ESI, m/z): 378 $(M+H)^+$.

Example 42-2

3-Hydroxy-N-[(1S)-2-methyl-1-({4-[(pyridin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Analogously to Example 2-2, (2S)-3-methyl-1-oxo-1-{4-[(pyridin-4-yl)oxy]piperidin-1-yl}butan-2-amine dihydrochloride (734 mg, yield 91%) was obtained from t-butyl [(1S)-2-methyl-1-({4-[(pyridin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate (948 mg, 2.21 mmol) as an amorphous substance. The resulting compound (150 mg, 0.430 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (81.0 mg, 0.430 mmol) to afford the desired title compound (71.0 mg, yield 43%) as a

white solid.

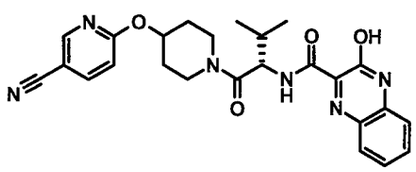
^{1}H-NMR ($CDCl_3$ 400 MHz) δ: 12.77 and 10.14 (1H, brs), 8.14 (1H, t, J=4.9 Hz), 7.98 (1H, d, J=8.1 Hz), 7.66-7.50 (3H, m), 7.37 (1H, brs), 6.86 (1H, dd, J=11.7 Hz, 4.9 Hz), 6.73 (1H, t, J=8.8 Hz), 5.40-5.32 (1H, m), 5.09 (1H, t, J=7.1 Hz), 4.10-3.91 (2H, m), 3.82-3.62 (2H, m), 2.39-2.17 (1H, m), 2.12-1.98 (2H, m), 1.95-1.83 (2H, m), 1.11 (6H, d, J=6.6 Hz).

IR (ATR) cm^{-1}: 1685, 1630, 1525, 1470, 1430, 1270, 1250, 1215.

MS (ESI, m/z): 450 $(M+H)^+$.

Anal. Calcd for $C_{24}H_{27}N_5O_3 \cdot 0.75H_2O$: C, 62.26; H, 6.20, N, 15.13. Found: C, 61.95; H, 5.86; N, 15.15.

Example 43



N-[(1S)-1-({4-[(5-Cyanopyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 43-1

t-Butyl 4-[(5-cyanopyridin-2-yl)oxy]piperidine-1-carboxylate

t-Butyl 4-hydroxypiperidine-1-carboxylate (2.49 g, 12.0 mmol) was added to a N,N-dimethylformamide suspension (10 ml) of 60% sodium hydride (419 mg, 11.0 mmol), at 0°C, and stirring was carried out at room temperature for 30 minutes. Further, at 0°C, 6-chloropyridine-3-carbonitrile (1.43 g, 10.0 mmol) was added, and stirring was carried out for 1.25 hours. Water was added to the reaction solution, followed by extraction with ethyl acetate and subsequent sequential washing with water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by silica gel column chromatography to afford t-butyl 4-[(5-cyanopyridin-2-yl)oxy]piperidine-1-carboxylate (2.71 g, yield 89%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.45 (1H, dd, J=2.4 Hz, 0.8 Hz), 7.78 (1H, dd, J=8.6 Hz, 2.4 Hz), 6.79 (1H, dd, J=8.6 Hz, 0.8 Hz), 5.32-5.26 (1H, m), 3.81-3.75 (2H, m), 3.32-3.25 (2H, m), 2.01-1.96 (2H, m), 1.77-1.69 (2H, m), 1.47 (9H, s).

MS (ESI, m/z): 304 $(M+H)^+$, 204 $(M-Boc+H)^+$.

Example 43-2

t-Butyl [(1S)-1-({4-[(5-cyanopyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-

methylpropyl]carbamate

Concentrated hydrochloric acid (8.9 ml) was added to an ethanol solution (17.8 ml) of t-butyl 4-[(5-cyanopyridin-2-yl)oxy]piperidine-1-carboxylate (2.71 g, 8.93 mmol), at 0°C, and stirring was carried out at room temperature overnight. The organic layer was concentrated to afford 6-(piperidin-4-yl)oxypyridine-3-carbonitrile dihydrochloride (2.34 g) as a white solid.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (2.57 g, 13.4 mmol) was added to a methylene chloride solution (90 ml) of the resulting compound (2.34 g), N-(t-butoxycarbonyl)-L-valine (1.94 g, 8.93 mmol), 1-hydroxybenzotriazole monohydrate (1.45 g, 10.7 mmol) and N-methylmorpholine (4.91 ml, 44.7 mmol), at room temperature, and stirring was carried out at room temperature for 3 days. Water was added to the reaction solution, followed by extraction with ethyl acetate and subsequent sequential washing with a saturated aqueous sodium hydrogencarbonate solution, water and saline, and the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by silica gel column chromatography to afford t-butyl [(1S)-1-({4-[(5-cyanopyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (3.50 g, yield 97%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.46-8.45 (1H, m), 7.79 (1H, dd, J=8.6 Hz. 2.3 Hz), 6.80 (1H, d, J=8.6 Hz), 5.42-5.30 (2H, m), 4.52-4.48 (1H, m), 4.03-3.43 (4H, m), 2.11-1.76 (5H, m), 1.44 (9H, s), 0.97 (3H, d, J=6.6 Hz), 0.90 (3H, d, J=7.0 Hz).

MS (ESI, m/z): 302 $(M-Boc+H)^+$.

Example 43-3

6-[(1-L-Valylpiperidin-4-yl)oxy]nicotinonitrile dihydrochloride

Analogously to Example 29-3, 6-[(1-L-valylpiperidin-4-yl)oxy]nicotinonitrile dihydrochloride (3.28 g, yield 100%) was obtained from t-butyl [(1S)-1-({4-(5-cyanopyridin-2-yl)oxy}piperidin-1-yl)carbonyl]-2-methylpropyl]carbamate (3.50 g, 8.70 mmol) as a colorless amorphous substance.

^{1}H-NMR (CD_3OD, 400 MHz) δ: 8.54 (1H, d, J=2.4 Hz), 8.00-7.97 (1H, m), 6.94 (1H, dd, J=12.0 Hz, 8.4 Hz), 5.48-5.39 (1H, m), 4.37 (1H, d, J=3.9 Hz), 4.12-3.41 (4H, m), 2.24-1.74 (5H, m), 1.11 (3H, d, J=6.6 Hz), 1.03 (3H, d, J=6.6 Hz).

MS (ESI, m/z): 303 $(M+H)^+$.

Example 43-4

N-[(1S)-1-({4-[(5-Cyanopyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 29-4, the desired title compound (182 mg, yield 72%) was obtained from 6-[(1-L-valylpiperidin-4-yl)oxy]nicotinonitrile dihydrochloride (200 mg, 0.530 mmol) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 12.00 (1H, brs), 10.11 (1H, brs), 8.47 (1H, dd, J=6.0 Hz, 2.4 Hz), 8.04-8.02 (1H, m), 7.82-7.78 (1H, m), 7.63 (1H, brs), 7.44-7.22 (2H, m), 6.82 (1H, t, J=9.6 Hz), 5.45-5.39 (1H, m), 5.08 (1H, t, J=7.6 Hz), 4.11-3.53 (4H, m), 2.35-1.85 (5H, m), 1.10 (5H, d, J=6.6 Hz).

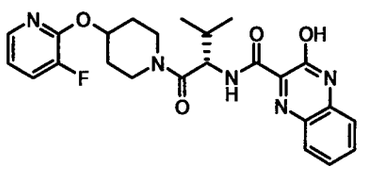
IR (KBr) cm^{-1}: 2965, 2225, 1685, 1630, 1480.

MS (ESI, m/z): 475 $(M+H)^+$, 497 $(M+Na)^+$.

HRMS (ESI, m/z): 497.1920 (Calcd for $C_{25}H_{26}N_6NaO_4$: 497.1913).

Anal. Calcd for $C_{25}H_{26}N_6O_4 \cdot 1/4H_2O$: C, 62.68; H, 5.58; N, 17.54. Found: C, 62.76; H, 5.47; N, 17.48.

Example 44



N-[(1S)-1-({4-[(3-Fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 44-1

t-Butyl 4-[(3-fluoropyridin-2-yl)oxy]piperidine-1-carboxylate

t-Butyl 4-(methanesulfonyloxy)piperidine-1-carboxylate (2.96 g, 10.6 mmol) and potassium carbonate (2.69 g, 19.5 mmol) were added to a N,N-dimethylformamide solution (45 ml) of 3-fluoro-2-hydroxypyridine (1.00 g, 8.84 mmol), at room temperature, and stirring was carried out at 75°C overnight. The reaction solution was cooled to room temperature, and water was added to the residue resulting from concentration, followed by extraction with methylene chloride. After the resulting organic layer was dried over anhydrous sodium sulfate, the residue resulting from concentration was purified by silica gel column chromatography to afford t-butyl 4-[(3-fluoropyridin-2-yl)oxy]piperidine-1-carboxylate (1.63 g, yield 62%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.88 (1H, d, J=3.9 Hz), 7.33-7.29 (1H, m), 6.84-6.81 (1H, m), 5.32-5.27 (1H, m), 3.81-3.77 (2H, m), 3.33-3.28 (2H,

m), 2.02-1.98 (2H, m), 1.82-1.75 (2H, m), 1.47 (9H, s).
MS (ESI, m/z): 241 $(M-tBu+H)^+$.

Example 44-2
t-Butyl [(1S)-1-({4-[(3-fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate

Concentrated hydrochloric acid (2.7 ml) was added to an ethanol solution (5.4 ml) of t-butyl 4-[(3-fluoropyridin-2-yl)oxy]piperidine-1-carboxylate (800 mg, 2.70 mmol), at 0°C, and stirring was carried out under room temperature overnight. The reaction solution was concentrated to afford 3-fluoro-2-[(piperidin-4-yl)oxy]pyridine dihydrochloride (633 mg) as a white solid.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (776 mg, 4.05 mmol) was added to a methylene chloride solution (27 ml) of the resulting compound (633 mg), N-(t-butoxycarbonyl)-L-valine (586 mg, 2.70 mmol), 1-hydroxybenzotriazole monohydrate (438 mg, 3.24 mmol) and N-methylmorpholine (1.48 ml, 13.5 mmol), at room temperature, and stirring was carried out under room temperature overnight. Water was added to the reaction solution, followed by extraction with ethyl acetate and subsequent sequential washing with a saturated aqueous sodium hydrogencarbonate solution, water and saline, and the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by silica gel column chromatography to afford t-butyl [(1S)-1-({4-[(3-fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (1.00 g, yield 94%) as a colorless amorphous substance.
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.90-7.88 (1H, m), 7.35-7.31 (1H, m), 6.87-6.84 (1H, m), 5.42-5.34 (2H, m), 4.53-4.50 (1H, m), 3.98-3.46 (4H, m), 2.11-1.80 (5H, m), 1.44 (9H, s), 0.98 (3H, d, J=5.5 Hz), 0.90 (3H, dd, J=5.5 Hz, 2.0 Hz).
MS (ESI, m/z): 295 $(M-Boc+H)^+$.

Example 44-3
(2S)-1-{4-[(3-Fluoropyridin-2-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine dihydrochloride

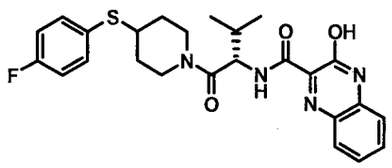
Analogously to Example 29-3, (2S)-1-{4-[(3-fluoropyridin-2-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine dihydrochloride (975 mg, yield 100%) was obtained from t-butyl [(1S)-1-({4-[(3-fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (1.00 g, 2.53 mmol) as a colorless amorphous substance.

^{1}H-NMR (CD_3OD, 400 MHz) δ: 7.92 (1H, d, J=4.8 Hz), 7.53-7.48 (1H, m), 6.99-6.95 (1H, m), 5.45-5.39 (1H, m), 4.37 (1H, d, J=5.2 Hz), 4.08-3.45 (4H, m), 2.24-2.01 (3H, m), 1.95-1.77 (2H, m), 1.12 (3H, d, J=6.6 Hz), 1.03 (3H, d, J=7.0 Hz).
MS (ESI, m/z): 296 $(M+H)^+$.

Example 44-4
N-[(1S)-1-({4-[(3-Fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 29-4, the desired title compound (189 mg, yield 74%) was obtained from (2S)-1-{4-[(3-fluoropyridin-2-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine dihydrochloride (200 mg, 0.540 mmol) as a yellow solid.
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 12.20 (1H, brs), 10.13 (1H, brs), 8.02 (1H, brs), 7.92-7.89 (1H, m), 7.62-7.26 (4H, m), 6.89-6.84 (1H, m), 5.44 (1H, brs), 5.13-5.09 (1H, m), 4.07-3.65 (4H, m), 2.37-1.90 (5H, m), 1.11 (6H, d, J=6.3 Hz).
IR (KBr) cm^{-1}: 2965, 1685, 1635, 1530, 1460.
MS (ESI, m/z): 490 $(M+Na)^+$.
HRMS (ESI, m/z): 490.1852 (Calcd for $C_{25}H_{26}FN_5NaO_4$: 490.1867).
Anal. Calcd for $C_{25}H_{26}FN_5O_4$: C, 61.66; H, 5.61; N, 14.98; F, 4.06. Found: C, 61.54; H, 5.51; N, 14.95; F, 4.03.

Example 45



N-[(1S)-1-({4-[(4-Fluorophenyl)thio]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide
Example 45-1
t-Butyl [(1S)-1-({4-[(4-fluorophenyl)thio]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (947 mg, 4.94 mmol) was added to a methylene chloride solution (41 ml) of 4-[(4-fluorophenyl)sulfanyl]piperidine hydrochloride (1.02 g, 4.12 mmol), N-(t-butoxycarbonyl)-L-valine (894 mg, 4.12 mmol), 1-hydroxybenzotriazole monohydrate (612 mg, 4.53 mmol) and N-methylmorpholine (1.36 ml, 12.4 mmol), at room temperature, and stirring was carried out at room temperature overnight. Water was added to the reaction solution, followed

by extraction with ethyl acetate and subsequent sequential washing with a saturated aqueous sodium hydrogencarbonate solution, water and saline, and the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by silica gel column chromatography to afford t-butyl [(1S)-1-({4-[(4-fluorophenyl)thio]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (1.64 g, yield 97%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.43 (2H, dd, J=8.6 Hz, 5.6 Hz), 7.02 (2H, td, J=8.6 Hz, 2.4 Hz), 5.31 (1H, t, J=7.8 Hz), 4.46-4.27 (2H, m), 3.96-3.85 (1H, m), 3.25-3.12 (2H, m), 3.03-2.87 (1H, m), 2.03-1.84 (3H, m), 1.57-1.46 (2H, m), 1.43 (9H, d, J=6.0 Hz), 0.94 (3H, dd, J=8.4 Hz, 6.8 Hz), 0.86 (3H, dd, J=6.8 Hz, 4.4 Hz).

MS (ESI, m/z): 312 $(M-Boc+H)^+$.

Example 45-2

N-[(1S)-1-({4-[(4-Fluorophenyl)thio]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 2-2, the desired title compound (213 mg, yield 73%) was obtained from t-butyl [(1S)-1-({4-[(4-fluorophenyl)thio]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (248 mg, 0.600 mmol) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 12.78-12.45 (1H, m), 10.13 (1H, brs), 8.04-7.98 (1H, m), 7.62-6.98 (7H, m), 5.08-5.01 (1H, m), 4.48-4.16 (2H, m), 3.43-3.00 (3H, m), 2.29-1.55 (5H, m), 1.12-1.05 (6H, m).

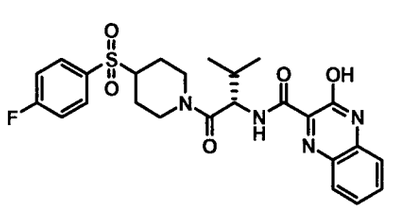
IR (KBr) cm^{-1}: 2965, 1685, 1635, 1525, 1490.

MS (ESI, m/z): 505 $(M+Na)^+$.

HRMS (ESI, m/z): 505.1675 (Calcd for $C_{25}H_{27}FN_4NaO_3S$: 505.1686).

Anal. Calcd for $C_{25}H_{27}FN_4O_3S$: C, 62.22; H, 5.64; N, 11.61; F, 3.94; S, 6.64. Found: C, 62.03; H, 5.36; N, 11.59; F, 4.24; S, 6.82.

Example 46



N-[(1S)-1-({4-[(4-Fluorophenyl)sulfonyl]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 46-1

t-Butyl [(1S)-1-({4-[(4-fluorophenyl)sulfonyl]piperidin-1-yl}carbonyl)-2-

methylpropyl]carbamate

m-Chloroperbenzoic acid (504 mg, 1.90 mmol) was added to a methylene chloride solution (6.3 ml) of t-butyl [(1S)-1-({4-[(4-fluorophenyl)thio]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (260 mg, 0.630 mmol), at room temperature, and stirring was carried out at room temperature for 30 minutes. Further m-chloroperbenzoic acid (504 mg, 1.90 mmol) was added at room temperature, and stirring was carried out at room temperature for 30 minutes. The reaction solution was diluted with methylene chloride, followed by sequential washing with a 1N aqueous sodium hydroxide solution and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by silica gel column chromatography to afford t-butyl [(1S)-1-({4-[(4-fluorophenyl)sulfonyl]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (282 mg, yield 100%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.92-7.86 (2H, m), 7.30-7.24 (2H, m), 5.26-5.19 (1H, m), 4.79-4.66 (1H, m), 4.43-4.35 (1H, m), 4.17-4.08 (1H, m), 3.16-2.98 (2H, m), 2.65-2.51 (1H, m), 2.10-1.57 (5H, m), 1.41 (9H, s), 0.94-0.85 (6H, m).

MS (ESI, m/z): 343 $(M-Boc+H)^+$.

Example 46-2

N-[(1S)-1-({4-[(4-Fluorophenyl)sulfonyl]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 2-2, the desired title compound (221 mg, yield 68%) was obtained from t-butyl [(1S)-1-({4-[(4-fluorophenyl)sulfonyl]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (280 mg, 0.630 mmol) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 12.36 (1H, brs), 10.12 (1H, brs), 8.08-7.21 (8H, m), 5.07-4.74 (2H, m), 4.42 (1H, brs), 3.29-3.10 (2H, m), 2.77-2.63 (1H, m), 2.31-2.05 (3H, m), 1.86-1.57 (2H, m), 1.10-1.03 (6H, m).

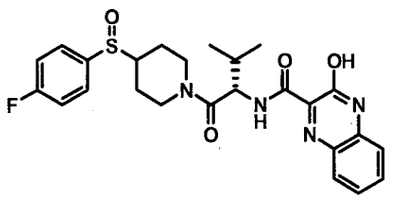
IR (KBr) cm^{-1}: 3470, 2965, 1690, 1645, 1530.

MS (ESI, m/z): 537 $(M+Na)^+$.

HRMS (ESI, m/z): 537.1587 (Calcd for $C_{25}H_{27}FN_4NaO_5S$: 537.1584).

Anal. Calcd for $C_{25}H_{27}FN_4O_5S$: C, 58.35; H, 5.29; N, 10.89; F, 3.69; S, 6.23. Found:: C, 58.09; H, 5.26; N, 10.82; F, 3.72; S, 6.28.

Example 47



N-[(1S)-1-({4-[(4-Fluorophenyl)sulfinyl]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 47-1

t-Butyl [(1S)-1-({4-[(4-fluorophenyl)sulfinyl]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate

m-Chloroperbenzoic acid (268 mg, 1.01 mmol) was added to a methylene chloride solution (10 ml) of t-butyl [(1S)-1-({4-[(4-fluorophenyl)thio]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (415 mg, 1.01 mmol), at 0°C, and stirring was carried out at 0°C for 1 hour. A 1N aqueous sodium hydroxide solution was added to the reaction solution, followed by extraction with methylene chloride. After the extract was washed with saline, the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by silica gel column chromatography to afford t-butyl [(1S)-1-({4-[(4-fluorophenyl)sulfinyl]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (379 mg, yield 88%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.62-7.58 (2H, m), 7.26-7.22 (2H, m), 5.30-5.24 (1H, m), 4.75-4.62 (1H, m), 4.44-4.38 (1H, m), 4.15-4.04 (1H, m), 3.15-3.00 (1H, m), 2.82-2.56 (2H, m), 1.93-1.54 (5H, m), 1.44-1.41 (9H, m), 0.96-0.84 (6H, m).

MS (ESI, m/z): 328 $(M-Boc+H)^+$.

Example 47-2

N-[(1S)-1-({4-[(4-Fluorophenyl)sulfinyl]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 2-2, the desired title compound (203 mg, yield 46%) was obtained from t-butyl [(1S)-1-({4-[(4-fluorophenyl)sulfinyl]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (377 mg, 0.880 mmol) as a yellow solid.

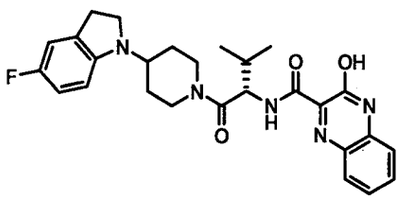
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 9.95 (1H, brs), 8.05-8.00 (1H, m), 7.64-7.20 (7H, m), 5.06-4.98 (1H, m), 4.85-4.69 (1H, m), 4.40-4.35 (1H, m), 3.72 (1H, t, J=3.6 Hz), 3.32-3.12 (1H, m), 2.81-2.67 (2H, m), 2.42-1.55 (5H, m), 1.10-1.02 (6H, m).

IR (KBr) cm^{-1}: 2960, 1685, 1640, 1530, 1450.

MS (ESI, m/z): 521 $(M+Na)^+$.

HRMS (ESI, m/z): 521.1623 (Calcd for $C_{25}H_{27}FN_4NaO_4S$: 521.1635).

Example 48



N-[(1S)-1-{[4-(5-Fluoro-2,3-dihydro-1H-indol-1-yl)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 48-1

t-Butyl 4-(5-fluoro-2,3-dihydro-1H-indol-1-yl)piperidine-1-carboxylate

Sodium triacetoxy borohydride (1.79 g, 8.04 mmol) was added to a methylene chloride solution (33.5 ml) of 5-fluoro-2,3-dihydro-1H-indol (919 mg, 6.70 mmol), t-butyl 4-oxopiperidine-1-carboxylate (1.35 g, 6.70 mmol) and acetic acid (0.384 ml, 6.70 mmol), at 0°C, and stirring was carried out at room temperature for 3 hours. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, followed by extraction with methylene chloride. The extract was concentrated and the resulting residue was purified by silica gel column chromatography to afford t-butyl 4-(5-fluoro-2,3-dihydro-1H-indol-1-yl)piperidine-1-carboxylate (1.68 g, yield 78%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.80 (1H, dd, J=8.4 Hz, 2.8 Hz), 6.76-6.71 (1H, m), 6.29 (1H, dd, J=8.6 Hz, 4.3 Hz), 4.25 (2H, brs), 3.47-3.39 (1H, m), 3.33 (2H, t, J=8.2 Hz), 2.92 (2H, t, J=8.2 Hz), 2.80-2.73 (2H, m), 1.77 (2H, d, J=12.5 Hz), 1.55-1.48 (2H, m), 1.47 (9H, s).

MS (ESI, m/z): 220 $(M-tBu+H)^+$.

Example 48-2

t-Butyl N-[(1S)-1-{[4-(5-fluoro-2,3-dihydro-1H-indol-1-yl)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate

Analogously to Example 29-2, t-butyl N-[(1S)-1-{[4-(5-fluoro-2,3-dihydro-1H-indol-1-yl)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate (2.05 g, yield 93%) was obtained from t-butyl 4-(5-fluoro-2,3-dihydro-1H-indol-1-yl)piperidine-1-carboxylate (1.68 g, 5.24 mmol) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.81 (1H, dd, J=8.4 Hz, 2.4 Hz), 6.78-6.71 (1H, m), 6.33-6.28 (1H, m), 5.34 (1H, d, J=8.4 Hz), 4.80-4.75 (1H, m), 4.52-4.48 (1H, m), 4.13-4.07 (1H, m), 3.58-3.50 (1H, m), 3.31 (2H, dd, J=16.8

Hz, 8.4 Hz), 3.19-3.09 (1H, m), 2.94-2.90 (2H, m), 2.68-2.60 (1H, m), 1.96-1.82 (3H, m), 1.69-1.49 (2H, m), 1.44 (9H, s), 0.97 (3H, dd, J=9.2 Hz, 6.8 Hz), 0.89 (3H, dd, J=9.6 Hz, 6.8 Hz).
MS (ESI, m/z): 420 $(M+H)^+$.

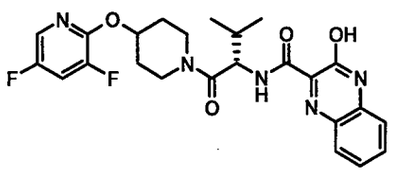
Example 48-3
(2S)-1-[4-(5-Fluoro-2,3-dihydro-1H-indol-1-yl)piperidin-1-yl]-3-methyl-1-oxobutan-2-amine dihydrochloride

Analogously to Example 29-3, (2S)-1-[4-(5-fluoro-2,3-dihydro-1H-indol-1-yl)piperidin-1-yl]-3-methyl-1-oxobutan-2-amine dihydrochloride (1.96 g, yield 100%) was obtained from t-butyl [(1S)-1-{[4-(5-fluoro-2,3-dihydro-1H-indol-1-yl)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate (2.05 g, 4.89 mmol) as a pale red amorphous substance.
^{1}H-NMR (CD_3OD, 400 MHz) δ: 7.71-7.67 (1H, m), 7.31 (1H, d, J=8.2 Hz), 7.28-7.23 (1H, m), 4.70 (1H, d, J=13.6 Hz), 4.40-4.05 (5H, m), 3.36 (2H, t, J=7.2 Hz), 3.31-3.24 (1H, m), 2.81 (1H, t, J=12.8 Hz), 2.25-1.65 (5H, m), 1.14-1.00 (6H, m).
MS (ESI, m/z): 320 $(M+H)^+$.

Example 48-4
N-[(1S)-1-{[4-(5-Fluoro-2,3-dihydro-1H-indol-1-yl)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 29-4, the desired title compound (171 mg, yield 68%) was obtained from (2S)-1-[4-(5-fluoro-2,3-dihydro-1H-indol-1-yl)piperidin-1-yl]-3-methyl-1-oxobutan-2-amine dihydrochloride (200 mg, 0.510 mmol) as a yellow solid.
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 12.45 (1H, brs), 10.18 (1H, brs), 8.04-8.01 (1H, m), 7.64-7.39 (3H, m), 6.83-6.72 (2H, m), 6.35-6.30 (1H, m), 5.17-5.07 (1H, m), 4.90-4.86 (1H, m), 4.38 (1H, brs), 3.62-3.56 (1H, m), 3.38-3.21 (3H, m), 2.95 (1H, t, J=6.6 Hz), 2.90 (1H, t, J=6.6 Hz), 2.74 (1H, t, J=10.0 Hz), 2.36-2.28 (1H, m), 2.03-1.60 (4H, m), 1.16-1.09 (6H, m).
IR (KBr) cm^{-1}: 2960, 1685, 1640, 1490, 1475.
MS (ESI, m/z): 492 $(M+H)^+$, 514 $(M+Na)^+$.
HRMS (ESI, m/z): 492.2422 (Calcd for $C_{27}H_{31}FN_5O_3$: 492.2411).
Anal. Calcd for $C_{27}H_{30}FN_5O_3$: C, 65.97; H, 6.15; N, 14.25; F, 3.86. Found:: C, 65.74; H, 5.92; N, 14.07; F, 3.77.

Example 49



N-[(1S)-1-({4-[(3,5-Difluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl}-3-hydroxyquinoxaline-2-carboxamide

Example 49-1

t-Butyl 4-[(3,5-difluoropyridin-2-yl)oxy]piperidine-1-carboxylate and t-butyl 4-[(2,3-difluoropyridin-5-yl)oxy]piperidine-1-carboxylate

t-Butyl 4-hydroxypiperidine-1-carboxylate (1.38 g, 6.63 mmol) was added to a N,N-dimethylformamide suspension (5.5 ml) of 60% sodium hydride (232 mg, 6.08 mmol), at 0°C, and stirring was carried out at room temperature for 30 minutes. Further, at 0°C, 2,3,5-trifluoropyridine (750 mg, 5.52 mmol) was added, and stirring was carried out at room temperature for 2 hours. Water was added to the reaction solution, followed by extraction with ethyl acetate and subsequent sequential washing with water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by silica gel column chromatography to afford t-butyl 4-[(3,5-difluoropyridin-2-yl)oxy]piperidine-1-carboxylate (654 mg, yield 38%) as a colorless oil, and t-butyl 4-[(2,3-difluoropyridin-5-yl)oxy]piperidine-1-carboxylate (1.00 g, yield 58%) as a colorless oil.

t-butyl 4-[(3,5-difluoropyridin-2-yl)oxy]piperidine-1-carboxylate

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.80 (1H, d, J=2.8 Hz), 7.22-7.17 (1H, m), 5.26-5.20 (1H, m), 3.81-3.75 (2H, m), 3.33-3.27 (2H, m), 2.02-1.96 (2H, m), 1.81-1.73 (2H, m), 1.47 (9H, s).

MS (ESI, m/z): 215 $(M-Boc+H)^+$.

t-butyl 4-[(2,3-difluoropyridin-5-yl)oxy]piperidine-1-carboxylate

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.63 (1H, t, J=2.4 Hz), 7.12-7.07 (1H, m), 4.52-4.46 (1H, m), 3.73-3.67 (2H, m), 3.41-3.34 (2H, m), 1.97-1.90 (2H, m), 1.84-1.76 (2H, m), 1.47 (9H, s).

MS (ESI, m/z): 215 $(M-Boc+H)^+$.

Example 49-2

t-Butyl [(1S)-1-({4-[(3,5-difluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate

Analogously to Example 29-2, t-butyl [(1S)-1-({4-[(3,5-difluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (803 mg, yield 86%) was obtained from t-butyl 4-

[(3,5-difluoropyridin-2-yl)oxy]piperidine-1-carboxylate (654 mg, 2.08 mmol) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.80 (1H, t, J=3.2 Hz), 7.24-7.19 (1H, m), 5.37-5.28 (2H, m), 4.53-4.48 (1H, m), 3.97-3.45 (4H, m), 2.10-1.78 (5H, m), 1.44 (9H, s), 0.98-0.88 (6H, m).

MS (ESI, m/z): 414 $(M+H)^+$.

Example 49-3

(2S)-1-{4-[(3,5-Difluoropyridin-2-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine dihydrochloride

Analogously to Example 29-3, (2S)-1-{4-[(3,5-difluoropyridin-2-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine dihydrochloride (673 mg, yield 90%) was obtained from t-butyl [(1S)-1-({4-[(3,5-difluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl]-2-methylpropyl}carbamate (803 mg, 1.94 mmol) as a colorless amorphous substance.

^{1}H-NMR (CD_3OD, 400 MHz) δ: 7.88 (1H, d, J=2.4 Hz), 7.57-7.51 (1H, m), 5.42-5.34 (1H, m), 4.35 (1H, d, J=5.2 Hz), 4.08-3.45 (4H, m), 2.25-1.75 (5H, m), 1.11 (3H, d, J=7.0 Hz), 1.03 (3H, d, J=7.0 Hz).

MS (ESI, m/z): 314 $(M+H)^+$.

Example 49-4

N-[(1S)-1-({4-[(3,5-Difluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 29-4, the desired title compound (148 mg, yield 59%) was obtained from (2S)-1-{4-[(3,5-difluoropyridin-2-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine dihydrochloride (200 mg, 0.520 mmol) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 12.58 (1H, brs), 10.16 (1H, brs), 8.00 (1H, brs), 7.81 (1H, dd, J=7.0 Hz, 2.0 Hz), 7.62-7.19 (4H, m), 5.40-5.33 (1H, m), 5.11-5.08 (1H, m), 4.04-3.66 (4H, m), 2.35-1.88 (5H, m), 1.14-1.10 (6H, m).

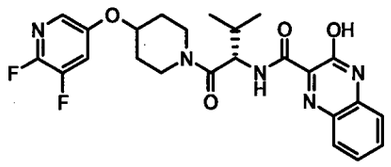
IR (KBr) cm^{-1}: 2965, 1690, 1640, 1470, 1440.

MS (ESI, m/z): 486 $(M+H)^+$, 508 $(M+Na)^+$.

HRMS (ESI, m/z): 486.1979 (Calcd for $C_{24}H_{26}F_2N_5O_4$: 486.1953).

Anal. Calcd for $C_{24}H_{25}F_2N_5O_4$: C, 59.38; H, 5.19; N, 14.43; F, 7.83. Found: C, 59.56; H, 5.15; N, 14.41; F, 8.09.

Example 50



N-[(1S)-1-({4-[(2,3-Difluoropyridin-5-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 50-1

t-Butyl [(1S)-1-({4-[(2,3-difluoropyridin-5-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate

Analogously to Example 29-2, t-butyl [(1S)-1-({4-[(2,3-difluoropyridin-5-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (1.13 g, yield 89%) was obtained from t-butyl 4-[(2,3-difluoropyridin-5-yl)oxy]piperidine-1-carboxylate (893 mg, 2.84 mmol) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.66-7.64 (1H, m), 7.10 (1H, td, J=8.0 Hz, 2.8 Hz), 5.33-5.29 (1H, m), 4.63-4.46 (2H, m), 3.90-3.48 (4H, m), 2.06-1.82 (5H, m), 1.44 (9H, s), 0.97 (3H, d, J=6.6 Hz), 0.90 (3H, d, J=6.6 Hz).

MS (ESI, m/z): 314 $(M-Boc+H)^+$.

Example 50-2

(2S)-1-{4-[(2,3-Difluoropyridin-5-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine dihydrochloride

Analogously to Example 29-3, (2S)-1-{4-[(2,3-difluoropyridin-5-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine dihydrochloride (968 mg, yield 92%) was obtained from t-butyl [(1S)-1-({4-[(2,3-difluoropyridin-5-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl}carbamate (1.13 g, 2.73 mmol) as a colorless amorphous substance.

^{1}H-NMR (CD_3OD, 400 MHz) δ: 7.65-7.59 (2H, m), 4.82-4.74 (1H, m), 4.35 (1H, d, J=4.0 Hz), 4.04-3.59 (3H, m), 3.53-3.47 (1H, m), 2.24-2.16 (1H, m), 2.12-1.99 (2H, m), 1.90-1.75 (2H, m), 1.11 (3H, d, J=5.6 Hz), 1.02 (3H, d, J=5.6 Hz).

MS (ESI, m/z): 314 $(M+H)^+$.

Example 50-3

N-[(1S)-1-({4-[(2,3-Difluoropyridin-5-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 29-4, the desired title compound (196 mg, yield 78%) was obtained from (2S)-1-{4-[(2,3-difluoropyridin-5-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine dihydrochloride (200

mg, 0.520 mmol) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 12.55 (1H, brs), 10.17 (1H, brs), 8.00 (1H, dd, J=12.6 Hz, 6.6 Hz), 7.66-7.39 (4H, m), 7.16-7.11 (1H, m), 5.07 (1H, q, J=5.7 Hz), 4.67-4.60 (1H, m), 4.12-3.63 (4H, m), 2.36-1.93 (5H, m), 1.15-1.09 (6H, m).

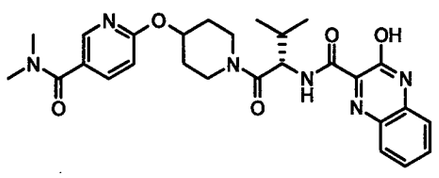
IR (KBr) cm^{-1}: 2965, 1690, 1630, 1525, 1460.

MS (ESI, m/z): 486 $(M+H)^+$, 508 $(M+Na)^+$.

HRMS (ESI, m/z): 486.1944 (Calcd for $C_{24}H_{26}F_2N_5O_4$: 486.1953).

Anal. Calcd for $C_{24}H_{25}F_2N_5O_4$: C, 59.38; H, 5.19; N, 14.43; F, 7.83. Found: C, 59.29; H, 5.11; N, 14.42; F, 7.58.

Example 51



N-{(1S)-1-[(4-{[5-(Dimethylcarbamoyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]-2-methylpropyl}-3-hydroxyquinoxaline-2-carboxamide

Example 51-1

6-Chloro-N,N-dimethylnicotinamide

A tetrahydrofuran solution (14.2 ml, 28.4 mmol) of 2M-N,N-dimethylamine was added to a methylene chloride solution (17 ml) of 6-chloronicotinyl chloride (1.00 g, 5.68 mmol), at 0°C, and stirring was carried out at room temperature overnight. The reaction solution was concentrated and the resulting residue was diluted with methylene chloride, followed by sequential washing with water and saline, and the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by silica gel column chromatography to afford 6-chloro-N,N-dimethylnicotinamide (1.02 g, yield 97%) as a pale red oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.47 (1H, d, J=2.4 Hz), 7.75 (1H, dd, J=8.2 Hz, 2.4 Hz), 7.40 (1H, d, J=8.2 Hz), 3.13 (3H, s), 3.03 (3H, s).

MS (ESI, m/z): 185 $(M+H)^+$.

Example 51-2

t-Butyl 4-{[5-(dimethylcarbamoyl)pyridin-2-yl]oxy}piperidine-1-carboxylate

t-Butyl 4-hydroxypiperidine-1-carboxylate (1.38 g, 6.63 mmol) was added to a N,N-dimethylformamide suspension (3.0 ml) of 60% sodium hydride (232 mg, 6.08 mmol), at 0°C, and stirring was carried out at room

temperature for 30 minutes. Further, at 0°C, a N,N-dimethylformamide solution (2.5 ml) of 6-chloro-N,N-dimethylnicotinamide (1.02 g, 5.52 mmol) was added, and stirring was carried out at room temperature for 3 hours. Water was added to the reaction solution, followed by extraction with ethyl acetate, the extract was washed sequentially with water and saline, and the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by silica gel column chromatography to afford t-butyl 4-{[5-(dimethylcarbamoyl)pyridin-2-yl]oxy}piperidine-1-carboxylate (1.63 g, yield 84%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.26-8.25 (1H, m), 7.70-7.67 (1H, m), 6.73 (1H, d, J=8.6 Hz), 5.29-5.22 (1H, m), 3.80-3.76 (2H, m), 3.32-3.26 (2H, m), 3.13-3.03 (6H, m), 2.01-1.96 (2H, m), 1.74-1.60 (2H, m), 1.47 (9H, s).

MS (ESI, m/z): 350 $(M+H)^+$.

Example 51-3

t-Butyl {(1S)-1-[(4-{[5-(dimethylcarbamoyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]-2-methylpropyl}carbamate

Analogously to Example 29-2, t-butyl {(1S)-1-[(4-{[5-(dimethylcarbamoyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]-2-methylpropyl}carbamate (1.57 g, yield 78%) was obtained from t-butyl 4-{[5-(dimethylcarbamoyl)pyridin-2-yl]oxy}piperidine-1-carboxylate (1.56 g, 4.46 mmol) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.25-8.25 (1H, m), 7.71-7.68 (1H, m), 6.74 (1H, d, J=6.6 Hz), 5.38-5.32 (2H, m), 4.53-4.50 (1H, m), 3.99-3.44 (4H, m), 3.09 (6H, brs), 2.09-1.80 (5H, m), 1.44 (9H, s), 0.98 (3H, d, J=5.6 Hz), 0.89 (3H, d, J=5.2 Hz).

MS (ESI, m/z): 349 $(M-Boc+H)^+$.

Example 51-4

N,N-Dimethyl-6-[(1-L-valylpiperidin-4-yl)oxy]nicotinamide dihydrochloride

Analogously to Example 29-3, N,N-dimethyl-6-[(1-L-valylpiperidin-4-yl)oxy]nicotinamide dihydrochloride (1.61 g, yield 100%) was obtained from t-butyl {(1S)-1-[(4-{[5-(dimethylcarbamoyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]-2-methylpropyl}carbamate (1.57 g, 3.50 mmol) as a colorless amorphous substance.

^{1}H-NMR (CD_3OD, 400 MHz) δ: 8.39 (1H, t, J=3.2 Hz), 8.08 (1H, dq, J=8.8 Hz, 2.4 Hz), 7.22 (1H, t, J=8.8 Hz), 5.42-5.32 (1H, m), 4.38 (1H, d, J=4.3 Hz), 4.13-3.44 (4H, m), 3.09 (6H, d, J=10.9 Hz), 2.25-1.81 (5H, m), 1.12 (3H, d, J=7.0 Hz), 1.03 (3H, d, J=6.6 Hz).

MS (ESI, m/z): 349 $(M+H)^+$.

Example 51-5

N-{(1S)-1-[(4-{[5-(Dimethylcarbamoyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]-2-methylpropyl}-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 29-4, the desired title compound (157 mg, yield 64%) was obtained from N,N-dimethyl-6-[(1-L-valylpiperidin-4-yl)oxy]nicotinamide dihydrochloride (200 mg, 0.470 mmol) as a yellow solid.

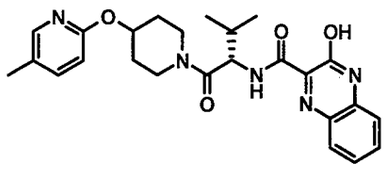
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 12.73 (1H, brs), 10.19 (1H, brs), 8.27 (1H, s), 8.00 (1H, d, J=7.4 Hz), 7.74-7.27 (4H, m), 6.79-6.73 (1H, m), 5.39 (1H, brs), 5.10 (1H, t, J=7.0 Hz), 4.11-3.60 (4H, m), 3.10 (6H, s), 2.35-1.89 (5H, m), 1.14-1.10 (6H, m);

IR (KBr) cm^{-1}: 3470, 2960, 1690, 1635, 1600, 1475.

MS (ESI, m/z): 521 $(M+H)^+$, 543 $(M+Na)^+$.

HRMS (ESI, m/z): 521.2527 (Calcd for $C_{27}H_{33}N_6O_5$: 521.2512).

Example 52



3-Hydroxy-N-[(1S)-1-({4-[(5-methylpyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]quinoxaline-2-carboxamide

A 40% toluene solution of diisopropyl azodicarboxylate (2.10 ml, 3.99 mmol)was added to a toluene solution (15 ml) of t-butyl {(1S)-1-[(4-hydroxypiperidin-1-yl)carbonyl]-2-methylpropyl}carbamate (1.00 g, 3.33 mmol), 2-hydroxy-5-methylpyridine (400 mg, 3.66 mmol) and triphenylphosphine (1.05 g, 3.99 mmol), at room temperature, and stirring was carried out at room temperature overnight. The reaction solution was concentrated and the resulting residue was purified by silica gel column chromatography to afford t-butyl [(1S)-1-({4-[(5-methylpyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (2.06 g) as a mixture with impurities. This product was used as it is in the next reaction without further purification.

Concentrated hydrochloric acid (1.7 ml)was added to an ethanol solution (3.4 ml) of the resulting mixture (2.06 g), at 0°C, and stirring was carried out at room temperature overnight. The reaction solution was concentrated and the resulting residue was diluted with water, and washed with ethyl acetate. A saturated aqueous sodium hydrogencarbonate solution

was added to the aqueous layer, followed by extraction with ethyl acetate. The resulting organic layer was dried over anhydrous sodium sulfate, and then concentrated to afford (2S)-3-methyl-1-{4-[(5-methylpyridin-2-yl)oxy]piperidin-1-yl}-1-oxobutan-2-amine (815 mg).

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (157 mg, 0.820 mmol) was added to a methylene chloride solution (6.9 ml) of the resulting compound (200 mg), 3-hydroxyquinoxaline-2-carboxylic acid (135 mg, 0.690 mmol), 1-hydroxybenzotriazole monohydrate (102 mg, 0.760 mmol) and N-methylmorpholine (0.226 ml, 2.06 mmol), at room temperature, and stirring was carried out at room temperature overnight. Water was added to the reaction solution, followed by extraction with methylene chloride and subsequent sequential washing with a saturated aqueous sodium hydrogencarbonate solution, water and saline, and the resulting organic layer was dried over anhydrous sodium sulfate. After the organic layer was concentrated and the resulting residue was purified by silica gel column chromatography and molecular sieving, the residue resulting from concentration was suspended in a mixed solvent of ethanol-diethyl ether, and the solid substance was collected by filtration to afford the desired title compound (161 mg, 10%) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 12.59 (1H, brs), 10.05 (1H, brs), 8.00 (1H, d, J=6.6 Hz), 7.95-7.93 (1H, m), 7.62-7.36 (4H, m), 6.64 (1H, dd, J=12.0 Hz, 8.4 Hz), 5.32-5.27 (1H, m), 5.13-5.09 (1H, m), 4.05-3.91 (2H, m), 3.77-3.63 (2H, m), 2.32-1.85 (8H, m), 1.10 (6H, d, J=6.6 Hz).

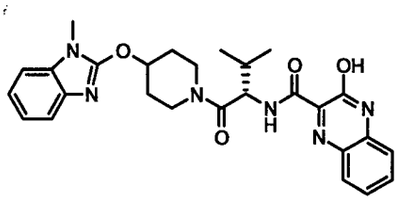
IR (KBr) cm^{-1}: 3440, 2965, 1690, 1640, 1485.

MS (ESI, m/z): 464 $(M+H)^+$, 486 $(M+Na)^+$.

HRMS (ESI, m/z): 464.2319 (Calcd for $C_{25}H_{30}N_5O_4$: 464.2298).

Anal. Calcd for $C_{25}H_{29}N_5O_4 \cdot 0.5H_2O$: C, 63.54; H, 6.40; N, 14.82. Found: C, 63.36; H, 6.20; N, 14.72.

Example 53



3-Hydroxy-N-[(1S)-2-methyl-1-({4-[(1-methyl-1H-benzimidazol-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Example 53-1

2-Chloro-1-methyl-1H-benzimidazole

Sodium hydride (purity 55%)(516 mg, 12.0 mmol) was added to a N,N-

dimethylformamide solution (8.0 ml) of 2-chloro-1H-benzimidazole (1.52 g, 10.0 mmol), at 0°C, under nitrogen stream, and stirring was carried out for 20 minutes. Methyl iodide (0.750 ml, 12.0 mmol) was further added, and stirring was carried out under room temperature for 2 hours. Water was added to the reaction solution, and the resulting solid substance was collected by filtration to afford 2-chloro-1-methyl-1H-benzimidazole (1.51 g, yield 91%) as a white solid.

Example 53-2

t-Butyl 4-[(1-methyl-1H-benzimidazol-2-yl)oxy]piperidine-1-carboxylate

Sodium hydride (purity 55%)(129 mg, 3.00 mmol) was added to a N,N-dimethylformamide solution (4.0 ml) of 2-chloro-1-methyl-1H-benzimidazole (333 mg, 2.00 mmol) and t-butyl 4-hydroxypiperidine-1-carboxylate (402 mg, 2.00 mmol), at 0°C, under nitrogen stream, and stirring was carried out at room temperature overnight. The reaction solution was poured into water, followed by extraction with ethyl acetate and subsequent sequential washing with water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by silica gel column chromatography to afford t-butyl 4-[(1-methyl-1H-benzimidazol-2-yl)oxy]piperidine-1-carboxylate (548 mg, yield 83%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.53 (1H, m), 7.17 (3H, m), 5.32 (1H, m), 3.77 (2H, m), 3.56 (3H, s), 3.34 (2H, m), 2.11 (2H, m), 1.84 (2H, m), 1.48 (9H, s).

MS (ESI, m/z): 332 $(M+H)^+$.

Example 53-3

t-Butyl [(1S)-2-methyl-1-({4-[(1-methyl-1H-benzimidazol-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate

Analogously to Example 29-2, t-butyl [(1S)-2-methyl-1-({4-[(1-methyl-1H-benzimidazol-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate (504 mg, yield 71%) was obtained from t-butyl 4-[(1-methyl-1H-benzimidazol-2-yl)oxy]piperidine-1-carboxylate (548 mg, 1.66 mmol) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.53 (1H, m), 7.17 (3H, m), 5.38 (1H, m), 5.34 (1H, d, J=9.2 Hz), 4.19-3.60 (2H, m), 3.57 and 3.56 (3H, s), 3.47 (2H, m), 2.13 (2H, m), 1.92 (3H, m), 1.44 (9H, s), 0.99 (3H, d, J=6.4 Hz), 0.90 (3H, d, J=6.4 Hz).

MS (ESI, m/z): 431 $(M+H)^+$.

Example 53-4

3-Hydroxy-N-[(1S)-2-methyl-1-({4-[(1-methyl-1H-benzimidazol-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Analogously to Example 1-3, (2S)-3-methyl-1-{4-[(1-methyl-1H-benzimidazol-2-yl)oxy]piperidin-1-yl}-1-oxobutan-2-amine hydrochloride was afforded from t-butyl [(1S)-2-methyl-1-({4-[(1-methyl-1H-benzimidazol-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate (504 mg, 1.17 mmol) as a white solid. The resulting compound was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (222 mg, 1.17 mmol) to afford the desired title compound (524 mg, yield 89%) as a pale yellow solid.

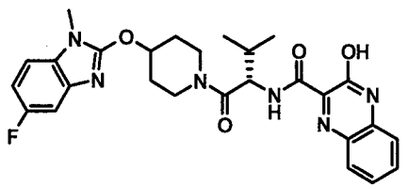
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.83 (1H, s), 9.50 (1H, d, J=8.4 Hz), 7.87 (1H, t, J=6.8 Hz), 7.64 (1H, dt, J=8.0 Hz, 1.6 Hz), 7.41-7.32 (4H, m), 7.12-7.07 (2H, m), 5.31 (1H, m), 4.94 (1H, q, J=7.6 Hz), 3.96-3.28 (4H, m), 3.57 and 3.56 (3H, s), 2.30-1.70 (5H, m), 0.95 (6H, m).

IR (KBr) cm^{-1}: 2965, 1690, 1630, 1530, 1450, 1020.

MS (ESI, m/z): 503 $(M+H)^+$.

HRMS (ESI, m/z): 503.2425 (Calcd for $C_{27}H_{31}N_6O_4$: 503.2407).

Example 54



N-[(1S)-1-({4-[(5-Fluoro-1-methyl-1H-benzimidazol-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 54-1

N-Methyl-4-fluoro-2-nitroaniline

Potassium carbonate (2.61 g, 18.9 mmol) was added to a N,N-dimethylformamide solution (20 ml) of 2,5-difluoronitrobenzene (1.00 g, 6.29 mmol) and methylamine hydrochloride (509 mg, 7.54 mmol), under nitrogen stream, and stirring was carried out at 120°C for 1.5 hours. The reaction solution was filtered, water was added to the filtrate, followed by extraction with ethyl acetate and sequential washing with water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., 40+M) to afford N-methyl-4-fluoro-2-nitroaniline (919 mg, yield 87%) as an orange solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.94 (1H, brs), 7.90 (1H, dd, J=9.4 Hz, 2.9

Hz), 7.31-7.27 (1H, m), 6.83 (1H, dd, J=9.4 Hz, 4.7 Hz), 3.04 (3H, d, J=5.5 Hz).

Example 54-2

5-Fluoro-1-methyl-1H-benzimidazol-2-ol

5% Palladium carbon catalyst (1.15 g) was added to a methanol solution (30 ml) of N-methyl-4-fluoro-2-nitroaniline (919 mg, 5.40 mmol), under hydrogen atmosphere, and stirring was carried out at room temperature for 4 hours. After the reaction solution was celite filtered, the filtrate was concentrated and the resulting residue was dissolved in a 1,4-dioxane solution (30 ml), and N,N'-carbonyldiimidazole (1.31 g, 8.10 mmol) was added, followed by heating to reflux overnight. The reaction solution was cooled to room temperature, and water was added, followed by extraction with ethyl acetate. The extract was washed sequentially with water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., 25+M) to afford 5-fluoro-1-methyl-1H-benzimidazol-2-ol (583 mg, yield 65%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.86 (1H, brs), 7.12-7.06 (1H, m), 6.87-6.82 (2H, m), 3.42 (3H, d, J=6.3 Hz).

MS (EI, m/z): 166 (M^+).

Example 54-3

t-Butyl 4-[(5-fluoro-1-methyl-1H-benzimidazol-2-yl)oxy]piperidine-1-carboxylate

Phosphorus oxychloride (5.0 ml) was added to 5-fluoro-1-methyl-1H-benzimidazol-2-ol (225 mg, 1.35mmol), under nitrogen stream, followed by heating to reflux for 5 hours. A saturated aqueous sodium hydrogencarbonate solution was poured under ice cooling into the residue resulting from concentration of the reaction solution under reduced pressure, followed by extraction with ethyl acetate. The extract was washed sequentially with water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting compound was dissolved in a N,N-dimethylformamide solution (10 ml), and, at 0°C, 63% sodium hydride (93.0 mg, 2.44 mmol) and t-butyl 4-hydroxypiperidine-1-carboxylate (491 mg, 2.44 mmol) were added, followed by stirring under room temperature for 6 hours. Water was added to the reaction solution under ice cooling,

followed by extraction with ethyl acetate. The extract was washed sequentially with water, a saturated aqueous sodium hydrogencarbonate solution, water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., 25+M) to afford t-butyl 4-[(5-fluoro-1-methyl-1H-benzimidazol-2-yl)oxy]piperidine-1-carboxylate (108 mg, yield 20%) as a white solid.

^{1}H-NMR ($CDCl_3$) δ: 7.22 (1H, dd, J=9.6 Hz, 2.0 Hz), 7.04 (1H, dd, J=8.0 Hz, 4.7 Hz), 6.89 (1H, ddd, J=10.5 Hz, 8.0 Hz, 2.0 Hz), 5.32-5.26 (1H, m), 3.80-3.78 (2H, m), 3.54 (3H, s), 3.36-3.32 (2H, m), 2.11-2.09 (2H, m), 1.85-1.82 (2H, m), 1.48-1.46 (9H, m).

MS (FAB, m/z): 350 $(M+H)^+$.

Example 54-4

t-Butyl [(1S)-1-({4-[(5-fluoro-1-methyl-1H-benzimidazol-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate

Analogously to Example 29-2, t-butyl [(1S)-1-({4-[(5-fluoro-1-methyl-1H-benzimidazol-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (128 mg, yield 93%) was obtained from t-butyl 4-[(5-fluoro-1-methyl-1H-benzimidazol-2-yl)oxy]piperidine-1-carboxylate (108 mg, 0.309 mmol) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 7.22 (1H, dd, J=9.6 Hz, 2.0 Hz), 7.04 (1H, dd, J=8.0 Hz, 4.7 Hz), 6.89 (1H, ddd, J=10.5 Hz, 8.0 Hz, 2.0 Hz), 5.37-5.36 (2H, m), 4.52-4.50 (1H, m), 4.07-3.76 (2H, m), 3.68-3.46 (2H, m), 3.55 (3H, d, J=7.3 Hz), 2.24-2.10 (2H, m), 1.96-1.89 (3H, m), 1.44-1.40 (9H, m), 0.98 (3H, t, J=6.6 Hz), 0.91 (3H, t, J=6.6 Hz).

MS (FAB, m/z): 406 $(M+H)^+$.

Example 54-5

N-[(1S)-1-({4-[(5-Fluoro-1-methyl-1H-benzimidazol-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 1-3, (2S)-1-{4-[(5-fluoro-1-methyl-1H-benzimidazol-2-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine hydrochloride (119 mg) was obtained from t-butyl [(1S)-1-({4-[(5-fluoro-1-methyl-1H-benzimidazol-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (128 mg, 0.285 mmol) as a white solid. The resulting compound (119 mg, 0.285 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (81.0 mg, 0.428 mmol) to afford the desired title compound (111 mg, yield 75%) as a pale yellow solid.

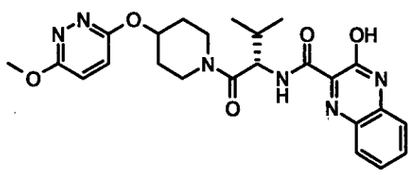
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.84 (1H, brs), 9.57 (1H, brs), 7.87 (1H, t, J=6.8 Hz), 7.64 (1H, d, J=16.4 Hz), 7.40-7.33 (3H, m), 7.24 (1H, dd, J=9.6 Hz, 2.0 Hz), 6.96 (1H, ddd, J=10.5 Hz, 8.0 Hz, 2.0 Hz), 5.31-5.29 (1H, m), 4.96-4.92 (1H, m), 3.94-3.63 (4H, m), 3.57 (3H, d, J=9.4 Hz), 2.00-1.89 (5H, m), 0.96 (6H, t, J=6.6 Hz).

IR (KBr) cm^{-1}: 2965, 1690, 1640, 1530, 1440, 1140.

MS (ESI, m/z): 521 $(M+H)^+$.

HRMS (ESI, m/z): 521.2320 (Calcd for $C_{27}H_{30}FN_6O_4$: 521.2312).

Example 55



3-Hydroxy-N-[(1S)-1-({4-[(6-methoxypyridazin-3-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]quinoxaline-2-carboxamide

Example 55-1

t-Butyl 4-[(6-methoxypyridazin-3-yl)oxy]piperidine-1-carboxylate

Analogously to Example 53-2, t-butyl 4-[(6-methoxypyridazin-3-yl)oxy]piperidine-1-carboxylate (964 mg, yield 78%) was obtained from 3-chloro-6-methoxypyridazine (578 mg, 4.00 mmol) and t-butyl 4-hydroxypiperidine-1-carboxylate (924 mg, 4.60 mmol) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.94 (1H, d, J=8.8 Hz), 6.89 (1H, d, J=8.8 Hz), 5.32 (1H, m), 4.04 (3H, s), 3.80 (2H, m), 3.22 (2H, m), 2.10 (2H, m), 1.75 (2H, m), 1.47 (9H, s).

MS (ESI, m/z): 310 $(M+H)^+$.

Example 55-2

t-Butyl [(1S)-1-({4-[(6-methoxypyridazin-3-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate

Analogously to Example 29-2, t-butyl [(1S)-1-({4-[(6-methoxypyridazin-3-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (157 mg, yield 68%) was obtained from t-butyl 4-[(6-methoxypyridazin-3-yl)oxy]piperidine-1-carboxylate (175 mg, 0.566 mmol) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.93 (1H, d, J=9.2 Hz), 6.90 (1H, dd, J=9.2 Hz, 2.4 Hz), 5.40 (1H, m), 5.37 (1H, m), 4.50 (1H, q, J=5.6 Hz), 4.05 (3H, s), 4.05-3.75 (2H, m), 3.55-3.35 (2H, m), 2.20-2.05 (2H, m), 1.95 (1H, m), 1.95-1.75 (2H, m), 1.44 (9H, s), 0.98 (3H, d, J=6.8 Hz), 0.89 (3H, d, J=6.8 Hz).

MS (ESI, m/z): 409 $(M+H)^+$.

Example 55-3

3-Hydroxy-N-[(1S)-1-({4-[(6-methoxypyridazin-3-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]quinoxaline-2-carboxamide

Analogously to Example 1-3, (2S)-1-{4-[(6-methoxypyridazin-3-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine hydrochloride was obtained from t-butyl [(1S)-1-({4-[(6-methoxypyridazin-3-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (156 mg, 0.382 mmol) as a white solid. The resulting compound was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (72.6 mg, 0.382 mmol) to afford the desired title compound (82.7 mg, yield 45%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.83 (1H, brs), 9.52 (1H, brs), 7.86 (1H, t, J=6.8 Hz), 7.64 (1H, dt, J=8.0 Hz, 1.6 Hz), 7.41-7.36 (2H, m), 7.22-7.16 (2H, m), 5.31 (1H, m), 4.92 (1H, q, J=7.6 Hz), 4.08-3.28 (4H, m), 3.94 (3H, s), 2.13-2.00 (2H, m), 2.05 (1H, m), 1.79-1.57 (2H, m), 0.95 (6H, t, J=6.4 Hz).

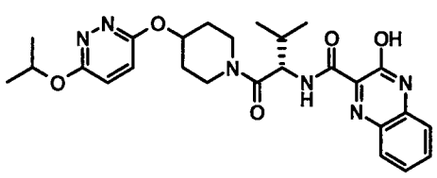
IR (KBr) cm^{-1}: 2960, 1685, 1640, 1670, 1420, 1270, 1015.

MS (ESI, m/z): 481 $(M+H)^+$.

HRMS (ESI, m/z): 481.2206 (Calcd for $C_{24}H_{29}N_6O_5$: 481.2199).

Anal. Calcd for $C_{24}H_{28}N_6O_5 \cdot 0.5H_2O$: C, 58.89; H, 5.97; N, 17.17. Found: C, 59.01; H, 5.82; N, 16.77.

Example 56



3-Hydroxy-N-[(1S)-1-({4-[(6-isopropoxypyridazin-3-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]quinoxaline-2-carboxamide

Example 56-1

3-Chloro-6-isopropoxypyridazine

2-Propanol (0.770 ml, 10.0 mmol) was added to a N,N-dimethylformamide solution (2.0 ml) of sodium hydride (purity 55%)(218 mg, 5.00 mmol), under nitrogen stream, and stirring was carried out for 15 minutes. Further, 3,6-dichloropyridazine (745 mg, 5.00 mmol) was added, and stirring was carried out at room temperature for 1 hour. The reaction solution was poured into a saturated aqueous ammonium chloride solution, followed by extraction with ethyl acetate and subsequent sequential washing with water and saline, and then the resulting organic

layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by silica gel column chromatography to afford 3-chloro-6-isopropoxypyridazine (486 mg, yield 56%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.33 (1H, d, J=7.2 Hz), 6.87 (1H, d, J=7.2 Hz), 5.18 (1H, m), 1.40 (6H, d, J=6.0 Hz).

Example 56-2

t-Butyl 4-[(6-isopropoxypyridazin-3-yl)oxy]piperidine-1-carboxylate

Analogously to Example 53-2, t-butyl 4-[(6-isopropoxypyridazin-3-yl)oxy]piperidine-1-carboxylate (631 mg, yield 66%) was obtained from 3-chloro-6-isopropoxypyridazine (486 mg, 2.86 mmol) and t-butyl 4-hydroxypiperidine-1-carboxylate (790 mg, 3.92 mmol) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.87 (2H, s), 5.41 (1H, m), 5.32 (1H, m), 3.80 (2H, brs), 3.22 (2H, m), 2.05 (2H, m), 1.75 (2H, m), 1.46 (9H, s), 1.38 (6H, d, J=6.0 Hz).

Example 56-3

t-Butyl [(1S)-1-({4-[(6-isopropoxypyridazin-3-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate

Analogously to Example 29-2, t-butyl [(1S)-1-({4-[(6-isopropoxypyridazin-3-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (586 mg, yield 72%) was obtained from t-butyl 4-[(6-isopropoxypyridazin-3-yl)oxy]piperidine-1-carboxylate (631 mg, 1.87 mmol) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.88 (2H, s), 6.88-5.44 (3H, m), 6.88-5.44 (1H, m), 4.10-3.76 (2H, m), 3.53-3.37 (2H, m), 2.19-1.76 (5H, m), 1.44 (9H, s), 1.39 (6H, d, J=5.9 Hz), 0.99 (3H, d, J=6.8 Hz), 0.89 (3H, d, J=6.8 Hz).

MS (ESI, m/z): 437 $(M+H)^+$.

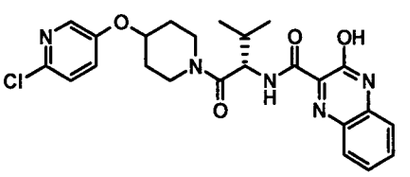
Example 56-4

3-Hydroxy-N-[(1S)-1-({4-[(6-isopropoxypyridazin-3-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]quinoxaline-2-carboxamide

Analogously to Example 1-3, (2S)-1-{4-[(6-isopropoxypyridazin-3-yl)oxy]piperidin-1-yl}-3-methyl-1-oxybutan-2-amine hydrochloride was obtained from t-butyl [(1S)-1-({4-[(6-isopropoxypyridazin-3-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (574 mg, 1.31 mmol) as a white solid. The resulting compound was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (249 mg, 1.31 mmol) to afford the

desired title compound (581 mg, yield 87%) as a pale yellow solid.
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.83 (1H, brs), 9.51 (1H, m), 7.88 (1H, m), 7.66 (1H, t, J=3.2 Hz), 7.41-7.37 (2H, m), 7.19-7.11 (2H, m), 5.35-5.26 (2H, m), 4.96-4.91 (1H, m), 4.08-3.92 (2H, m), 3.60-3.21 (2H, m), 2.20-2.02 (3H, m), 1.80-1.53 (2H, m), 1.34 (6H, d, J=6.0 Hz), 0.97-0.94 (6H, m).
IR (KBr) cm^{-1}: 2970, 1690, 1645, 1630, 1440, 1270.
MS (ESI, m/z): 509 $(M+H)^+$.
HRMS (ESI, m/z): 509.2523 (Calcd for $C_{26}H_{33}N_6O_5$: 509.2512).
Anal. Calcd for $C_{26}H_{32}N_6O_5 \cdot 1/2H_2O$: C, 60.34; H, 6.43; N, 16.24. Found: C, 60.43; H, 6.27; N, 16.15.

Example 57



N-[(1S)-1-({4-[(2-Chloropyridin-5-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 57-1

t-Butyl 4-[(2-chloropyridin-5-yl)oxy]piperidine-1-carboxylate

Analogously to Example 53-2, t-butyl 4-[(2-chloropyridin-5-yl)oxy]piperidine-1-carboxylate (811 mg, yield 86%) was obtained from 2-chloro-5-fluoropyridine (393 mg, 3.00 mmol) and t-butyl 4-hydroxypiperidine-1-carboxylate (603 mg, 3.00 mmol) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.07 (1H, dd, J=2.8 Hz, 0.8Hz), 7.25 (1H, d, J=8.2 Hz), 7.20 (1H, dd, J=8.8 Hz, 2.8 Hz), 4.49-4.45 (1H, m), 3.73-3.67 (2H, m), 3.38-3.32 (2H, m), 1.97-1.90 (2H, m), 1.79-1.71 (2H, m), 1.47 (9H, s).

Example 57-2

t-Butyl [(1S)-1-({4-[(2-chloropyridin-5-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate

Analogously to Example 29-2, t-butyl [(1S)-1-({4-[(2-chloropyridin-5-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (321 mg, yield 52%) was obtained from t-butyl 4-[(2-chloropyridin-5-yl)oxy]piperidine-1-carboxylate (468 mg, 1.50 mmol) as a colorless amorphous substance.
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.08 (1H, d, J=2.8 Hz), 7.26 (1H, d, J=9.4 Hz), 7.21 (1H, dd, J=8.8 Hz, 3.0 Hz), 5.33 (1H, d, J=8.2 Hz), 4.62-4.53 (1H, m), 4.50 (1H, dd, J=9.2 Hz, 5.7 Hz), 3.86-3.47 (4H, m), 2.04-1.78 (5H,

m), 1.44 (9H, s), 0.97 (3H, d, J=6.7 Hz), 0.90 (3H, d, J=7.1Hz).

Example 57-3

N-[(1S)-1-({4-[(2-Chloropyridin-5-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 1-3, (2S)-1-{4-[(2-chloropyridin-5-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine hydrochloride was obtained from t-butyl [(1S)-1-({4-[(2-chloropyridin-5-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (315 mg, 0.766 mmol) as a white solid. The resulting compound was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (146 mg, 0.766 mmol) to afford the desired title compound (298 mg, yield 80%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.85 (1H, brs), 9.51 (1H, brs), 8.19 (1H, dd, J=5.4 Hz, 3.2 Hz), 7.87 (1H, dd, J=7.6 Hz, 4.9 Hz), 7.65 (1H, t, J=7.8 Hz), 7.62-7.57 (1H, m), 7.46 (1H, d, J=8.6 Hz), 7.41-7.37 (2H, m), 4.91 (1H, dd, J=13.8 Hz, 7.7 Hz), 4.81-4.71 (1H, m), 4.04-3.84 (2H, m), 3.58-3.20 (2H, m), 2.12-1.90 (3H, m), 1.76-1.47 (2H, m), 0.96 (3H, d, J=3.9 Hz), 0.94 (3H, d, J=3.9 Hz).

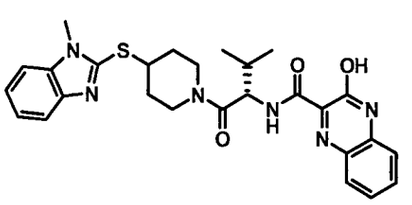
IR (KBr) cm^{-1}: 2960, 1685, 1640, 1450, 1270.

MS (ESI, m/z): 484 $(M+H)^+$.

HRMS (ESI, m/z): 484.1769 (Calcd for $C_{24}H_{27}ClN_5O_4$: 484.1752).

Anal. Calcd for $C_{24}H_{26}ClN_5O_4$: C, 59.56; H, 5.42; N, 14.47. Found: C, 59.60; H, 5.42; N, 14.38.

Example 58



3-Hydroxy-N-[(1S)-2-methyl-1-({4-[(1-methyl-1H-benzimidazol-2-yl)thio]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Example 58-1

t-Butyl 4-[(1H-benzimidazol-2-yl)thio]piperidine-1-carboxylate

Potassium carbonate (414 mg, 3.00 mmol) was added to an ethanol solution (10 ml) of 4-methanesulfonyloxypiperidine (834 mg, 3.00 mmol) and 2-mercaptobenzimidazole (450 mg, 3.00 mmol), at room temperature, under nitrogen stream, and stirring was carried out for 16 hours under heating to reflux. The reaction solution was poured into a saturated aqueous ammonium chloride solution, followed by extraction with ethyl

acetate. The extract was washed sequentially with water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was suspended in a mixed solvent of ethyl acetate-methanol, and the resulting precipitate was collected by filtration to afford t-butyl 4-[(1H-benzimidazol-2-yl)thio]piperidine-1-carboxylate (473 mg, yield 47%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 9.19 (1H, brs), 7.68 (1H, brs), 7.35 (1H, brs), 7.22 (2H, m), 4.01 (1H, m), 3.39 (2H, m), 3.06 (1H, t, J=10.8 Hz), 2.13 (2H, m), 1.70 (2H, m), 1.46 (9H, s).

Example 58-2

t-Butyl 4-[(1-methyl-1H-benzimidazol-2-yl)thio]piperidine-1-carboxylate

Butyllithium (1.58M hexane solution)(1.08 ml, 1.70 mmol) was added to a tetrahydrofuran solution (10 ml) of t-butyl 4-[(1H-benzimidazol-2-yl)thio]piperidine-1-carboxylate (473 mg, 1.42 mmol), at 0°C, under nitrogen stream, and stirring was carried out for 15 minutes, followed by further addition of methyl iodide (0.180 ml, 2.84 mmol) and stirring at room temperature for 2 hours. The reaction solution was poured into a saturated aqueous ammonium chloride solution, followed by extraction with ethyl acetate. The extract was washed sequentially with water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by silica gel column chromatography to afford t-butyl 4-[(1-methyl-1H-benzimidazol-2-yl)thio]piperidine-1-carboxylate (493 mg, yield 100%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.66 (1H, m), 7.26-7.22 (3H, m), 4.11 (1H, m), 3.95 (2H, m), 3.70 (3H, s), 3.11 (1H, t, J=10.8 Hz), 2.16 (2H, m), 1.71 (2H, m), 1.46 (9H, s).

Example 58-3

t-Butyl [(1S)-1-({4-[(1-methyl-1H-benzimidazol-2-yl)thio]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate

Analogously to Example 29-2, t-butyl [(1S)-1-({4-[(1-methyl-1H-benzimidazol-2-yl)thio]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (361 mg, yield 57%) was obtained from t-butyl 4-[(1-methyl-1H-benzimidazol-2-yl)thio]piperidine-1-carboxylate (493 mg, 1.42 mmol) as a colorless amorphous substance.

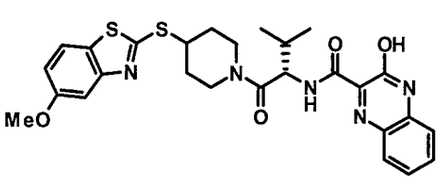
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.67 (1H, m), 7.24 (3H, m), 5.34 (1H, d, J=7.2 Hz), 4.48 (1H, dd, J=7.2 Hz, 3.2 Hz), 4.39-4.29 (1H, m), 4.20 (1H, m),

3.93 (1H, t, J=12.0 Hz), 3.70 and 3.69 (3H, s), 3.43-3.33 (1H, m), 3.19-3.08 (1H, m), 2.34-2.20 (2H, m), 1.92 (1H, m), 1.81-1.68 (2H, m), 1.44 (9H, s), 0.97 (3H, t, J=6.4 Hz), 0.89 (3H, d, J=6.4 Hz).
MS (ESI, m/z): 447 $(M+H)^+$.

Example 58-4
3-Hydroxy-N-[(1S)-2-methyl-1-({4-[(1-methyl-1H-benzimidazol-2-yl)thio]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Analogously to Example 1-3, (2S)-3-methyl-1-{4-[(1-methyl-1H-benzimidazol-2-yl)thio]piperidin-1-yl}-1-oxobutan-2-amine hydrochloride was obtained from t-butyl [(1S)-1-({4-[(1-methyl-1H-benzimidazol-2-yl)thio]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (361 mg, 0.809 mmol) as a white solid. The resulting compound was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (154 mg, 0.809 mmol) to afford the desired title compound (331 mg, yield 79%) as a pale yellow solid.
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.85 (1H, brs), 9.50 (1H, t, J=9.6 Hz), 7.88 (1H, dd, J=8.4 Hz, 1.4 Hz), 7.63 (1H, t, J=17.0 Hz), 7.57 (1H, d, J=16.2 Hz), 7.50 (1H, m), 7.41-7.37 (2H, m), 7.24-7.15 (2H, m), 4.91 (1H, dd, J=13.3 Hz, 7.8 Hz), 4.33-4.06 (3H, m), 3.70 (3H, d, J=7.8 Hz), 3.49-3.38 (1H, m), 3.12-2.99 (1H, m), 2.29-2.15 (2H, m), 2.06 (1H, m), 1.85-1.53 (2H, m), 0.96-0.93 (6H, m).
IR (KBr) cm^{-1}: 2960, 1690, 1630, 1530, 1450, 1275.
MS (ESI, m/z): 519 $(M+H)^+$.
HRMS (ESI, m/z): 519.2178 (Calcd for $C_{27}H_{31}N_6O_3S$: 519.2178).
Anal. Calcd for $C_{27}H_{30}N_6O_3S$: C, 62.53; H, 5.83; N, 16.20. Found: C, 62.39; H, 5.79; N, 16.09.

Example 59



3-Hydroxy-N-[(1S)-1-({4-[(5-methoxybenzothiazol-2-yl)thio]piperidin-1-yl}carbonyl)-2-methylpropyl]quinoxaline-2-carboxamide
Example 59-1
t-Butyl 4-[(5-methoxybenzothiazol-2-yl)thio]piperidine-1-carboxylate

Analogously to Example 58-1, t-butyl 4-[(5-methoxybenzothiazol-2-yl)thio]piperidine-1-carboxylate (922 mg, yield 81%) was obtained from 4-methanesulfonyloxypiperidine (834 mg, 3.00 mmol) and 2-mercapto-5-methoxybenzothiazole (592 mg, 3.00 mmol) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.61 (1H, d, J=8.8 Hz), 7.39 (1H, d, J=2.4 Hz), 6.95 (1H, dd, J=8.8 Hz, 2.4 Hz), 4.06 (1H, m), 3.95 (2H, m), 3.88 (3H, s), 3.12 (2H, t, J=10.8 Hz), 2.20-2.10 (2H, m), 1.76-1.70 (2H, m), 1.47 (9H, s).

Example 59-2

t-Butyl N-[(1S)-1-({4-[(5-methoxybenzothiazol-2-yl)thio]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate

Analogously to Example 29-2, t-butyl [(1S)-1-({4-[(5-methoxybenzothiazol-2-yl)thio]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (873 mg, yield 98%) was obtained from t-butyl 4-[(5-methoxybenzothiazol-2-yl)thio]piperidine-1-carboxylate (921 mg, 2.42 mmol) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.61 (1H, d, J=8.8 Hz), 7.39 (1H, d, J=2.4 Hz), 6.97 (1H, dd, J=8.8 Hz, 2.4 Hz), 5.38 (1H, t, J=7.2 Hz), 4.49 (1H, m), 4.39-4.29 (1H, m), 4.20 (1H, m), 3.88 (3H, s), 3.41-3.14 (3H, m), 2.40-2.20 (2H, m), 1.95 (1H, m), 1.88-1.68 (2H, m), 1.44 (9H, s), 0.97 (3H, t, J=6.4 Hz), 0.89 (3H, d, J=6.4 Hz).

MS (ESI, m/z): 448 $(M+H)^+$.

Example 59-3

3-Hydroxy-N-[(1S)-1-({4-[(5-methoxybenzthiazol-2-yl)thio]piperidin-1-yl}carbonyl)-2-methylpropyl]quinoxaline-2-carboxamide

Analogously to Example 1-3, (2S)-1-{4-[(5-methoxybenzothiazol-2-yl)thio]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine hydrochloride was obtained from t-butyl [(1S)-1-({4-[(5-methoxybenzthiazol-2-yl)thio]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (873 mg, 1.95 mmol) as a white solid. The resulting compound was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (380 mg, 2.00 mmol) to afford the desired title compound (883 mg, yield 82%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6, 500 MHz) δ: 12.83 (1H, s), 9.50 (1H, brs), 7.88 (1H, dd, J=8.8 Hz, 5.3 Hz), 7.86 (1H, t, J=7.5 Hz), 7.64 (1H, t, J=7.5 Hz), 7.45 (1H, brs), 7.39-7.36 (2H, m), 7.04-6.98 (1H, m), 4.89 (1H, dd, J=18.6 Hz, 8.3 Hz), 4.31-4.07 (3H, m), 3.83 (3H, s), 3.49-3.39 (1H, m), 3.13-3.01 (1H, m), 2.31-2.18 (2H, m), 2.06 (1H, m), 1.85-1.56 (2H, m), 0.97-0.94 (6H, m).

IR (KBr) cm^{-1}: 2960, 1690, 1640, 1450, 1430, 1275.

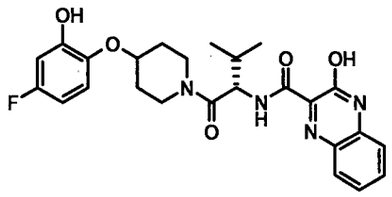
MS (ESI, m/z): 552 $(M+H)^+$.

HRMS (ESI, m/z): 574.1609 (Calcd for $C_{27}H_{29}N_5NaO_4S_2$: 574.1559).

Anal. Calcd for $C_{27}H_{29}N_5O_4S_2 \cdot 0.5H_2O$, C: 57.84, H: 5.39, N: 12.49; Found: C,

57.69; H, 5.13; N, 12.46.

Example 60



N-[(1S)-1-{[4-(4-Fluoro-2-hydroxyphenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 60-1

1-[2-(Benzyloxy)-4-fluorophenyl]ethanone

Benzyl bromide (1.03 g, 6.00 mmol) was added to a N,N-dimethylformamide solution (5 ml) of 1-(4-fluoro-2-hydroxyphenyl)ethanone (770 mg, 5.00 mmol) and potassium carbonate (860 mg, 5.00 mmol), at room temperature, under nitrogen stream, and stirring was carried out at 70°C for 1.5 hours. The reaction solution was poured into a 2N aqueous hydrochloric acid solution, followed by extraction with ethyl acetate. The extract was washed sequentially with water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by silica gel column chromatography to afford 1-[2-(benzyloxy)-4-fluorophenyl]ethanone (1.20 g, yield 98%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.83 (1H, dd, J=8.0 Hz, 7.2 Hz), 7.44-7.39 (5H, m), 6.76-6.70 (2H, m), 5.15 (2H, s), 2.58 (3H, s).

Example 60-2

2-(benzyloxy)-4-fluorophenyl acetate

m-Chloroperbenzoic acid (2.54 g, 14.7 mmol) was added to a methylene chloride solution (20 ml) of 1-[2-(benzyloxy)-4-fluorophenyl]ethanone (1.20 g, 4.91 mmol), at room temperature, under nitrogen stream, and stirring was carried out for 10 hours under heating to reflux. The reaction solution was cooled to room temperature, the solid substance was filtered out, and then an aqueous sodium thiosulfate solution was added, followed by stirring for 15 minutes. The solution was separated, and the resulting organic layer was washed sequentially with a saturated aqueous sodium hydrogencarbonate solution, water and saline, followed by drying over anhydrous sodium sulfate. The organic layer was concentrated to afford 2-(benzyloxy)-4-fluorophenyl acetate (1.19 g, yield 93%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.40-7.34 (5H, m), 7.01 (1H, dd, J=8.8 Hz, 5.7 Hz), 6.74 (1H, dd, J=10.0 Hz, 3.0 Hz), 6.66 (1H, dt, J=12.1 Hz, 4.2 Hz), 5.07 (2H, s), 2.27 (3H, s).

Example 60-3

2-(Benzyloxy)-4-fluorophenol

Sodium methoxide (494 mg, 9.14 mmol) was added to a methanol solution (20 ml) of 2-(benzyloxy)-4-fluorophenyl acetate (1.19 g, 4.57 mmol), at room temperature, under nitrogen stream, and stirring was carried out for 1.5 hours. The reaction solution was concentrated, followed by pouring into a 2N aqueous hydrochloric acid solution and extraction with ethyl acetate, and the extract was washed sequentially with water and saturated saline. The resulting organic layer was dried over anhydrous sodium sulfate, and then the residue resulting from concentration was purified by silica gel chromatography to afford 2-(benzyloxy)-4-fluorophenol (900 mg, yield 90%) as a colorless oil.
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.42-7.34 (5H, m), 6.87 (1H, dd, J=8.8 Hz, 5.7 Hz), 6.69 (1H, dd, J=10.0 Hz, 3.0 Hz), 6.60 (1H, dt, J=12.1 Hz, 4.2 Hz), 5.41 (1H, s), 5.08 (2H, s).

Example 60-4

t-Butyl [(1S)-1-{[4-(2-benzyloxy-4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate

Analogously to Example 1-2, t-butyl [(1S)-1-{[4-(2-benzyloxy-4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate (1.18 g) was obtained from t-butyl [(1S)-1-{(4-hydroxypiperidin-1-yl)carbonyl}-2-methylpropyl]carbamate (1.24 g, 4.12 mmol) and 2-(benzyloxy)-4-fluorophenol (900 mg, 4.12 mmol) as a mixture of colorless oil.
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.40-7.34 (5H, m), 6.90 (1H, m), 6.70 (1H, m), 6.60 (1H, m), 5.36 (1H, d, J=8.8 Hz), 5.41 (1H, s), 5.07 (2H, s), 4.48 (1H, m), 4.38 (1H, m), 4.10-3.40 (4H, m), 1.93-1.81 (5H, m), 1.44 (9H, s), 0.97 (3H, d, J=6.4 Hz), 0.89 (3H, d, J=6.4 Hz).
MS (ESI, m/z): 501 $(M+H)^+$.

Example 60-5

t-Butyl [(1S)-1-{[4-(4-fluoro-2-hydroxyphenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate

10% Palladium carbon catalyst (120 mg) was added to t-butyl [(1S)-1-{[4-(2-benzyloxy-4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate (1.18 g, 2.36 mmol), and stirring was carried out

at room temperature for 2 hours under hydrogen stream. The reaction solution was celite filtered, the filtrate was concentrated and the resulting residue was purified by silica gel chromatography to afford t-butyl [(1S)-1-{[4-(4-fluoro-2-hydroxyphenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate (478 mg, yield 49%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.81(1H, dd, J=9.0 Hz, 5.1 Hz), 6.71 (1H, dd, J=9.2 Hz, 2.9 Hz), 6.58-6.53 (1H, m), 5.75 (1H, d, J=4.3 Hz), 5.33 (1H, t, J=8.0 Hz), 4.52-4.42 (2H, m), 4.10-3.75 (2H, m), 3.58-3.31 (2H, m), 2.11-1.72 (5H, m), 1.44 (9H, s), 0.97 (3H, t, J=6.0 Hz), 0.90 (3H, d, J=6.7 Hz).

MS (ESI, m/z): 411 $(M+H)^+$.

Example 60-6

N-[(1S)-1-{[4-(4-Fluoro-2-hydroxyphenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 1-3, (2S)-1-[4-(4-fluoro-2-hydroxyphenoxy)piperidin-1-yl]-3-methyl-1-oxobutan-2-amine hydrochloride was obtained from t-butyl [(1S)-1-{[4-(4-fluoro-2-hydroxyphenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate (478 mg, 1.16 mmol) as a white solid. The resulting compound was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (220 mg, 1.16 mmol) to afford the desired title compound (411 mg, yield 73%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.84 (1H, s), 9.50 (1H, t, J=8.0 Hz), 9.46 (1H, s), 7.88 (1H, dd, J=7.8 Hz, 4.3 Hz), 7.65 (1H, t, J=7.6 Hz), 7.39 (2H, t, J=6.5 Hz), 7.04-7.00 (1H, m), 6.82 (1H, dt, J=10.0 Hz, 3.2 Hz), 6.57-6.52 (1H, m), 4.92 (1H, t, J=7.0 Hz), 4.48-4.47 (1H, m), 4.00-3.86 (2H, m), 3.54-3.25 (2H, m), 2.09-1.52 (5H, m), 0.96 (3H, d, J=6.8 Hz), 0.93 (3H, d, J=6.8 Hz).

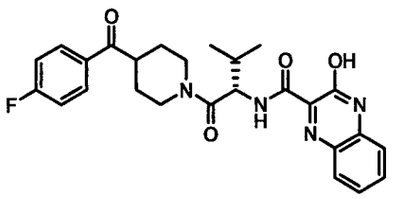
IR (KBr) cm^{-1}: 2965, 1690, 1630, 1525, 1505, 1230.

MS (ESI, m/z): 483 $(M+H)^+$.

HRMS (ESI, m/z): 505.1882 (Calcd for $C_{25}H_{27}FN_4NaO_5$: 505.1863).

Anal. Calcd for $C_{25}H_{27}FN_4O_5 \cdot H_2O$: C, 59.99; H, 5.84; N, 11.19. Found: C, 60.23; H, 5.57; N, 11.00.

Example 61



N-[(1S)-1-{[4-(4-Fluorobenzoyl)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 61-1

t-Butyl [(1S)-1-{[4-(4-fluorobenzoyl)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate

Analogously to Example 2-1, t-butyl [(1S)-1-{[4-(4-fluorobenzoyl)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate (3.88 g, yield 96%) was obtained from 4-(4-fluorobenzoyl)piperidine hydrochloride (2.44 g, 10.0 mmol) and N-(t-butoxycarbonyl)-L-valine (2.17 g, 10.0 mmol) as a colorless amorphous substance.

Example 61-2

[(1S)-1-{[4-(4-Fluorobenzoyl)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 2-2, (4-fluorophenyl)(1-L-valylpiperidin-4-yl)methanone hydrochloride (3.17 g, yield 97%) was obtained from t-butyl [(1S)-1-{[4-(4-fluorobenzoyl)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate (3.88 g, 9.55 mmol) as a colorless amorphous substance. The resulting compound (200 mg, 0.580 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (110 mg, 0.580 mmol) to afford the desired title compound (143 mg, yield 51%) as a pale yellow solid.

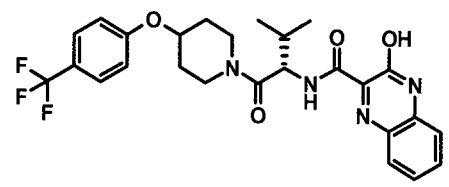
^{1}H-NMR ($CDCl_3$ 400 MHz) δ: 12.90 and 10.21 (1H, brs), 8.05-7.97 (2H, m), 7.61 (1H, d, J=6.8 Hz), 7.58 (1H, m), 7.37 (1H, brs), 7.21-7.13 (2H, m), 5.14-5.07 (1H, m), 4.68 and 4.59 (1H, m), 4.34 (1H, d, J=11.7 Hz), 3.60-3.35 (2H, m), 3.10-2.96 (1H, m), 3.10-2.96 (1H, m), 2.38-2.29 (1H, m), 2.11-0.96 (5H, m), 1.12-1.09 (6H, m).

IR (ATR) cm^{-1}: 1680, 1630, 1595, 1525, 1505, 1475.

MS (ESI, m/z): 479 $(M+H)^+$.

Anal. Calcd for $C_{26}H_{27}FN_4O_4 \cdot 0.5H_2O$: C, 64.05; H, 5.79; N, 11.49. Found: C, 64.20; H, 5.58; N, 11.34.

Example 62



3-Hydroxy-N-[(1S)-2-methyl-1-({4-[4-(trifluoromethyl)phenoxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Example 62-1

t-Butyl [(1S)-2-methyl-1-({4-[4-(trifluoromethyl)phenoxy]piperidin-1-yl}carbonyl)propyl]carbamate

Analogously to Example 2-1, t-butyl [(1S)-2-methyl-1-({4-[4-(trifluoromethyl)phenoxy]piperidin-1-yl}carbonyl)propyl]carbamate (1.41 g, yield 98%) was obtained from 4-[4-(trifluoromethyl)phenoxy]piperidine hydrochloride (913 mg, 3.24 mmol) and N-(t-butoxycarbonyl)-L-valine (704 mg, 3.24 mmol) as a colorless oil.

^{1}H-NMR ($CDCl_3$ 400 MHz) δ: 7.55 (2H, d, J=8.5 Hz), 6.97 (2H, d, J=8.5 Hz), 5.33 (1H, d, J=8.8 Hz), 4.68-4.60 (1H, m), 4.49 (1H, dd, J=8.1 Hz, 6.4 Hz), 3.90-3.49 (4H, m), 2.04-1.80 (5H, m), 1.44 (9H, s), 0.98 (3H, d, J=6.8 Hz), 0.90 (3H, d, J=6.8 Hz).

IR (ATR) cm^{-1}: 2965, 1705, 1635, 1615, 1515, 1440, 1320, 1250.

MS (ESI, m/z): 445 $(M+H)^+$.

Example 62-2

3-Hydroxy-N-[(1S)-2-methyl-1-({4-[4-(trifluoromethyl)phenoxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Analogously to Example 2-2, (2S)-3-methyl-1-oxo-1-{4-[4-(trifluoromethyl)phenoxy]piperidin-1-yl}butan-2-amine hydrochloride (1.14 g, yield 95%) was obtained from t-butyl [(1S)-2-methyl-1-({4-[4-(trifluoromethyl)phenoxy]piperidin-1-yl}carbonyl)propyl]carbamate (1.41 g, 3.16 mmol) as an amorphous substance. The resulting compound (220 mg, 0.580 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (110 mg, 0.580 mmol) to afford the desired title compound (132 mg, yield 45%) as a white solid.

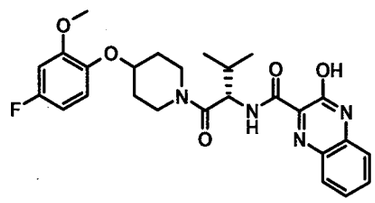
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 12.57 and 10.15 (1H, brs), 7.98 (1H, d, J=4.6 Hz), 7.65-7.53 (4H, m), 7.37 (1H, brs), 6.99 (2H, d, J=8.6 Hz), 5.07 (1H, t, J=7.3 Hz), 4.72-4.65 (1H, m), 4.03-3.62 (5H, m), 2.36-2.10 (2H, m), 2.02-1.80 (3H, m), 1.12 (3H, d, J=6.8 Hz), 1.11 (3H, d, J=6.8 Hz).

IR (ATR) cm^{-1}: 1685, 1630, 1610, 1515, 1445, 1320, 1250.

MS (ESI, m/z): 517 $(M+H)^+$.

Anal. Calcd for $C_{26}H_{27}F_3N_4O_4$: C, 60.46; H, 5.27; N, 10.85. Found: C, 60.23; H, 5.23; N, 10.82.

Example 63



N-[(1S)-1-{[4-(4-Fluoro-2-methoxyphenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 63-1

t-Butyl [(1S)-1-{[4-(4-fluoro-2-methoxyphenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate

A 40% toluene solution of diisopropyl azodicarboxylate (0.930 ml, 1.83 mmol) was added to a toluene solution (15 ml) of t-butyl {(1S)-1-[(4-hydroxypiperidin-1-yl)carbonyl]-2-methylpropyl}carbamate (500 mg, 1.66 mmol), 4-fluoro-2-methoxyphenol (260 mg, 1.83 mmol) and triphenylphosphine (480 mg, 1.83 mmol), at room temperature, under nitrogen stream, and stirring was carried out at room temperature overnight. The reaction solution was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Yamazen Corporation, W-Prep 2XY) to afford t-butyl [(1S)-1-{[4-(4-fluoro-2-methoxyphenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate (520 mg, yield 74%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.89 and 6.87 (1H, d, J=8.8 Hz), 6.65 (1H, m), 6.66 and 6.65 (1H, d, J=2.4 Hz), 6.58 and 6.57 (1H, dd, J=8.8 Hz, 2.4 Hz), 5.36 (1H, d, J=9.2 Hz), 4.50 (1H, dd, J=9.2 Hz, 5.4 Hz), 3.92-3.78 (5H, m), 3.63-3.39 (2H, m), 1.98-1.75 (5H, m), 1.44 and 1.43 (9H, s), 0.97 (3H, t, J=7.3 Hz), 0.89 (3H, dd, J=6.4 Hz).

MS (ESI, m/z): 425 $(M+H)^+$.

Example 63-2

N-[(1S)-1-{[4-(4-Fluoro-2-methoxyphenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Concentrated hydrochloric acid (5.0 ml) was added to an ethanol solution (10 ml) of t-butyl [(1S)-1-{[4-(4-fluoro-2-methoxyphenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate (400 mg, 0.940 mmol), under nitrogen stream, and the mixture was allowed to react at room temperature overnight. The reaction solution was concentrated to afford (2S)-1-[4-(4-fluoro-2-methoxyphenoxy)piperidin-1-yl]-3-methyl-1-

oxobutan-2-amine hydrochloride (340 mg) as a colorless amorphous substance.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (270 mg, 1.41 mmol), 1-hydroxybenzotriazole monohydrate (150 mg, 1.13 mmol) and N-methylmorpholine (0.410 ml, 3.77 mmol) were added to a methylene chloride solution (10 ml) of the resulting compound (340 mg, 0.940 mmol) and 3-hydroxyquinoxaline-2-carboxylic acid (180 mg, 0.940 mmol), at room temperature, under nitrogen stream, and stirring was carried out at room temperature overnight. The reaction solution was washed sequentially with water, a saturated aqueous sodium hydrogencarbonate solution, water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated, the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Yamazen Corporation, W-Prep 2XY), the residue resulting from concentration was suspended in diethyl ether, and the solid substance was collected by filtration to afford the desired title compound (459 mg, yield 98%) as a pale yellow solid.

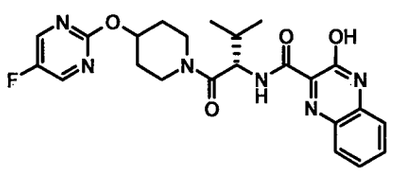
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.86 (1H, brs), 9.55 (1H, brs), 7.89 (1H, d, J=8.3 Hz), 7.66 (1H, t, J=7.2 Hz), 7.43-7.37 (2H, m), 7.11-7.06 (1H, m), 6.98-6.93 (1H, m), 6.78-6.73 (1H, m), 4.93 (1H, q, J=7.8 Hz), 4.51-4.43 (1H, m), 3.99-3.87 (2H, m), 3.81 (3H, d, J=6.8 Hz), 3.58-3.45 (2H, m), 2.11-1.84 (3H, m), 1.75-1.49 (2H, m), 0.98 (3H, d, J=6.8 Hz), 0.97 (3H, d, J=6.8 Hz).

IR (KBr) cm^{-1}: 2960, 1685, 1640, 1500, 1450, 1215, 1190, 1150, 1030.

MS (ESI, m/z): 497 $(M+H)^+$.

Anal. Calcd for $C_{26}H_{29}FN_4O_5 \cdot 1/4H_2O$: C, 62.33; H, 5.93; N, 11.18; F, 3.79. Found: C, 62.07; H, 6.02; N, 11.04; F, 3.68.

Example 64



N-[(1S)-1-({4-[(5-Fluoropyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 64-1

t-Butyl [(1S)-1-({4-[(5-fluoropyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate

63% Sodium hydride (278 mg, 7.32 mmol) was added to a N,N-dimethylformamide solution (20 ml) of 2-chloro-5-fluoropyrimidine (452

mg, 3.66 mmol) and t-butyl N-{(1S)-1-[(4-hydroxypiperidin-1-yl)carbonyl]-2-methylpropyl}carbamate (1.00 g, 3.32 mmol), at 0°C, under nitrogen stream, and stirring was carried out at room temperature overnight. Water was added to the reaction solution under ice cooling, followed by extraction with ethyl acetate. The extract was washed sequentially with water, a saturated aqueous sodium hydrogencarbonate solution, water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., 25+M) to afford t-butyl [(1S)-1-({4-[(5-fluoropyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (568 mg, yield 43%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.36 (2H, s), 5.41 (1H, d, J=9.0 Hz), 5.26-5.16 (1H, m), 4.53-4.47 (1H, m), 4.06-3.78 (2H, m), 3.74-3.45 (2H, m), 2.02-1.92 (5H, m), 1.50-1.39 (9H, m), 0.98 (3H, t, J=6.8 Hz), 0.86 (3H, t, J=6.8 Hz).

MS (FAB, m/z): 397 $(M+H)^+$.

Example 64-2

N-[(1S)-1-({4-[(5-Fluoropyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 1-3, (2S)-1-{4-[(5-fluoropyrimidin-2-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine hydrochloride (163 mg) was obtained from t-butyl [(1S)-1-({4-[(5-fluoropyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (194 mg, 0.489 mmol) as a white solid. The resulting compound (163 mg, 0.489 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (139 mg, 0.734 mmol) to afford the desired title compound (90.0 mg, yield 39%) as a pale yellow solid.

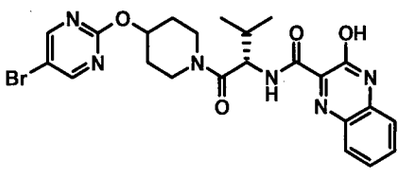
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.80 (1H, brs), 9.46 (1H, brs), 8.68 (1H, d, J=3.1 Hz), 8.60 (1H, d, J=3.1 Hz), 7.84 (1H, d, J=8.2 Hz), 7.62 (1H, t, J=7.6 Hz), 7.37-7.35 (2H, m), 4.92-4.85 (2H, m), 3.95-3.90 (2H, m), 3.55-3.19 (2H, m), 2.07-1.55 (5H, m), 0.94-0.92 (6H, m).

IR (KBr) cm^{-1} : 2960, 1685, 1640, 1530, 1430, 1275.

MS (FAB, m/z): 469 $(M+H)^+$.

HRMS (ESI, m/z): 469.2001 (Calcd for $C_{23}H_{26}FN_6O_4$: 469.1999).

Example 65



N-[(1S)-1-({4-[(5-Bromopyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 65-1

t-Butyl [(1S)-1-({4-[(5-bromopyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate

Analogously to Example 64-1, t-butyl N-[(1S)-1-({4-(5-bromopyrimidin-2-yl)oxy}piperidin-1-yl)carbonyl]-2-methylpropyl]carbamate (1.74 g, yield 57%) was obtained from 5-bromo-2-chloropyrimidine (1.42 g, 7.32 mmol) and t-butyl {(1S)-1-[(4-hydroxypiperidin-1-yl)carbonyl]-2-methylpropyl}carbamate (2.00 g, 6.66 mmol) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.53 (2H, s), 5.36-5.35 (1H, m), 5.27-5.18 (1H, m), 4.51-4.49 (1H, m), 4.02-3.68 (3H, m), 3.59-3.44 (1H, m), 2.10-1.82 (5H, m), 1.44 (9H, brs), 0.97 (3H, d, J=6.6 Hz), 0.89 (3H, d, J=6.6 Hz).

MS (FAB, m/z): 457 $(M+H)^+$.

Example 65-2

N-[(1S)-1-({4-[(5-Bromopyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 1-3, (2S)-1-{4-[(5-bromopyrimidin-2-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine hydrochloride (1.50 g) was obtained from t-butyl [(1S)-1-({4-[(5-bromopyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (1.74 g, 3.80 mmol) as a white solid. The resulting compound (200 mg, 0.508 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (145 mg, 0.762 mmol) to afford the desired title compound (136 mg, yield 51%) as a pale yellow solid.

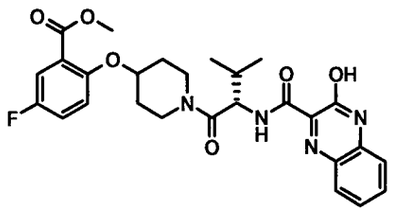
^{1}H-NMR (DMSO-d_6, 500 MHz) δ: 12.83 (1H, brs), 9.55 (1H, brs), 8.77 (2H, d, J=3.9 Hz), 7.86 (1H, d, J=7.8 Hz), 7.63 (1H, t, J=7.8 Hz), 7.38-7.36 (2H, m), 5.19 (1H, brs), 4.91 (1H, q, J=7.8 Hz), 4.04-3.91 (2H, m), 3.59-3.22 (2H, m), 2.06-2.01 (3H, m), 1.78-1.57 (2H, m), 0.96-0.95 (6H, m).

IR (KBr) cm^{-1}: 2965, 1690, 1630, 1540, 1425, 1320.

MS (ESI, m/z): 529 $(M+H)^+$.

HRMS (ESI, m/z): 529.1197 (Calcd for $C_{23}H_{26}BrN_6O_4$: 529.1198).

Example 66



Methyl 5-fluoro-2-[(1-{N-[(3-hydroxyquinoxalin-2yl)carbonyl]-L-valyl}piperidin-4-yl)oxy]benzoate

Example 66-1

t-Butyl 4-[4-fluoro-2-(methoxycarbonyl)phenoxy]piperidine-1-carboxylate

Analogously to Example 23-1, t-butyl 4-[4-fluoro-2-(methoxycarbonyl)phenoxy]piperidine-1-carboxylate (2.39 g, yield 91%) was obtained from t-butyl 4-hydroxypiperidine-1-carboxylate (1.50 g, 7.45 mmol) and methyl 5-fluoro-2-hydroxybenzoate (1.40 g, 8.20 mmol) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.52-7.49 (1H, m), 7.17-7.12 (1H, m), 6.95 (1H, dd, J=9.4 Hz, 4.3 Hz), 4.52-4.48 (1H, m), 3.90 (3H, s), 3.66-3.60 (2H, m), 3.48-3.42 (2H, m), 1.91-1.78 (4H, m), 1.49-1.43 (9H, m).

MS (FAB, m/z): 354 $(M+H)^+$.

Example 66-2

Methyl 2-({1-[N-(t-Butoxycarbonyl)-L-valyl]piperidin-4-yl}oxy)-5-fluorobenzoate

Analogously to Example 23-2, methyl 5-fluoro-2-[(piperidin-4-yl)oxy]benzoate hydrochloride (1.87 g, yield 95%) was obtained from t-butyl 4-[4-fluoro-2-(methoxycarbonyl)phenoxy]piperidine-1-carboxylate (2.39 g, 6.76 mmol) as a white solid. The resulting compound (1.87 g, 6.45 mmol) was condensed with N-(t-butoxycarbonyl)-L-valine (1.54 g, 7.10 mmol) to afford methyl 2-({1-[N-(t-butoxycarbonyl)-L-valyl]piperidin-4-yl}oxy)-5-fluorobenzoate (2.62 g, yield 90%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.53 (1H, dd, J=8.6 Hz, 4.3 Hz), 7.18-7.16 (1H, m), 6.94 (1H, dd, J=9.0 Hz, 4.3 Hz), 5.36-5.34 (1H, m), 4.62-4.60 (1H, m), 4.50 (1H, dd, J=9.0 Hz, 5.5 Hz), 3.97 (3H, s), 3.89-3.54 (4H, m), 1.97-1.83 (5H, m), 1.44 (9H, s), 0.98 (3H, d, J=6.8 Hz), 0.89 (3H, d, J=6.8 Hz).

MS (FAB, m/z): 453 $(M+H)^+$.

Example 66-3

Methyl 5-fluoro-2-[(1-{N-[(3-hydroxyquinoxalin-2-yl)carbonyl]-L-valyl}piperidin-4-yl)oxy]benzoate

Analogously to Example 23-3, methyl 5-fluoro-2-[(1-L-valylpiperidin-4-yl)oxy]benzoate hydrochloride (1.72 g) was obtained from methyl 2-({1-[N-(t-butoxycarbonyl)-L-valyl]piperidin-4-yl}oxy)-5-fluorobenzoate (1.86 g, 5.79 mmol) as a white solid. The resulting compound (1.00 g, 2.57 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (734 mg, 3.86 mmol) to afford the desired title compound (1.09 g, yield 74%) as a pale yellow solid.

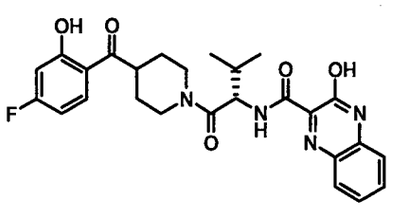
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.83 (1H, s), 9.49 (1H, d, J=8.2 Hz), 7.87 (1H, d, J=8.2 Hz), 7.65 (1H, t, J=8.2 Hz), 7.50-7.29 (5H, m), 4.92 (1H, q, J=7.4 Hz), 4.78 (1H, brs), 3.81 (3H, s), 3.71-3.69 (4H, m), 2.09-1.67 (5H, m), 0.97-0.95 (6H, m).

IR (KBr) cm^{-1}: 2960, 1685, 1640, 1495, 1270, 1185.

MS (FAB, m/z): 525 $(M+H)^+$.

HRMS (ESI, m/z): 525.2127 (Calcd for $C_{27}H_{30}FN_4O_6$: 525.2149).

Example 67



N-[(1S)-1-{[4-(4-Fluoro-2-hydroxybenzoyl)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 67-1

t-Butyl [(1S)-1-{[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]carbonyl}-2-methylpropyl}carbamate

Analogously to Example 2-1, 6-fluoro-3-(piperidin-4-yl)-1,2-benzisoxazole (2.00 g, 9.08 mmol) was condensed with N-(t-butoxycarbonyl)-L-valine (2.17 g, 9.99 mmol) to afford t-butyl [(1S)-1-{[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]carbonyl}-2-methylpropyl}carbamate (3.70 g, yield 97%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.71-7.61 (1H, m), 7.29-7.25 (1H, m), 7.09-7.04 (1H, m), 5.35 (1H, dd, J=17.8 Hz, 9.2 Hz), 4.67-4.55 (2H, m), 4.19-4.09 (1H, m), 3.42-3.27 (2H, m), 3.02-2.92 (1H, m), 2.24-1.82 (5H, m), 1.48-1.46 (9H, m), 1.00 (3H, t, J=6.6 Hz), 0.90 (3H, t, J=6.6 Hz).

MS (FAB, m/z): 420 $(M+H)^+$.

Example 67-2

N-[(1S)-1-{[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]carbonyl}-2-methylpropyl}-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 1-3, (2S)-1-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]-3-methyl-1-oxobutan-2-amine hydrochloride (3.20 g) was obtained from t-butyl [(1S)-1-{[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]carbonyl}-2-methylpropyl}carbamate (3.70 g, 8.78 mmol) as a white solid. The resulting compound (400 mg, 1.12 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (319 mg, 1.68 mmol) to afford N-[(1S)-1-{[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]carbonyl}-2-methylpropyl}-3-hydroxyquinoxaline-2-carboxamide (220 mg, yield 40%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 9.50 (1H, t, J=7.6 Hz), 8.07-8.03 (1H, m), 7.88-7.61 (3H, m), 7.42-7.21 (3H, m), 4.95-4.91 (1H, m), 4.51 (1H, t, J=12.1 Hz), 4.27 (1H, d, J=12.1 Hz), 3.53-3.51 (1H, m), 3.41-3.25 (1H, m), 3.00-2.93 (2H, m), 2.11-1.75 (5H, m), 0.97 (6H, t, J=6.8 Hz).

IR (KBr) cm^{-1}: 2960, 1685, 1635, 1530, 1450, 1275, 1120.

MS (FAB, m/z): 492 $(M+H)^+$.

HRMS (ESI, m/z): 492.2035 (Calcd for $C_{26}H_{27}FN_5O_4$: 492.2047).

Example 67-3

N-[(1S)-1-{[4-(4-Fluoro-2-hydroxybenzoyl)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

5% Palladium carbon catalyst (50.0 mg) was added to a methanol solution (3.0 ml) of N-[(1S)-1-{[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide (150 mg, 0.305 mmol), and stirring was carried out at room temperature for 3 hours under hydrogen atmosphere. The reaction solution was celite filtered, and the filtrate was concentrated. The resulting residue was dissolved in a tetrahydrofuran solution (3.0 ml), and a 2N aqueous sodium hydroxide solution (3.0 ml) was added, followed by reaction at room temperature overnight. Under ice cooling, the reaction solution was poured into a 2N aqueous hydrochloric acid solution, followed by extraction with ethyl acetate and sequential washing with water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated to afford the desired title compound (122 mg, yield 81%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.83 (1H, brs), 12.25 (1H, d, J=6.3 Hz), 9.48 (1H, dd, J=16.2 Hz, 8.8 Hz), 8.11-8.07 (1H, m), 7.87 (1H, dd, J=8.8 Hz, 4.0 Hz), 7.65 (1H, t, J=7.8 Hz), 7.40-7.38 (2H, m), 6.86-6.84 (2H, m), 4.93-4.92 (1H, m), 4.49-4.46 (1H, m), 4.22-4.20 (1H, m), 3.81-3.79

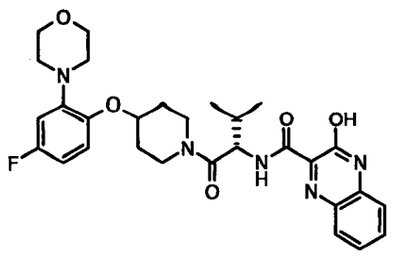
(1H, m), 3.33-3.30 (1H, m), 2.83 (1H, m), 2.05-1.88 (3H, m), 1.67-1.40 (2H, m), 0.96 (6H, t, J=6.8 Hz).

IR (KBr) cm^{-1}: 2965, 1685, 1635, 1530, 1200.

MS (ESI, m/z): 517 $(M+Na)^+$.

HRMS (ESI, m/z): 517.1827 (Calcd for $C_{26}H_{27}FN_4NaO_5$: 517.1863).

Example 68



N-[(1S)-1-({4-[4-Fluoro-2-(morpholin-4-yl)phenoxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 68-1

t-Butyl 4-(2-bromo-4-fluorophenoxy)piperidine-1-carboxylate

Analogously to Example 1-2, t-butyl 4-(2-bromo-4-fluorophenoxy)piperidine-1-carboxylate (2.45 g, yield 88%) was obtained from t-butyl 4-hydroxypiperidine-1-carboxylate (1.50 g, 7.45 mmol) and t-butyl 2-bromo-4-fluorophenol (1.57 g, 8.20 mmol) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.31-7.27 (1H, m), 6.99-6.93 (1H, m), 6.91-6.86 (1H, m), 4.47-4.43 (1H, m), 3.69-3.62 (2H, m), 3.47-3.44 (2H, m), 1.91-1.78 (4H, m), 1.47-1.43 (9H, m).

MS (FAB, m/z): 374 $(M+H)^+$.

Example 68-2

t-Butyl 4-[4-fluoro-2-(morpholin-4-yl)phenoxy]piperidine-1-carboxylate

Sodium t-butoxide (77.0 mg, 0.801 mmol), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (200 mg, 0.320 mmol) and tris(dibenzylideneacetone)dipalladium (61.0 mg, 0.107 mmol) were added sequentially to a toluene solution (5 ml) of t-butyl 4-(2-bromo-4-fluorophenoxy)piperidine-1-carboxylate (910 mg, 3.67 mmol) and morpholine (0.0700 ml, 0.801 mmol), at room temperature, under nitrogen stream, followed by heating to reflux for 10 hours. The reaction solution was poured into ice water, followed by extraction with ethyl acetate, the extract was washed sequentially with a saturated aqueous sodium hydrogencarbonate solution, water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by a medium-

pressure preparative liquid chromatograph (manufactured by Biotage, Inc., 25+M) to afford t-butyl 4-[4-fluoro-2-(morpholin-4-yl)phenoxy]piperidine-1-carboxylate (154 mg, yield 76%) as a yellow oily substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.83-6.80 (1H, m), 6.63-6.61 (2H, m), 4.47-4.42 (1H, m), 3.84 (4H, t, J=4.7 Hz), 3.73-3.67 (2H, m), 3.35-3.31 (2H, m), 3.08 (4H, t, J=4.7 Hz), 1.91-1.84 (2H, m), 1.77-1.69 (2H, m), 1.51-1.43 (9H, m).

MS (FAB, m/z): 381 $(M+H)^+$.

Example 68-3

t-Butyl [(1S)-1-{[4-(4-fluoro-2-morpholin-4-ylphenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate

Analogously to Example 23-2, 4-{5-fluoro-2-[(piperidin-4-yl)oxy]phenyl}morpholine hydrochloride (128 mg, yield 100%) was obtained from t-butyl 4-[4-fluoro-2-(morpholin-4-yl)phenoxy]piperidine-1-carboxylate (154 mg, 0.405 mmol) as a white solid. The resulting compound (128 mg, 0.405 mmol) was condensed with N-(t-butoxycarbonyl)-L-valine (132 mg, 0.607 mmol) to afford t-butyl [(1S)-1-({4-[4-fluoro-2-(morpholin-4-yl)phenoxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (199 mg, yield 100%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.85-6.81 (1H, m), 6.66-6.62 (2H, m), 5.35 (1H, t, J=4.5 Hz), 4.53-4.51 (2H, m), 3.85-3.43 (4H, m), 3.84 (4H, t, J=4.7 Hz), 3.08 (4H, t, J=4.7 Hz), 1.99-1.76 (5H, m), 1.43-1.41 (9H, m), 1.00 (3H, t, J=6.8 Hz), 0.90 (3H, t, J=6.8 Hz).

MS (FAB, m/z): 480 $(M+H)^+$.

Example 68-4

N-[(1S)-1-({4-[4-Fluoro-2-(morpholin-4-yl)phenoxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 2-2, (2S)-1-{4-[4-fluoro-2-(morpholin-4-yl)phenoxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine hydrochloride (223 mg) was obtained from t-butyl [(1S)-1-({4-[4-fluoro-2-(morpholin-4-yl)phenoxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (195 mg, 0.405 mmol) as a white solid. The resulting compound (223 mg, 0.405 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (116 mg, 0.608 mmol) to afford the desired title compound (133 mg, yield 57%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.81 (1H, s), 9.51 (1H, d, J=7.4 Hz), 7.86 (1H, d, J=7.4 Hz), 7.64-7.63 (1H, m), 7.39-7.37 (2H, m), 7.05-7.02 (1H, m), 6.75-6.73 (2H, m), 4.91 (1H, dd, J=14.5 Hz, 4.5 Hz), 4.60 (1H, brs),

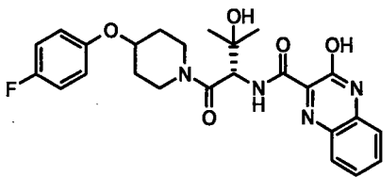
3.85-3.57 (8H, m), 3.01 (4H, t, J=4.7 Hz), 2.07-1.59 (5H, m), 0.97-0.93 (6H, m).

IR (KBr) cm^{-1}: 2965, 1685, 1630, 1495, 1215, 1120.

MS (FAB, m/z): 552 $(M+H)^+$.

HRMS (ESI, m/z): 552.2600 (Calcd for $C_{29}H_{35}FN_5O_5$: 552.2622).

Example 69



N-[(1S)-1-{[4-(4-Fluorophenoxy)piperidin-1-yl]carbonyl}-2-hydroxy-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 69-1

t-Butyl [(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-hydroxy-2-methylpropyl]carbamate

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (115 mg, 0.600 mmol), 1-hydroxybenzotriazole monohydrate (81.0 mg, 0.600 mmol) and N-methylmorpholine (0.440 ml, 2.00 mmol) were added to a methylene chloride solution (2.0 ml) of 4-(4-fluorophenoxy)piperidine hydrochloride (116 mg, 0.500 mmol) and N-(t-butoxycarbonyl)-(S)-2-amino-3-hydroxy-3-methylbutanoic acid (117 mg, 0.500 mmol), at 0°C, under nitrogen stream, and stirring was carried out at room temperature overnight. The reaction solution was diluted with methylene chloride, followed by sequential washing with a saturated aqueous sodium hydrogencarbonate solution, a saturated aqueous ammonium chloride solution, water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by silica gel chromatography to afford t-butyl [(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-hydroxy-2-methylpropyl]carbamate (89.0 mg, yield 44%) as a colorless amorphous substance.

Major: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 7.00-6.96 (2H, m), 6.86-6.85 (2H, m), 5.50 (1H, d, J=8.4 Hz), 4.72 (1H, s), 4.50-4.48 (1H, m), 4.45 (1H, s), 3.81-3.79 (2H, m), 3.66-3.64 (2H, m), 1.99-1.84 (4H, m), 1.44 (9H, s), 1.25 (6H, s).

Minor: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 7.00-6.96 (2H, m), 6.86-6.85 (2H, m), 5.52 (1H, d, J=8.4 Hz), 4.79 (1H, s), 4.45-4.43 (1H, m), 4.43 (1H, s), 3.96-3.94 (2H, m), 3.82-3.79 (2H, m), 1.99-1.84 (4H, m), 1.44 (9H, s), 1.21 (6H, s).

MS (FAB, m/z): 410 $(M+H)^+$.

Example 69-2

N-[(1S)-1-{[4-(4-Fluorophenoxy)piperidin-1-yl]carbonyl}-2-hydroxy-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Water (0.5 ml) and concentrated hydrochloric acid (0.5 ml) were added to a 1,4-dioxane solution (2.0 ml) of t-butyl [(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-hydroxy-2-methylpropyl]carbamate (86.0 mg, 0.210 mmol), and the mixture was allowed to react at room temperature overnight. The reaction solution was concentrated to afford (3S)-3-amino-4-[4-(4-fluorophenoxy)piperidin-1-yl]-2-methyl-4-oxobutan-2-ol hydrochloride as a colorless oil. This product was used as it is in the next reaction without purification.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (48.0 mg, 0.250 mmol), 1-hydroxybenzotriazole monohydrate (34.0 mg, 0.250 mmol) and N-methylmorpholine (0.0930 ml, 0.840 mmol), were added to a methylene chloride solution (4.0 ml) of the resulting compound and 3-hydroxyquinoxaline-2-carboxylic acid (40.0 mg, 0.210 mmol), at room temperature, under nitrogen stream, and stirring was carried out at room temperature overnight. The reaction solution was poured into a 2N aqueous hydrochloric acid solution, followed by extraction with ethyl acetate. The extract was washed sequentially with water and saline, and then dried over anhydrous sodium sulfate. The organic layer was concentrated, the resulting residue was purified by silica gel chromatography, the resulting residue was suspended in diethyl ether, and then the solid substance was collected by filtration to afford the desired title compound (62.0 mg, yield 62%) as a pale yellow solid.

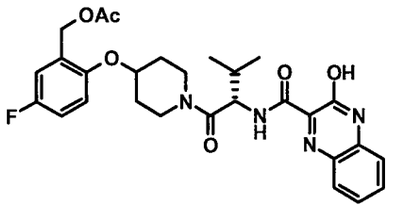
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.86 (1H, s), 9.74 (1H, m), 7.88 (1H, dd, J=8.8 Hz, 1.6 Hz), 7.41-7.38 (2H, m), 7.15-7.10 (2H, m), 7.04-7.01 (2H, m), 5.11 (1H, m), 4.93 (1H, s), 4.62-4.58 (1H, m), 4.02-3.93 (2H, m), 3.57-3.53 (1H, m), 3.32-3.30 (1H, m), 2.01-1.98 (1H, m), 1.93-1.89 (1H, m), 1.70-1.68 (1H, m), 1.53-1.49 (1H, m), 1.24 (3H, s), 1.17 (3H, s).

IR (KBr) cm^{-1}: 2975, 1685, 1625, 1505, 1205.

HRMS (ESI, m/z): 483.2050 (Calcd for $C_{25}H_{28}FN_4O_5$: 483.2043).

Anal. Calcd for $C_{24}H_{27}FN_4O_5 \cdot 0.2H_2O$: C, 61.77; H, 5.68; N, 11.53; F, 3.91. Found: C, 61.73; H, 5.51; N, 11.59; F, 4.14.

Example 70



5-fluoro-2-[(1-{N-[(3-hydroxyquinoxalin-2-yl)carbonyl]-L-valyl}piperidin-4-yl)oxy]benzyl acetate

Example 70-1

2-({1-[N-(t-butoxycarbonyl)-L-valyl]piperidin-4-yl}oxy)-5-fluorobenzyl acetate

A toluene solution of diisobutylaluminium hydride (0.990 M, 13.6 ml, 13.5 mmol) was slowly added dropwise to a tetrahydrofuran solution (50 ml) of t-butyl 4-(4-fluoro-2-methoxycarbonyphenoxy)piperidine-1-carboxylate (1.59 g, 4.50 mmol), at 0°C, under nitrogen stream, and stirring was carried out at 0°C for 1 hour. After completion of the reaction, an aqueous Rochelle salt solution and ethyl acetate were sequentially added, and stirring was carried out at room temperature overnight. The reaction solution was extracted with ethyl acetate, and then the extract was washed sequentially with a saturated aqueous sodium hydrogencarbonate solution, water and saline. The resulting organic layer was dried over anhydrous sodium sulfate, and then the residue resulting from concentration was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., 25+M) to afford t-butyl 4-(4-fluoro-2-hydroxymethylphenoxy)piperidine-1-carboxylate (1.13 g, yield 77%) as a colorless oil.

Acetic anhydride (0.304 ml, 3.24 mmol) was added to a pyridine solution (5 ml) of the resulting compound (350 mg, 1.08 mmol), under nitrogen stream, and stirring was carried out at room temperature overnight. The reaction solution was concentrated to afford t-butyl 4-(2-acetoxymethyl-4-fluorophenoxy)piperidine-1-carboxylate (396 mg) as a colorless oil.

Analogously to Example 23-2, 5-fluoro-2-[(piperidin-4-yl)oxy]benzyl acetate hydrochloride (328 mg) was obtained from the resulting compound (396 mg, 1.08 mmol) as a white solid. The resulting compound (328 mg, 1.08 mmol) was condensed with N-(t-butoxycarbonyl)-L-valine (352 mg, 1.62 mmol) to afford 2-({1-[N-(t-butoxycarbonyl)-L-valyl]piperidin-4-yl}oxy)-5-fluorobenzyl acetate (475 mg, yield 94%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.08 (1H, dd, J=9.0 Hz, 2.9 Hz), 6.99-6.96 (1H, m), 6.82 (1H, dd, J=9.0 Hz, 4.3 Hz), 5.35 (1H, d, J=9.0 Hz), 5.14 (2H, d, J=8.6 Hz), 4.58-4.48 (2H, m), 3.88-3.48 (4H, m), 2.11 (3H, s), 1.99-1.81

(5H, m), 1.47-1.44 (9H, m), 0.97 (3H, d, J=6.6 Hz), 0.89 (3H, d, J=6.6 Hz).

MS (FAB, m/z): 467 $(M+H)^+$.

Example 70-2

5-fluoro-2-[(1-{N-[(3-hydroxyquinoxalin-2-yl)carbonyl]-L-valyl}piperidin-4-yl)oxy]benzyl acetate

Analogously to Example 23-3, 5-fluoro-2-[(1-valylpiperidin-4-yl)oxy]benzyl acetate hydrochloride (410 mg) was obtained from 2-({1-[N-(t-butoxycarbonyl)-L-valyl]piperidin-4-yl}oxy)-5-fluorobenzyl acetate (475 mg, 1.02 mmol) as a white solid. The resulting compound (230 mg, 0.571 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (163 mg, 0.856 mmol) to afford the desired title compound (240 mg, yield 78%) as a pale yellow solid.

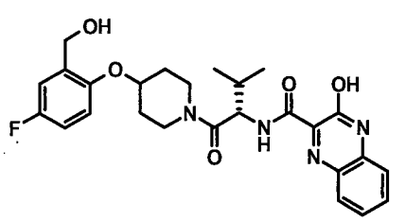
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 9.57 (1H, d, J=9.0 Hz), 7.86-7.85 (1H, m), 7.64-7.62 (1H, m), 7.38 (2H, d, J=7.8 Hz), 7.19-7.15 (3H, m), 5.07 (2H, d, J=8.6 Hz), 4.91 (1H, m), 4.71 (1H, brs), 4.10 (1H, brs), 3.70-3.54 (4H, m), 2.08-1.60 (8H, m), 0.95 (6H, t, J=5.9 Hz).

IR (KBr) cm^{-1}: 2960, 1685, 1640, 1495, 1225, 1030.

MS (ESI, m/z): 539 $(M+H)^+$, 561 $(M+Na)^+$.

HRMS (ESI, m/z): 561.2138 (Calcd for $C_{28}H_{31}FN_4NaO_6$: 561.2125).

Example 71



N-[(1S)-1-({4-[4-Fluoro-2-(hydroxymethyl)phenoxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

A 2N aqueous sodium hydroxide solution (3 ml) was added to a tetrahydrofuran solution (3.0 ml) of methyl 5-fluoro-2-[(1-{N-[(3-hydroxyquinoxalin-2-yl)carbonyl]-L-valyl}piperidin-4-yl)oxy]benzoate (120 mg, 0.223 mmol), and stirring was carried out at room temperature overnight. Under ice cooling, the reaction solution was poured into a 2N aqueous hydrochloric acid solution, followed by extraction with ethyl acetate, and the extract was washed sequentially with water and saline. The resulting organic layer was dried over anhydrous sodium sulfate, and then concentrated to afford the desired title compound (84.0 mg, yield 76%) as a pale yellow solid.

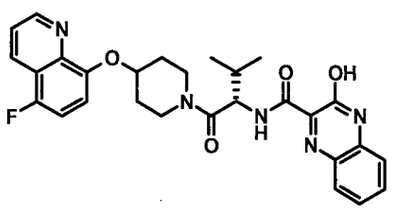
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.82 (1H, s), 9.52 (1H, d, J=8.8 Hz), 7.87 (1H, d, J=7.8 Hz), 7.64 (1H, m), 7.39-7.37 (2H, m), 7.18-7.16 (1H, m), 7.07-6.98 (2H, m), 5.19-5.18 (1H, m), 4.92 (1H, dd, J=14.7 Hz, 6.5 Hz), 4.64 (1H, brs), 4.53-4.51 (2H, m), 3.85-3.37 (4H, m), 2.10-1.58 (5H, m), 0.95 (6H, t, J=5.9 Hz).

IR (KBr) cm^{-1}: 2960, 1685, 1635, 1490, 1195, 1045.

MS (ESI, m/z): 497 $(M+H)^+$.

HRMS (ESI, m/z): 519.2026 (Calcd for $C_{26}H_{29}FN_4NaO_5$: 519.2019).

Example 72



N-[(1S)-1-({4-[(5-Fluoroquinolin-8-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 72-1

t-Butyl 4-[(5-fluoroquinolin-8-yl)oxy]piperidine-1-carboxylate

Analogously to Example 23-1, t-butyl 4-[(5-fluoroquinolin-8-yl)oxy]piperidine-1-carboxylate (1.14 g, yield 90%) was obtained from t-butyl 4-hydroxypiperidine-1-carboxylate (740 mg, 3.68 mmol) and 5-fluoro-8-hydroxyquinolin (600 mg, 3.68 mmol) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 8.99 (1H, dd, J=4.2 Hz, 1.5 Hz), 8.40 (1H, dd, J=8.3 Hz, 1.5 Hz), 7.49 (1H, dd, J=8.8 Hz, 4.2 Hz), 7.12 (1H, t, J=8.8 Hz), 7.06 (1H, dd, J=8.3 Hz, 4.9 Hz), 4.72-4.67 (1H, m), 3.95 (2H, brs), 3.22-3.17 (2H, m), 2.09-2.05 (2H, m), 1.94-1.91 (2H, m), 1.47-1.45 (9H, m).

MS (FAB, m/z): 347 $(M+H)^+$.

Example 72-2

t-Butyl [(1S)-1-({4-[(5-fluoroquinolin-8-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate

Analogously to Example 23-2, 5-fluoro-8-[(piperidin-4-yl)oxy]quinolinhydrochloride (1.02 g) was obtained from t-butyl 4-[(5-fluoro-quinolin-8-yl)oxy]piperidine-1-carboxylate (1.14 g, 3.29 mmol) as a white solid. The resulting compound (720 mg, 2.26 mmol) was condensed with N-(t-butoxycarbonyl)-L-valine (588 mg, 2.71 mmol) to afford t-butyl [(1S)-1-({4-[(5-fluoroquinolin-8-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (772 mg, yield 77%) as a colorless amorphous

substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.99 (1H, dd, J=4.2 Hz, 1.5 Hz), 8.42 (1H, dd, J=8.4 Hz, 1.5 Hz), 7.51 (1H, dd, J=8.4 Hz, 4.2 Hz), 7.17-7.06 (2H, m), 5.38-5.36 (1H, m), 4.82-4.80 (1H, m), 4.55-4.52 (1H, m), 4.15-4.09 (1H, m), 4.02-3.94 (1H, m), 3.56-3.42 (2H, m), 2.18-1.93 (5H, m), 1.45-1.45 (9H, m), 0.99 (3H, t, J=6.8 Hz), 0.90 (3H, t, J=6.8 Hz).

MS (FAB, m/z): 445 $(M+H)^+$.

Example 72-3

N-[(1S)-1-({4-[(5-Fluoroquinolin-8-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 23-3, (2S)-1-{4-[(5-fluoroquinolin-8-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine dihydrochloride (725 mg) was obtained from t-butyl [(1S)-1-({4-[(5-fluoroquinolin-8-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (772 mg, 1.73 mmol) as a white solid. The resulting compound (200 mg, 0.478 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (136 mg, 0.717 mmol) to afford the desired title compound (160 mg, yield 65%) as a pale yellow solid.

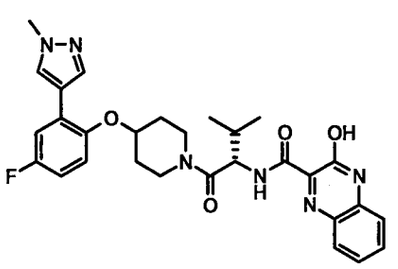
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.81 (1H, brs), 9.66 (1H, brs), 8.98 (1H, dd, J=4.2 Hz, 1.5 Hz), 8.45 (1H, dd, J=8.4 Hz, 1.5 Hz), 7.85 (1H, dd, J=8.4 Hz, 4.2 Hz), 7.66-7.63 (2H, m), 7.38-7.36 (4H, m), 4.95-4.91 (2H, m), 4.03-4.01 (2H, m), 3.59-3.33 (2H, m), 2.09-1.68 (5H, m), 0.97 (6H, t, J=7.0 Hz).

IR (KBr) cm^{-1}: 2960, 1685, 1630, 1530, 1475, 1255, 1090.

MS (ESI, m/z): 518 $(M+H)^+$.

HRMS (ESI, m/z): 518.2191 (Calcd for $C_{28}H_{28}FN_5O_4$: 518.2203).

Example 73



N-[(1S)-1-({4-[4-Fluoro-2-(1-methyl-1H-pyrazol-4-yl)phenoxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 73-1

t-Butyl 4-[4-fluoro-2-(1-methyl-1H-pyrazol-4-yl)phenoxy]piperidine-1-carboxylate

Potassium carbonate (775 mg, 5.61 mmol) and tetrakis(triphenylphosphine)palladium (108 mg, 0.0935 mmol) were added sequentially to a 1,2-dimethoxyethane-water (5.0 ml, 4:4, v/v) mixed solution of t-butyl 4-(2-bromo-4-fluorophenoxy)piperidine-1-carboxylate (350 mg, 0.935 mmol) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaboran-2-yl)-1H-pyrazol (233 mg, 1.12 mmol), under nitrogen stream, and stirring was carried out overnight under heating to reflux. After completion of the reaction, the reaction solution was cooled to room temperature, and poured into ice water, followed by extraction with ethyl acetate. The extract was washed sequentially with water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., 25+M) to afford t-butyl 4-[4-fluoro-2-(1-methyl-1H-pyrazol-4-yl)phenoxy]piperidine-1-carboxylate (253 mg, yield 72%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.83 (1H, d, J=15.2 Hz), 7.75 (1H, d, J=11.3 Hz), 7.20-7.16 (1H, m), 6.91-6.83 (2H, m), 4.45-4.43 (1H, m), 3.95 (3H, s), 3.74-3.72 (2H, m), 3.28-3.21 (2H, m), 1.94-1.88 (2H, m), 1.74-1.69 (2H, m), 1.47-1.46 (9H, m).

MS (FAB, m/z): 376 $(M+H)^+$.

Example 73-2

t-Butyl [(1S)-1-({4-[4-fluoro-2-(1-methyl-1H-pyrazol-4-yl)phenoxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate

Analogously to Example 23-2, 4-[4-fluoro-2-(1-methyl-1H-pyrazol-4-yl)phenoxy]piperidine hydrochloride (210 mg, yield 100%) was obtained from t-butyl 4-[4-fluoro-2-(1-methyl-1H-pyrazol-4-yl)phenoxy]piperidine-1-carboxylate as a white solid. The resulting compound (210 mg, 0.674 mmol) was condensed with N-(t-butoxycarbonyl)-L-valine (176 mg, 0.809 mmol) to afford t-butyl [(1S)-1-({4-[4-fluoro-2-(1-methyl-1H-pyrazol-4-yl)phenoxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (158 mg, yield 49%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.83 (1H, d, J=15.2 Hz), 7.75 (1H, d, J=11.3 Hz), 7.20-7.15 (1H, m), 6.91-6.84 (2H, m), 5.33 (1H, t, J=8.6 Hz), 4.53-4.47 (2H, m), 3.95 (3H, s), 3.79-3.60 (2H, m), 3.47-3.40 (2H, m), 2.05-1.80 (5H, m), 1.45-1.42 (9H, m), 0.96 (3H, d, J=6.8 Hz), 0.89 (3H, d, J=6.8 Hz).

MS (FAB, m/z): 475 $(M+H)^+$.

Example 73-3

N-[(1S)-1-({4-[4-Fluoro-2-(1-methyl-1H-pyrazol-4-yl)phenoxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 23-3, (2S)-1-{4-[4-fluoro-2-(1-methyl-1H-pyrazol-4-yl)phenoxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine hydrochloride (137 mg) was obtained from t-butyl [(1S)-1-({4-[4-fluoro-2-(1-methyl-1H-pyrazol-4-yl)phenoxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (158 mg, 0.333 mmol) as a white solid. The resulting compound (70.0 mg, 0.170 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (49.0 mg, 0.256 mmol) to afford the desired title compound (92.0 mg, yield 99%) as a pale yellow solid.

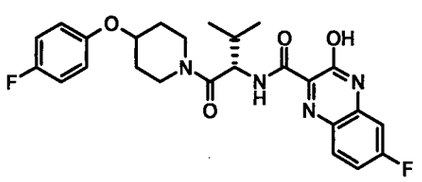
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.80 (1H, brs), 9.54 (1H, d, J=8.2 Hz), 8.13 (1H, d, J=5.9 Hz), 7.93 (1H, d, J=5.5 Hz), 7.84 (1H, dd, J=16.0 Hz, 7.6 Hz), 7.63 (1H, t, J=7.6 Hz), 7.44 (1H, dd, J=10.0 Hz, 2.9 Hz), 7.39-7.37 (2H, m), 7.18-7.16 (1H, m), 7.01-6.97 (1H, m), 4.94-4.91 (1H, m), 4.71-4.68 (1H, m), 4.02-3.87 (2H, m), 3.86 (3H, d, J=12.9 Hz), 3.53-3.16 (2H, m), 2.18-1.54 (5H, m), 1.05-0.85 (6H, m).

IR (KBr) cm^{-1}: 2960, 1685, 1640, 1530, 1495, 1450, 1210.

MS (ESI, m/z): 569 $(M+Na)^+$.

HRMS (ESI, m/z): 569.2304 (Calcd for $C_{29}H_{31}FN_6NaO_4$: 569.2288).

Example 74



N-[(1S)-1-{[4-(4-Fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-6-fluoro-3-hydroxyquinoxaline-2-carboxamide

Example 74-1

Ethyl 6-fluoro-3-hydroxyquinoxaline-2-carboxylate

4-Fluoro-2-nitroaniline (672 mg, 4.31 mmol) and diethyl ketomalonate (500 mg, 2.87 mmol) were dissolved in ethanol (30 ml), under nitrogen stream, and stirring was carried out at room temperature for 1.5 hours. Subsequently, tin (II) chloride dihydrate (1.62 g, 7.18 mmol) was added, and further stirring was carried out overnight. The reaction solution was concentrated to 5.0 ml under reduced pressure and poured into a 2N aqueous hydrochloric acid solution, followed by extraction with methylene chloride, the extract was washed sequentially with water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting

residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., 25+M) to afford ethyl 6-fluoro-3-oxo-1,2,3,4-tetrahydroquinoxaline-2-carboxylate (105 mg, yield 16%) as a pale yellow solid.

2,3-Dichloro-5,6-dicyanobenzoquinone (66.0 mg, 0.290 mmol) was added to a methylene chloride solution (3.0 ml) of the resulting compound (59.0 mg, 0.248 mmol), at room temperature, under nitrogen stream, and stirring was carried out at room temperature for 3 hours. After completion of the reaction, the reaction solution was poured into ice water, followed by extraction with ethyl acetate, and the extract was washed sequentially with water and saline and then dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., 25+M) to afford ethyl 6-fluoro-3-hydroxyquinoxaline-2-carboxylate (52.0 mg, yield 90%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.68 (1H, d, J=8.0 Hz), 7.45-7.43 (2H, m), 4.57 (2H, q, J=7.0 Hz), 1.49 (3H, t, J=7.0 Hz).

MS (FAB, m/z): 237 $(M+H)^+$.

Example 74-2

N-[(1S)-1-{[4-(4-Fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-6-fluoro-3-hydroxyquinoxaline-2-carboxamide

Lithium hydroxide monohydrate (32.0 mg, 0.773 mmol) was added to an aqueous solution (2.0 ml) of ethyl 6-fluoro-3-hydroxyquinoxaline-2-carboxylate (73.0 mg, 0.309 mmol), under nitrogen stream, and the mixture was allowed to react at room temperature for 2.5 hours. Under ice cooling, the reaction solution was poured into a 2N aqueous hydrochloric acid solution, and the precipitated solid was collected by filtration, followed by drying to afford 6-fluoro-3-hydroxy-2-quinoxaline carboxylic acid (52.0 mg, yield 81%) as a pale yellow solid.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (72.0 mg, 0.375 mmol) and 1-hydroxybenzotriazole monohydrate (51.0 mg, 0.375 mmol) were added to a methylene chloride solution (5.0 ml) of the resulting compound (52.0 mg, 0.250 mmol) and (2S)-1-[4-(4-fluorophenoxy)piperidin-1-yl]-3-methyl-1-oxobutan-2-amine (74.0 mg, 0.250 mmol), at room temperature, under nitrogen stream, and stirring was carried out at room temperature overnight. The reaction solution was poured into a 2N aqueous hydrochloric acid solution, followed by extraction with ethyl acetate, and the extract was washed sequentially

with water, a saturated aqueous sodium hydrogencarbonate solution, water and saline, and then dried over anhydrous sodium sulfate. After the organic layer was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., 25+M), the residue resulting from concentration was suspended in a mixed solvent of methylene chloride-diethyl ether, and the solid substance was collected by filtration to afford the desired title compound (90.0 mg, yield 74%) as a pale yellow solid.

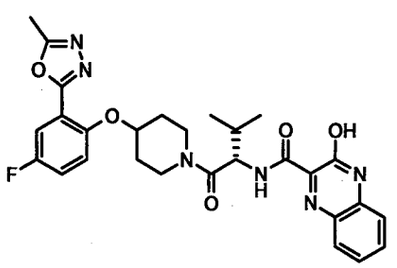
^{1}H-NMR (DMSO-d_6, 500 MHz) δ: 12.86 (1H, brs), 9.46 (1H, brs), 7.72 (1H, t, J=7.2 Hz), 7.57-7.55 (1H, m), 7.40 (1H, dd, J=9.3 Hz, 4.6 Hz), 7.13-7.11 (2H, m), 7.04-7.00 (2H, m), 4.90 (1H, dd, J=13.2 Hz, 7.3 Hz), 4.60-4.59 (1H, m), 3.93-3.90 (2H, m), 3.49-3.31 (2H, m), 2.09-1.91 (3H, m), 1.66-1.55 (2H, m), 0.94 (6H, t, J=6.8 Hz).

IR (KBr) cm^{-1}: 2965, 1690, 1640, 1505, 1245, 1205.

MS (ESI, m/z): 507 $(M+Na)^+$.

HRMS (ESI, m/z): 507.1804 (Calcd for $C_{25}H_{26}F_2N_4NaO_4$: 507.1819).

Example 75



N-[(1S)-1-({4-[4-Fluoro-2-(5-methyl-1,3,4-oxadiazol-2-yl)phenoxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 75-1

Methyl 2-[(1-{N-[(benzyloxycarbonyl)amino]-L-valyl}piperidin-4-yl)oxy]-5-fluorobenzoate

Analogously to Example 23-2, methyl 5-fluoro-2-[(piperidin-4-yl)oxy]benzoate hydrochloride (985 mg, yield 100%) was obtained from t-butyl 4-[4-fluoro-2-(methoxycarbonyl)phenoxy]piperidine-1-carboxylate (1.20 g, 3.40 mmol) as a white solid. The resulting compound (985 mg, 3.40 mmol) was condensed with N-(benzyloxycarbonyl)-L-valine (1.02 g, 4.07 mmol) to afford methyl 2-[(1-{N-[(benzyloxycarbonyl)amino]-L-valyl}piperidin-4-yl)oxy]-5-fluorobenzoate (1.49 g, yield 90%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.53 (1H, dd, J=8.6 Hz, 3.0 Hz), 7.35-7.32 (5H, m), 7.19-7.14 (1H, m), 6.93 (1H, dd, J=8.6 Hz, 4.3 Hz), 5.62 (1H, t,

J=8.0 Hz), 5.10-5.09 (2H, m), 4.62-4.55 (2H, m), 4.01-3.98 (1H, m), 3.88 (3H, s), 3.88-3.53 (3H, m), 1.93-1.89 (5H, m), 0.99 (3H, d, J=6.6 Hz), 0.89 (3H, d, J=6.6 Hz).

MS (FAB, m/z): 487 $(M+H)^+$.

Example 75-2

Benzyl {(1S)-1-[(4-{2-[(2-acetylhydrazino)carbonyl]-4-fluorophenoxy}piperidin-1-yl)carbonyl]-2-methylpropyl}carbamate

A 2N aqueous sodium hydroxide solution (30 ml) was added to a tetrahydrofuran solution (30 ml) of methyl 2-[(1-{N-[(benzyloxycarbonyl)amino]-L-valyl}piperidin-4-yl)oxy]-5-fluorobenzoate (1.23 g, 2.53 mmol), and the mixture was allowed to react at room temperature overnight. Under ice cooling, the reaction solution was poured into a 2N aqueous hydrochloric acid solution, followed by extraction with ethyl acetate. The extract was washed sequentially with water and saline and dried over anhydrous sodium sulfate, and then concentrated to afford 2-[(1-{N-[(benzyloxycarbonyl)amino]-L-valyl}piperidin-4-yl)oxy]-5-fluorobenzoic acid (840 mg).

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (512 mg, 2.67 mmol) and 1-hydroxybenzotriazole monohydrate (361 mg, 2.67 mmol) were added to a tetrahydrofuran solution (25 ml) of the resulting compound (840 mg, 1.78 mmol) and acetohydrazide (198 mg, 2.67 mmol), at room temperature, and stirring was carried out at room temperature overnight. The reaction solution was poured into a 2N aqueous hydrochloric acid solution, followed by extraction with ethyl acetate, the extract was washed sequentially with water, a saturated aqueous sodium hydrogencarbonate solution, water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., 25+M) to afford benzyl {(1S)-1-[(4-{2-[(2-acetylhydrazino)carbonyl]-4-fluorophenoxy}piperidin-1-yl)carbonyl]-2-methylpropyl}carbamate (854 mg, yield 91%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 10.82-10.74 (1H, m), 9.33-9.23 (1H, m), 7.90 (1H, dd, J=8.6 Hz, 3.0 Hz), 7.35-7.33 (5H, m), 7.21-7.18 (1H, m), 6.99 (1H, dd, J=8.6 Hz, 4.3 Hz), 5.67 (1H, m), 5.11-5.10 (2H, m), 4.73-4.70 (1H, m), 4.58-4.56 (1H, m), 4.11-3.95 (2H, m), 3.55-3.46 (2H, m), 2.12 (3H, d, J=7.4 Hz), 1.97-1.79 (5H, m), 1.01 (3H, t, J=6.6 Hz), 0.91 (3H, t, J=6.6 Hz).

Example 75-3

Benzyl [(1S)-1-({4-[4-fluoro-2-(5-methyl-1,3,4-oxadiazol-2-yl)phenoxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate

p-Toluenesulfonyl chloride (420 mg, 0.874 mmol) and triethylamine (0.244 ml, 1.75 mmol) were added to a methylene chloride solution (15 ml) of benzyl {(1S)-1-[(4-{2-[(2-acetylhydrazino)carbonyl]-4-fluorophenoxy}piperidin-1-yl)carbonyl]-2-methylpropyl}carbamate (420 mg, 0.795 mmol), under nitrogen stream, and stirring was carried out at room temperature overnight. Under ice cooling, the reaction solution was poured into a 2N aqueous hydrochloric acid solution, followed by extraction with ethyl acetate, the extract was washed sequentially with water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., 25+M) to afford benzyl [(1S)-1-({4-[4-fluoro-2-(5-methyl-1,3,4-oxadiazol-2-yl)phenoxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (227 mg, yield 56%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.69-7.63 (1H, m), 7.36-7.31 (5H, m), 7.19-7.16 (1H, m), 7.00 (1H, dd, J=8.6 Hz, 4.3 Hz), 5.60 (1H, d, J=8.6 Hz), 5.09 (2H, s), 4.72-4.67 (1H, m), 4.56 (1H, dd, J=8.6 Hz, 5.7 Hz), 4.07-3.49 (4H, m), 2.60 (3H, s), 1.97-1.91 (5H, m), 0.99 (3H, t, J=6.6 Hz), 0.89 (3H, t, J=6.6 Hz).

Example 75-4

N-[(1S)-1-({4-[4-Fluoro-2-(5-methyl-1,3,4-oxadiazol-2-yl)phenoxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

5% Palladium carbon catalyst (193 mg) was added to a methanol solution (10 ml) of benzyl [(1S)-1-({4-[4-fluoro-2-(5-methyl-1,3,4-oxadiazol-2-yl)phenoxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (464 mg, 0.909 mmol), and stirring was carried out at room temperature for 3 hours under hydrogen atmosphere. The reaction solution was celite filtered, and the filtrate was concentrated to afford (2S)-1-{4-[4-fluoro-2-(5-methyl-1,3,4-oxadiazol-2-yl)phenoxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine (334 mg, yield 98%) as white crystals.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (126 mg, 0.657 mmol) and 1-hydroxybenzotriazole monohydrate (89.0 mg, 0.657 mmol) were added to a methylene chloride solution (5.0 ml) of the

resulting compound (165 mg, 0.438 mmol) and 3-hydroxyquinoxaline-2-carboxylic acid (125 mg, 0.657 mmol), at room temperature, and stirring was carried out at room temperature overnight. The reaction solution was poured into a 2N aqueous hydrochloric acid solution, followed by extraction with ethyl acetate, the extract was washed sequentially with water, a saturated aqueous sodium hydrogencarbonate solution, water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated, the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., 25+M), the residue resulting from concentration was suspended in a mixed solvent of methylene chloride-dimethylether, and the solid substance was collected by filtration to afford the desired title compound (217 mg, yield 90%) as a pale yellow solid.

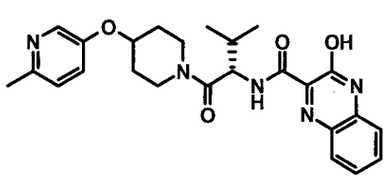
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.82 (1H, brs), 9.50 (1H, d, J=9.0 Hz), 7.86 (1H, t, J=7.0 Hz), 7.65-7.63 (2H, m), 7.49-7.36 (4H, m), 4.94-4.85 (2H, m), 3.71-3.61 (4H, m), 2.55 (3H, d, J=12.9 Hz), 1.96-1.84 (5H, m), 0.97-0.93 (6H, m).

IR (KBr) cm^{-1}: 2965, 1685, 1640, 1540, 1480, 1265.

MS (ESI, m/z): 571 $(M+Na)^+$.

HRMS (ESI, m/z): 571.2075 (Calcd for $C_{28}H_{29}FN_6NaO_5$: 571.2081).

Example 76



3-Hydroxy-N-[(1S)-2-methyl-1-({4-[(6-methylpyridin-3-yl)oxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Example 76-1

t-Butyl [(1S)-2-methyl-1-({4-[(6-methylpyridin-3-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate

A 40% toluene solution of diisopropyl azodicarboxylate (2.10 ml, 3.99 mmol) was added to a toluene solution (15 ml) of t-butyl [(1S)-4-(4-hydroxypiperidine-1-carbonyl)-2-methylpropyl]carbamate (1.00 g, 3.33 mmol), 5-hydroxy-2-methylpyridine (404 mg, 3.66 mmol) and triphenylphosphine (1.05 g, 3.99 mmol), at room temperature, and stirring was carried out for 4 days. The reaction solution was concentrated under reduced pressure and the resulting residue was diluted with ethyl acetate, followed by sequential washing with a 1N aqueous sodium

hydroxide solution, water and saline, and then the resulting organic layer was extracted with a 1N hydrochloric acid. A 5N aqueous sodium hydroxide solution was used to make the aqueous layer basic, followed by extraction with ethyl acetate. The resulting organic layer was dried over anhydrous sodium sulfate, and the organic layer was concentrated to afford t-butyl [(1S)-2-methyl-1-({4-[(6-methylpyridin-3-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate (980 mg, yield 72%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 8.20 (1H, s), 7.14-7.07 (2H, m), 5.34 (1H, d, J=7.8 Hz), 4.56-4.48 (2H, m), 3.82-3.46 (4H, m), 2.50 (3H, s), 1.99-1.80 (5H, m), 1.44 (9H, s), 0.97 (3H, d, J=6.6 Hz), 0.89 (3H, d, J=6.6 Hz).

MS (ESI, m/z): 392 $(M+H)^+$.

Example 76-2

(2S)-3-Methyl-1-{4-[(6-methylpyridin-3-yl)oxy]piperidin-1-yl}-1-oxobutan-2-amine dihydrochloride

Analogously to Example 29-3, (2S)-3-methyl-1-{4-[(6-methylpyridin-3-yl)oxy]piperidin-1-yl}-1-oxobutan-2-amine dihydrochloride (907 mg, yield 100%) was obtained from t-butyl [(1S)-2-methyl-1-({4-[(6-methylpyridin-3-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate (980 mg, 2.50 mmol) as a colorless amorphous substance.

^{1}H-NMR (CD_3OD) δ: 8.52 (1H, s), 8.21-8.18 (1H, m), 7.85 (1H, d, J=9.0 Hz), 4.96 (1H, s), 4.38 (1H, d, J=4.3 Hz), 4.12-3.43 (4H, m), 2.71 (3H, s), 2.24-2.03 (3H, m), 1.93-1.74 (2H, m), 1.11 (3H, d, J=6.6 Hz), 1.02 (3H, d, J=6.6 Hz).

MS (ESI, m/z): 292 $(M+H)^+$.

Example 76-3

3-Hydroxy-N-[(1S)-2-methyl-1-({4-[(6-methylpyridin-3-yl)oxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Analogously to Example 29-4, the desired title compound (228 mg, yield 90%) was obtained from (2S)-3-methyl-1-{4-[(6-methylpyridin-3-yl)oxy]piperidin-1-yl}-1-oxobutan-2-amine dihydrochloride (200 mg, 0.549 mmol) as a yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 12.73 (1H, br s), 10.04 (1H, br s), 8.23 (1H, dd, J=8.8 Hz, 2.9 Hz), 8.00 (1H, t, J=7.0 Hz), 7.63 (1H, t, J=7.4 Hz), 7.55 (1H, br s), 7.41-7.37 (1H, m), 7.17-7.13 (1H, m), 7.09 (1H, dd, J=8.6 Hz, 4.7 Hz), 5.10-5.05 (1H, m), 4.63-4.57 (1H, m), 4.03-3.68 (4H, m), 2.51 (3H, d, J=2.3 Hz), 2.40-1.87 (5H, m), 1.14-1.09 (6H, m).

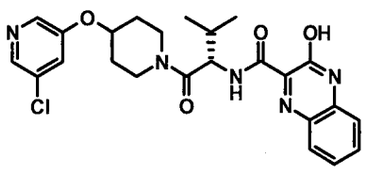
IR (KBr) cm^{-1}: 3440, 2960, 1685, 1635, 1525.

MS (ESI, m/z): 464 $(M+H)^+$.

HRMS (ESI, m/z): 464.2316 (Calcd for $C_{25}H_{30}N_5O_4$: 464.2298).

Anal. Calcd for $C_{25}H_{29}N_5O_4 \cdot 1/2H_2O$: C, 63.54; H, 6.40; N, 14.82. Found: C, 63.76; H, 6.13; N, 14.80.

Example 77



N-[(1S)-1-({4-[(5-Chloropyridin-3-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 77-1

t-Butyl [(1S)-1-({4-[(5-chloropyridin-3-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate

Analogously to Example 1-2, t-butyl [(1S)-1-({4-[(5-chloropyridin-3-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (253 mg, yield 18%) was obtained from t-butyl [(1S)-1-(4-hydroxypiperidine-1-carbonyl)-2-methylpropyl]carbamate (1.00 g, 3.33 mmol) and 3-chloro-5-hydroxypyridine (474 mg, 3.66 mmol) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 8.21 (2H, s), 7.24-7.22 (1H, m), 5.34-5.32 (1H, m), 4.64-4.48 (2H, m), 3.87-3.53 (4H, m), 2.05-1.86 (5H, m), 1.44 (9H, s), 0.97 (3H, d, J=6.6 Hz), 0.90 (3H, d, J=6.6 Hz).

MS (ESI, m/z): 412 $(M+H)^+$.

Example 77-2

(2S)-1-{4-[(5-Chloropyridin-3-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine dihydrochloride

Analogously to Example 29-3, (2S)-1-{4-[(5-chloropyridin-3-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine dihydrochloride (236 mg, yield 100%) was obtained from t-butyl [(1S)-1-({4-[(5-chloropyridin-3-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (253 mg, 0.614 mmol) as a colorless amorphous substance.

^{1}H-NMR (CD_3OD) δ: 8.56-8.51 (2H, m), 8.21-8.19 (1H, m), 4.97 (1H, s), 4.38 (1H, s), 4.10-3.45 (4H, m), 2.23-1.77 (5H, m), 1.12 (3H, d, J=6.6 Hz), 1.02 (3H, d, J=6.6 Hz).

MS (ESI, m/z): 312 $(M+H)^+$.

Example 77-3

N-[(1S)-1-({4-[(5-Chloropyridin-3-yl)oxy]piperidin-1-yl}carbonyl)-2-

methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 29-4, the desired title compound (189 mg, yield 64%) was obtained from (2S)-1-{4-[(5-chloropyridin-3-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine dihydrochloride (236 mg, 0.613 mmol) as a yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 12.35 (1H, br s), 10.18 (1H, br s), 8.25-8.22 (2H, m), 8.04-8.00 (1H, m), 7.64-7.22 (4H, m), 5.10-5.05 (1H, m), 4.68-4.62 (1H, m), 4.03-3.66 (4H, m), 2.35-1.88 (5H, m), 1.14-1.09 (6H, m).

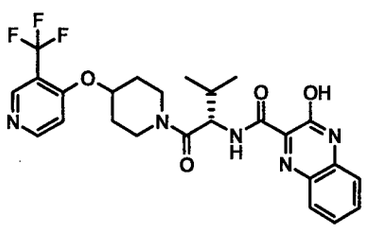
IR (KBr) cm^{-1}: 2965, 1685, 1640, 1520, 1420.

MS (ESI, m/z): 484 $(M+H)^+$.

HRMS (ESI, m/z): 506.1579 (Calcd for $C_{24}H_{26}ClN_5NaO_4$: 506.1571).

Anal. Calcd for $C_{24}H_{26}ClN_5O_4$: C, 59.56; H, 5.42; N, 14.47; Cl, 7.33. Found: C, 59.63; H, 5.32; N, 14.51; Cl, 7.64.

Example 78



3-Hydroxy-N-{(1S)-2-methyl-1-[(4-{[3-(trifluoromethyl)pyridin-4-yl]oxy}piperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide

Example 78-1

t-Butyl 4-{[3-(trifluoromethyl)pyridin-4-yl]oxy}piperidine-1-carboxylate

t-Butyl 4-hydroxypiperidine-1-carboxylate (1.30 g, 5.78 mmol) was added to a N,N-dimethylformamide suspension (4.8 ml) of 60% sodium hydride (404 mg, 10.6 mmol), at 0°C, and stirring was carried out at room temperature for 30 minutes. Further, at 0°C, 4-chloro-3-(trifluoromethyl)pyridine hydrochloride (1.00 g, 4.82 mmol) was added, and stirring was carried out at room temperature for 5 hours. Water was added to the reaction solution, and a 1N hydrochloric acid was used to make it acidic, followed by washing with ethyl acetate. A 1N aqueous sodium hydroxide solution was used to make the aqueous layer basic, followed by extraction with ethyl acetate, and then the extract was washed with water and saturated saline. The resulting organic layer was dried over anhydrous sodium sulfate, and subsequently concentrated to afford t-butyl 4-{[3-(trifluoromethyl)pyridin-4-yl]oxy}piperidine-1-carboxylate (884 mg, yield 53%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 8.70 (1H, s), 8.61 (1H, d, J=4.7 Hz), 6.90 (1H, d, J=4.7

Hz), 4.79-4.76 (1H, m), 3.65-3.60 (2H, m), 3.50-3.46 (2H, m), 1.92-1.87 (4H, m), 1.47 (9H, s).
MS (ESI, m/z): 347 $(M+H)^+$.

Example 78-2
t-Butyl {(1S)-2-methyl-1-[(4-{[3-(trifluoromethyl)pyridin-4-yl]oxy}piperidin-1-yl)carbonyl]propyl}carbamate

Analogously to Example 29-2, t-butyl {(1S)-2-methyl-1-[(4-{[3-(trifluoromethyl)pyridin-4-yl]oxy}piperidin-1-yl)carbonyl]propyl}carbamate (610 mg, yield 54%) was obtained from t-butyl 4-{[3-(trifluoromethyl)pyridin-4-yl]oxy}piperidine-1-carboxylate (884 mg, 2.55 mmol) as a colorless amorphous substance.
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.72 (1H, s), 8.64 (1H, d, J=4.7 Hz), 6.90 (1H, d, J=4.7 Hz), 5.32 (1H, d, J=7.4 Hz), 4.89-4.84 (1H, m), 4.49 (1H, dd, J=7.2 Hz, 4.5 Hz), 4.22-3.98 (1H, m), 3.76-3.29 (3H, m), 2.02-1.91 (5H, m), 1.44 (9H, s), 0.99-0.88 (6H, m).
MS (ESI, m/z): 446 $(M+H)^+$.

Example 78-3
(2S)-3-Methyl-1-oxo-1-(4-{[3-(trifluoromethyl)pyridin-4-yl]oxy}piperidin-1-yl)butan-2-amine dihydrochloride

Analogously to Example 29-3, (2S)-3-methyl-1-oxo-1-(4-{[3-(trifluoromethyl)pyridin-4-yl]oxy}piperidin-1-yl)butan-2-amine dihydrochloride (583 mg, yield 100%) was obtained from t-butyl {(1S)-2-methyl-1-[(4-{[3-(trifluoromethyl)pyridin-4-yl]oxy}piperidin-1-yl)carbonyl]propyl}carbamate (610 mg, 1.37 mmol) as a colorless amorphous substance.
^{1}H-NMR (CD_3OD) δ: 9.10 (1H, s), 8.95 (1H, d, J=7.0 Hz), 8.02 (1H, dd, J=10.2 Hz, 7.0 Hz), 5.46-5.37 (1H, m), 4.40 (1H, t, J=5.5 Hz), 4.07-3.52 (4H, m), 2.24-1.90 (5H, m), 1.14-1.02 (6H, m).
MS (ESI, m/z): 346 $(M+H)^+$.

Example 78-4
3-Hydroxy-N-{(1S)-2-methyl-1-[(4-{[3-(trifluoromethyl)pyridin-4-yl]oxy}piperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide

Analogously to Example 29-4, the desired title compound (152 mg, yield 61%) was obtained from (2S)-3-methyl-1-oxo-1-(4-{[3-(trifluoromethyl)pyridin-4-yl]oxy}piperidin-1-yl)butan-2-amine dihydrochloride (200 mg, 0.478 mmol) as a colorless solid.
^{1}H-NMR ($CDCl_3$) δ: 12.21 (1H, brs), 10.16 (1H, brs), 8.74-8.64 (2H, m),

8.06-8.00 (1H, m), 7.63-7.22 (3H, m), 6.92 (1H, d, J=5.9 Hz), 5.10-5.03 (1H, m), 4.93-4.88 (1H, m), 4.41-3.33 (4H, m), 2.34-2.01 (5H, m), 1.15-1.10 (6H, m).

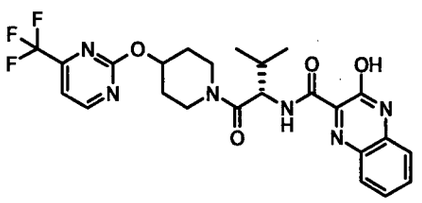
IR (KBr) cm^{-1}: 3430, 2965, 1690, 1645, 1600.

MS (ESI, m/z): 518 $(M+H)^+$.

HRMS (ESI, m/z): 540.1825 (Calcd for $C_{25}H_{26}F_3N_5NaO_4$: 540.1835).

Anal. Calcd for $C_{25}H_{26}F_3N_5O_4$: C, 58.02; H, 5.06; N, 13.53; F, 11.01. Found: C, 57.77; H, 4.93; N, 13.48; F, 11.19.

Example 79



3-Hydroxy-N-{(1S)-2-methyl-1-[(4-{[4-(trifluoromethyl)pyrimidin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide

Example 79-1

t-Butyl {(1S)-2-methyl-1-[(4-{[4-(trifluoromethyl)pyrimidin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}carbamate

Analogously to Example 64-1, t-butyl {(1S)-2-methyl-1-[(4-{[4-(trifluoromethyl)pyrimidin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}carbamate (2.74 g, yield 92%) was obtained from 2-chloro-4-(trifluoromethyl)pyrimidine (0.883 ml, 7.32 mmol) and t-butyl {(1S)-1-[(4-hydroxypiperidin-1-yl)carbonyl]-2-methylpropyl}carbamate (2.00 g, 6.66 mmol) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 8.80 (1H, d, J=4.8 Hz), 7.31 (1H, d, J=4.8 Hz), 5.41-5.33 (2H, m), 4.53 (1H, dd, J=8.8 Hz, 6.0 Hz), 4.04-3.49 (4H, m), 2.16-1.89 (5H, m), 1.47 (9H, s), 1.00 (3H, d, J=6.8 Hz), 0.92 (3H, d, J=6.8 Hz).

MS (FAB, m/z): 447 $(M+H)^+$.

Example 79-2

3-Hydroxy-N-{(1S)-2-methyl-1-[(4-{[4-(trifluoromethyl)pyrimidin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide

Analogously to Example 1-3, (2S)-3-methyl-1-oxo-1-(4-{[4-(trifluoromethyl)pyrimidin-2-yl]oxy}piperidin-1-yl)butan-2-amine hydrochloride (2.48 g) was obtained from t-butyl {(1S)-2-methyl-1-[(4-{[4-(trifluoromethyl)pyrimidin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}carbamate (2.74 g, 6.14 mmol) as a white solid. The

resulting compound (200 mg, 0.522 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (136 mg, 0.784 mmol) to afford the desired title compound (240 mg, yield 92%) as a pale yellow solid.

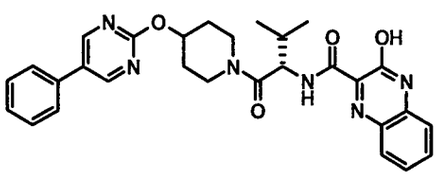
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.86 (1H, brs), 9.56 (1H, brs), 9.03 (1H, t, J=4.0 Hz), 7.89 (1H, dd, J=6.4 Hz, 3.2 Hz), 7.67-7.66 (2H, m), 7.42-7.40 (2H, m), 5.33-5.32 (1H, m), 4.95 (1H, q, J=8.0 Hz), 4.05-3.90 (2H, m), 3.59-3.40 (2H, m), 2.06-1.74 (5H, m), 1.12-0.97 (6H, m).

IR (KBr) cm^{-1}: 2965, 1690, 1645, 1425, 1155.

MS (ESI, m/z): 519 $(M+H)^+$.

HRMS (ESI, m/z): 519.1956 (Calcd for $C_{24}H_{26}F_3N_6O_4$: 519.1967).

Example 80



3-Hydroxy-N-[(1S)-2-methyl-1-({4-[(5-phenylpyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Example 80-1

t-Butyl 4-[(5-bromopyrimidin-2-yl)oxy]piperidine-1-carboxylate

Analogously to Example 64-1, t-butyl 4-[(5-bromopyrimidin-2-yl)oxy]piperidine-1-carboxylate (2.10 g, yield 44%) was obtained from 5-bromo-2-chloropyrimidine (2.84 g, 13.3 mmol) and t-butyl 4-hydroxypiperidine-1-carboxylate (2.68 g, 13.3 mmol) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.48 (2H, s), 5.10-5.06 (1H, m), 3.76-3.75 (2H, m), 3.29-3.23 (2H, m), 1.94-1.94 (2H, brm), 1.77-1.74 (2H, m), 1.42 (9H, s).

MS (EI, m/z): 355 $(M)^+$.

Example 80-2

t-Butyl 4-[(5-phenylpyrimidin-2-yl)oxy]piperidine-1-carboxylate

Potassium carbonate (1.73 g, 12.5 mmol) and tetrakis(triphenylphosphine)palladium (242 mg, 0.0209 mmol) were added sequentially to a 1,2-dimethoxyethane-water mixed solution (5.0 ml, 4:1, v/v) of t-butyl 4-[(5-bromopyrimidin-2-yl)oxy]piperidine-1-carboxylate (750 mg, 2.09 mmol) and phenylboronic acid (382 mg, 3.14 mmol), under nitrogen stream, and stirring was carried out overnight under heating to reflux. After completion of the reaction, the reaction solution was cooled to room temperature, and water was added, followed by extraction with ethyl acetate. The extract was washed sequentially with water, a

saturated aqueous sodium hydrogencarbonate solution, water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., 40+M) to afford t-butyl 4-[(5-phenylpyrimidin-2-yl)oxy]piperidine-1-carboxylate (584 mg, yield 79%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.68 (2H, s), 7.45-7.40 (5H, m), 5.23-5.18 (1H, m), 3.80-3.79 (2H, m), 3.33-3.26 (2H, m), 2.01-1.99 (2H, m), 1.83-1.80 (2H, m), 1.41 (9H, s).

MS (FAB, m/z): 455 $(M+H)^+$.

Example 80-3

t-Butyl [(1S)-2-methyl-1-({4-[(5-phenylpyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate

Analogously to Example 23-2, 5-phenyl-2-[(piperidin-4-yl)oxy]pyrimidine hydrochloride (0.476 mg) was obtained from t-butyl 4-[(5-phenylpyrimidin-2-yl)oxy]piperidine-1-carboxylate (580 mg, 1.63 mmol) as a colorless solid. The resulting compound (476 mg, 1.63 mmol) was condensed with N-(t-butoxycarbonyl)-L-valine (532 mg, 2.45 mmol) to afford t-butyl [(1S)-2-methyl-1-({4-[(5-phenylpyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate (740 mg, yield 100%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.68 (2H, s), 7.48-7.40 (5H, m), 5.32 (2H, s), 4.49 (1H, dd, J=7.2 Hz, 3.6 Hz), 3.76-3.62 (4H, m), 2.02-1.89 (5H, m), 1.41 (9H, s), 0.94 (3H, d, J=6.8 Hz), 0.86 (3H, d, J=6.8 Hz).

MS (FAB, m/z): 397 $(M+H)^+$.

Example 80-4

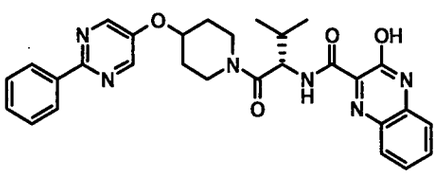
3-Hydroxy-N-[(1S)-2-methyl-1-({4-[(5-phenylpyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Analogously to Example 1-3, (2S)-3-methyl-1-oxo-1-{4-[(5-phenylpyrimidin-2-yl)oxy]piperidin-1-yl}butan-2-amine hydrochloride (0.636 mg) was obtained from t-butyl [(1S)-2-methyl-1-({4-[(5-phenylpyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate (740 mg, 1.63 mmol) as a white solid. The resulting compound (200 mg, 0.512 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (136 mg, 0.784 mmol) to afford the desired title compound (130 mg, yield 48%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6, 500 MHz) δ: 12.86 (1H, brs), 9.60 (1H, brs), 8.97 (2H, d,

J=4.4 Hz), 7.90 (1H, d, J=7.6 Hz), 7.76 (2H, d, J=7.6 Hz), 7.66 (1H, t, J=7.6 Hz), 7.54 (2H, t, J=7.6 Hz), 7.45-7.40 (3H, m), 5.34-5.32 (1H, br m), 4.96 (1H, q, J=7.6 Hz), 4.11-3.99 (2H, m), 3.65-3.28 (2H, m), 2.06-1.75 (5H, m), 1.07 (3H, d, J=6.8 Hz), 0.99 (3H, d, J=6.8 Hz).
IR (KBr) cm^{-1}: 2960, 1685, 1635, 1525, 1440, 1370.
MS (ESI, m/z): 527 $(M+H)^+$.
HRMS (ESI, m/z): 527.2422 (Calcd for $C_{29}H_{31}N_6O_4$: 527.2406).

Example 81



3-Hydroxy-N-[(1S)-2-methyl-1-({4-[(2-phenylpyrimidin-5-yl)oxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Example 81-1

t-Butyl [(1S)-1-({4-[(2-chloropyrimidin-5-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate

Analogously to Example 64-1, t-butyl [(1S)-1-({4-[(2-chloropyrimidin-5-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (575 mg, yield 42%) was obtained from 2-chloro-5-fluoropyrimidine (452 mg, 3.66 mmol) and t-butyl 4-hydroxypiperidine-1-carboxylate (1.00 g, 3.32 mmol) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.29 (2H, s), 5.33 (1H, d, J=9.2 Hz), 4.65-4.60 (1H, m), 4.45 (1H, dd, J=9.2 Hz, 5.6 Hz), 3.75-3.57 (4H, m), 1.96-1.88 (5H, m), 1.40 (9H, s), 0.94 (3H, d, J=6.8 Hz), 0.87 (3H, d, J=6.8 Hz).
MS (FAB, m/z): 413 $(M+H)^+$.

Example 81-2

t-Butyl [(1S)-2-methyl-1-({4-[(2-phenylpyrimidin-5-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate

Analogously to Example 80-2, t-butyl [(1S)-2-methyl-1-({4-[(2-phenylpiperidin-5-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate (297 mg, yield 94%) was obtained from t-butyl [(1S)-1-({4-[(2-chloropyrimidin-5-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (280 mg, 8.92 mmol) and phenylboronic acid (163 mg, 1.34 mmol) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.47 (2H, s), 8.34-8.32 (2H, m), 7.47-7.45 (3H, m), 5.32 (1H, d, J=9.2 Hz), 4.70-4.64 (1H, m), 4.48 (1H, dd, J=9.2 Hz, 5.6 Hz), 3.89-3.47 (4H, m), 2.09-1.87 (5H, m), 1.43 (9H, s), 0.97 (3H, d, J=6.8 Hz), 0.88 (3H, d, J=6.8 Hz).

MS (FAB, m/z): 455 $(M+H)^+$.

Example 81-3

3-Hydroxy-N-[(1S)-2-methyl-1-({4-[(2-phenylpyrimidin-5-yl)oxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Analogously to Example 1-3, (2S)-3-methyl-1-oxo-1-{4-[(2-phenylpyrimidin-5-yl)oxy]piperidin-1-yl}butan-2-amine hydrochloride (255 mg) was obtained from t-butyl [(1S)-2-methyl-1-({4-[(2-phenylpiperidin-5-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate (297 mg, 0.653 mmol) as a white solid.

The resulting compound (127 mg, 0.325 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (93.0 mg, 0.487 mmol) under nitrogen stream to afford the desired title compound (80.0 mg, yield 47%) as a pale yellow solid.

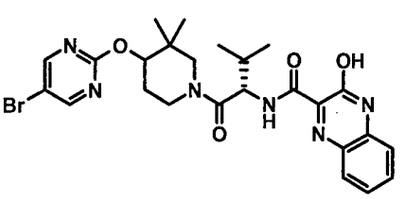
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.86 (1H, brs), 9.66 (1H, brs), 8.75 (2H, d, J=5.6 Hz), 8.34 (2H, d, J=7.6 Hz), 7.88 (1H, t, J=6.8 Hz), 7.66 (1H, t, J=7.6 Hz), 7.53-7.52 (3H, m), 7.41-7.39 (2H, m), 4.96-4.93 (2H, m), 4.05-3.95 (2H, m), 3.63-3.27 (2H, m), 2.11-2.07 (3H, m), 1.79-1.63 (2H, m), 0.99-0.98 (6H, m).

IR (KBr) cm^{-1}: 2965, 1690, 1645, 1525, 1435, 1270.

MS (ESI, m/z): 527 $(M+H)^+$.

HRMS (ESI, m/z): 527.2406 (Calcd for $C_{29}H_{31}N_6O_4$: 527.2406).

Example 82



N-[(1S)-1-({4-[(5-Bromopyrimidin-2-yl)oxy]-3,3-dimethylpiperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 82-1

t-Butyl 3,3-dimethyl-4-oxopiperidine-1-carboxylate

Methyl iodide (2.75 ml, 44.2 mmol) and 63% sodium hydride (2.29 g, 60.2 mmol) were added to a tetrahydrofuran solution (80 ml) of t-butyl 4-oxopiperidine-1-carboxylate (4.00 g, 20.1 mmol), at 0°C, under nitrogen stream, and stirring was carried out at 60°C for 5 hours. Water was added to the reaction solution under ice cooling, followed by extraction with ethyl acetate and sequential washing with water, a saturated aqueous sodium hydrogencarbonate solution, water and saline, and then the

resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., Si, 40+M) to afford t-butyl 3,3-dimethyl-4-oxopiperidine-1-carboxylate (2.17 g, yield 48%) as a white solid.

^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 3.76-3.74 (2H, brm), 3.47-3.45 (2H, brm), 2.52 (2H, t, J=6.4 Hz), 1.53 (9H, s), 1.14 (6H, s).

MS (FAB, m/z): 228 $(M+H)^+$.

Example 82-2

t-Butyl 4-[(5-bromopyrimidin-2-yl)oxy]-3,3-dimethylpiperidine-1-carboxylate.

Sodium borohydride (433 mg, 11.5 mmol) was added to a methanol solution (50 ml) of t-butyl 3,3-dimethyl-4-oxopiperidine-1-carboxylate (2.17 g, 9.55 mmol), at 0°C, under nitrogen stream, and stirring was carried out at room temperature for 3 hours. Water was added to the reaction solution under ice cooling, followed by extraction with ethyl acetate and sequential washing with water, a saturated aqueous sodium hydrogencarbonate solution, water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated to afford t-butyl 4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (2.19 g) as a colorless oil.

Analogously to Example 64-1, t-butyl 4-[(5-bromopyrimidin-2-yl)oxy]-3,3-dimethylpiperidine-1-carboxylate (1.41 g, yield 67%) was obtained from the resulting compound (1.25 g, 5.45 mmol) and 5-bromo-2-chloropyrimidine (1.58 g, 8.18 mmol) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.54 (2H, s), 4.90 (1H, dd, J=7.6 Hz, 4.0 Hz), 3.78 (1H, brs), 3.56 (1H, brs), 3.36-3.31 (1H, m), 3.05 (1H, d, J=13.6 Hz), 1.98 (1H, brs), 1.78 (1H, brs), 1.49 (9H, s), 1.07 (3H, s), 1.03 (3H, s).

MS (FAB, m/z): 411 $(M+H)^+$.

Example 82-3

t-Butyl [(1S)-1-({4-[(5-bromopyrimidin-2-yl)oxy]-3,3-dimethylpiperidin-1-yl}carbonyl)-2-methylpropyl]carbamate

Analogously to Example 23-2, 5-bromo-2-[(3,3-dimethylpiperidin-4-yl)oxy]pyrimidine hydrochloride (0.251 mg) was obtained from t-butyl 4-[(5-bromopyrimidin-2-yl)oxy]-3,3-dimethylpiperidine-1-carboxylate (300 mg, 0.777 mmol) as a white solid. The resulting compound (251 mg, 0.777 mmol) was condensed with N-(t-butoxycarbonyl)-L-valine (253 mg, 1.16

mmol) to afford t-butyl [(1S)-1-({4-[(5-bromopyrimidin-2-yl)oxy]-3,3-dimethylpiperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (322 mg, yield 85%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.49 (2H, s), 5.31-5.23 (1H, m), 4.90-4.85 (1H, m), 4.51-4.45 (1H, m), 4.09-4.05 (1H, m), 3.54-3.21 (3H, m), 2.09-1.74 (3H, m), 1.40 (9H, s), 1.05-0.85 (12H, m);

MS (FAB, m/z): 485 $(M+H)^+$.

Example 82-4

N-[(1S)-1-({4-[(5-Bromopyrimidin-2-yl)oxy]-3,3-dimethylpiperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 1-3, (2S)-1-{4-[(5-bromopyrimidin-2-yl)oxy]-3,3-dimethylpiperidin-1-yl}-3-methyl-1-oxobutan-2-amine hydrochloride (280 mg) was obtained from t-butyl [(1S)-1-({4-[(5-bromopyrimidin-2-yl)oxy]-3,3-dimethylpiperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (322 mg, 0.663 mmol) as a white solid. The resulting compound (140 mg, 0.332 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (95.0 mg, 0.497 mmol) to afford the desired title compound (70.0 mg, yield 38%) as a pale yellow solid.

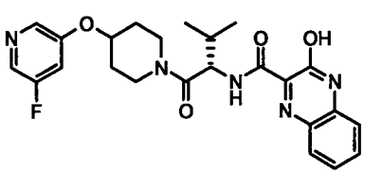
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.80 (1H, brs), 9.50 (1H, brs), 8.72 (2H, s), 7.83-7.82 (1H, m), 7.60 (1H, t, J=7.6 Hz), 7.35-7.34 (2H, m), 4.92-4.88 (2H, m), 3.73-3.01 (4H, m), 2.07-1.99 (3H, m), 0.95-0.90 (12H, m).

IR (KBr) cm^{-1}: 2965, 1690, 1640, 1540, 1425, 1325.

MS (ESI, m/z): 579 $(M+Na)^+$.

HRMS (ESI, m/z): 579.1329 (Calcd for $C_{25}H_{29}BrN_6NaO_4$: 579.1331).

Example 83



N-[(1S)-1-({4-[(5-Fluoropyridin-3-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 83-1

t-Butyl 4-[(5-fluoropyridin-3-yl)oxy]piperidine-1-carboxylate

t-Butyl 4-hydroxypiperidine-1-carboxylate (1.04 g, 5.00 mmol) was added to a N,N-dimethylformamide suspension (5.0 ml) of 60% sodium hydride (229 mg, 6.00 mmol), at 0°C, and stirring was carried out at room temperature for 30 minutes. Further, at 0°C, 3,5-difluoropyridine (645 mg, 5.50 mmol) was added, and stirring was carried out for 16.5 hours.

Water was added to the reaction solution, followed by extraction with ethyl acetate. The extract was washed sequentially with water and saline, and then dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by silica gel column chromatography to afford t-butyl 4-[(5-fluoropyridin-3-yl)oxy]piperidine-1-carboxylate (1.48 g, yield 99%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.16-8.11 (2H, m), 6.96 (1H, dt, J=10.2, 2.3 Hz), 4.52-4.47 (1H, m), 3.73-3.67 (2H, m), 3.39-3.33 (2H, m), 1.99-1.73 (4H, m), 1.47 (9H, s).

MS (ESI, m/z): 297 $(M+H)^+$.

Example 83-2

t-Butyl [(1S)-1-({4-[(5-fluoropyridin-3-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate

Concentrated hydrochloric acid (5.0 ml) was added to an ethanol solution (10 ml) of t-butyl 4-[(5-fluoropyridin-3-yl)oxy]piperidine-1-carboxylate (1.48 g, 4.99 mmol), at 0°C, and stirring was carried out under room temperature for 16 hours. The reaction solution was concentrated to afford 3-fluoro-5-(piperidin-4-yloxy)pyridine hydrochloride. This product was used as it is in the next reaction without purification.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.44 g, 7.49 mmol) was added to a methylene chloride solution (50 ml) of the resulting compound, N-(t-butoxycarbonyl)-L-valine (1.09 g, 4.99 mmol), 1-hydroxybenzotriazole monohydrate (810 mg, 5.99 mmol) and N-methylmorpholine (2.75 ml, 25.0 mmol), at room temperature, and stirring was carried out at room temperature overnight. Water was added to the reaction solution, followed by extraction with methylene chloride, sequential washing with a saturated aqueous sodium hydrogencarbonate solution, water and saline, and drying over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by silica gel column chromatography to afford t-butyl [(1S)-1-({4-[(5-fluoropyridin-3-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (1.89 g, yield 96%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.16 (1H, s), 8.13 (1H, d, J=2.3 Hz), 6.96 (1H, dt, J=10.2, 2.3 Hz), 5.34-5.30 (1H, m), 4.64-4.55 (1H, m), 4.51-4.47 (1H, m), 3.87-3.48 (4H, m), 2.04-1.81 (5H, m), 1.44 (9H, s), 0.98 (3H, d, J=7.0 Hz), 0.90 (3H, d, J=6.6 Hz).

MS (ESI, m/z): 396 $(M+H)^+$.

Example 83-3

(2S)-1-{4-[(5-Fluoropyridin-3-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine dihydrochloride

Concentrated hydrochloric acid (4.8 ml) was added to an ethanol solution (9.6 ml) of t-butyl [(1S)-1-({4-[(5-fluoropyridin-3-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (1.89 g, 4.78 mmol), at 0°C, and stirring was carried out at room temperature for 2 days. The reaction solution was concentrated to afford (2S)-1-{4-[(5-fluoropyridin-3-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine dihydrochloride (1.85 g, yield 100%) as a colorless amorphous substance.

^{1}H-NMR (CD_3OD, 400 MHz) δ: 8.65-8.63 (2H, m), 8.34 (1H, dt, J=10.3, 2.2 Hz), 5.06-4.94 (1H, m), 4.40 (1H, d, J=5.1 Hz), 4.13-3.45 (4H, m), 2.23-1.80 (5H, m), 1.13-1.02 (6H, m).

MS (ESI, m/z): 296 $(M+H)^+$.

Example 83-4

N-[(1S)-1-({4-[(5-Fluoropyridin-3-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (156 mg, 0.815 mmol) was added to a methylene chloride solution (5.4 ml) of (2S)-1-{4-[(5-fluoropyridin-3-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine dihydrochloride (200 mg, 0.543 mmol), 3-hydroxyquinoxaline-2-carboxylic acid (106 mg, 0.543 mmol), 1-hydroxybenzotriazole monohydrate (88.1 mg, 0.652 mmol) and N-methylmorpholine (0.299 ml, 2.72 mmol), at room temperature, and stirring was carried out at room temperature overnight. Water was added to the reaction solution, followed by extraction with methylene chloride, and the extract was washed sequentially with a saturated aqueous sodium hydrogencarbonate solution, water and saline, and dried over anhydrous sodium sulfate. After the organic layer was concentrated and the resulting residue was purified by silica gel column chromatography, the resulting residue was suspended in a mixed solvent of ethanol-diethyl ether, and the solid substance was collected by filtration to afford the desired title compound (160 mg, yield 63%) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 12.56 (1H, brs), 10.12 (1H, brs), 8.20-7.99 (3H, m), 7.66-7.31 (3H, m), 7.02-6.96 (1H, m), 5.10-5.05 (1H, m), 4.70-4.61 (1H, m), 4.03-3.67 (4H, m), 2.39-1.89 (5H, m), 1.15-1.10 (6H, m).

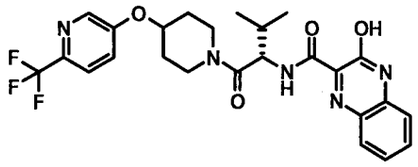
IR (KBr) cm^{-1}: 2960, 1690, 1640, 1530, 1430.

MS (ESI, m/z): 468 $(M+H)^+$.

HRMS (ESI, m/z): 490.1857 (Calcd for $C_{24}H_{26}FN_5NaO_4$: 490.1867).

Anal. Calcd for $C_{24}H_{26}FN_5O_4$: C, 61.66; H, 5.61; N, 14.98; F, 4.06. Found: C, 61.44; H, 5.71; N, 14.87; F, 4.21.

Example 84



3-Hydroxy-N-{(1S)-2-methyl-1-[(4-{[6-(trifluoromethyl)pyridin-3-yl]oxy}piperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide

Example 84-1

t-Butyl {(1S)-2-methyl-1-[(4-{[6-(trifluoromethyl)pyridin-3-yl]oxy}piperidin-1-yl)carbonyl]propyl}carbamate

A 40% toluene solution of diisopropyl azodicarboxylate (2.10 ml, 3.99 mmol) was added to a toluene solution (15 ml) of t-butyl {(1S)-1-[(4-hydroxypiperidin-1-yl)carbonyl]-2-methylpropyl}carbamate (1.00 g, 3.33 mmol) and 2-(trifluoromethyl)pyridin-5-ol (597 mg, 3.33 mmol) and triphenylphosphine (1.05 g, 3.99 mmol), at room temperature, and stirring was carried out at the same temperature for 2 days. The reaction solution was concentrated and the resulting residue was diluted with ethyl acetate, followed by sequential washing with a 1N aqueous sodium hydroxide solution, water and saline, and the resulting organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by silica gel column chromatography to afford t-butyl {(1S)-2-methyl-1-[(4-{[6-(trifluoromethyl)pyridin-3-yl]oxy}piperidin-1-yl)carbonyl]propyl}carbamate (1.11 g, yield 75%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.39 (1H, s), 7.63 (1H, d, J=8.6 Hz), 7.30 (1H, dd, J=8.6 Hz, 2.7 Hz), 5.31 (1H, d, J=8.2 Hz), 4.74-4.66 (1H, m), 4.51-4.48 (1H, m), 3.86-3.54 (4H, m), 2.06-1.84 (5H, m), 1.44 (9H, s), 0.98 (3H, d, J=6.6 Hz), 0.90 (3H, d, J=6.6 Hz).

MS (ESI, m/z): 346 $(M+H)^+$.

Example 84-2

(2S)-3-Methyl-1-oxo-1-(4-{[6-(trifluoromethyl)pyridin-3-yl]oxy}piperidin-1-yl)butan-2-amine dihydrochloride

Concentrated hydrochloric acid (2.5 ml) was added to an ethanol solution (5.0 ml) of t-butyl {(1S)-2-methyl-1-[(4-{[6-(trifluoromethyl)pyridin-3-yl]oxy}piperidin-1-

yl)carbonyl]propyl}carbamate (1.11 g, 2.49 mmol), at 0°C, and stirring was carried out at room temperature overnight. The reaction solution was concentrated to afford (2S)-3-methyl-1-oxo-1-(4-{[6-(trifluoromethyl)pyridin-3-yl]oxy}piperidin-1-yl)butan-2-amine dihydrochloride (970 mg, yield 100%) as a colorless amorphous substance.

^{1}H-NMR (CD_3OD, 400 MHz) δ: 8.39 (1H, dd, J=9.0 Hz, 2.7 Hz), 7.76 (1H, d, J=9.0 Hz), 7.61 (1H, d, J=8.6 Hz), 4.35 (1H, d, J=4.7 Hz), 4.09-3.46 (5H, m), 2.21-1.77 (5H, m), 1.11 (3H, d, J=7.0 Hz), 1.02 (3H, dd, J=6.8 Hz, 1.4 Hz).

MS (ESI, m/z): 346 $(M+H)^+$.

Example 84-3

3-Hydroxy-N-{(1S)-2-methyl-1-[(4-{[6-(trifluoromethyl)pyridin-3-yl]oxy}piperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (137 mg, 0.717 mmol) was added to a methylene chloride solution (4.8 ml) of (2S)-3-methyl-1-oxo-1-(4-{[6-(trifluoromethyl)pyridin-3-yl]oxy}piperidin-1-yl)butan-2-amine dihydrochloride (200 mg, 0.478 mmol), 3-hydroxyquinoxaline-2-carboxylic acid (93.7 mg, 0.478 mmol), 1-hydroxybenzotriazole monohydrate (77.5 mg, 0. 574 mmol) and N-methylmorpholine (0.263 ml, 2.39 mmol), at room temperature, and stirring was carried out at room temperature overnight. Water was added to the reaction solution, followed by extraction with methylene chloride, and the extract was washed sequentially with a saturated aqueous sodium hydrogencarbonate solution, water and saline, and dried over anhydrous sodium sulfate. After the organic layer was concentrated and the resulting residue was purified by silica gel column chromatography, the resulting residue was suspended in a mixed solvent of ethanol-diethyl ether, and then the solid substance was collected by filtration to afford the desired title compound (145 mg, yield 59%) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 12.08 (1H, brs), 10.15 (1H, brs), 8.41 (1H, dd, J=10.6 Hz, 2.7 Hz), 8.02 (1H, brs), 7.66-7.30 (5H, m), 5.09-5.04 (1H, m), 4.78-4.70 (1H, m), 4.10-3.64 (4H, m), 2.35-1.95 (5H, m), 1.14-1.09 (6H, m).

IR (KBr) cm^{-1}: 2965, 1685, 1640, 1530, 1340.

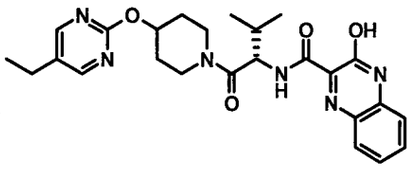
MS (ESI, m/z): 518 $(M+H)^+$.

HRMS (ESI, m/z): 518.2016 (Calcd for $C_{25}H_{27}F_3N_5O_4$: 518.2015).

Anal. Calcd for $C_{25}H_{26}F_3N_5O_4 \cdot 0.5H_2O$: C, 57.03; H, 5.17; N, 13.30; F, 10.83.

Found: C, 56.82; H, 4.98; N, 13.03; F, 10.89.

Example 85



N-[(1S)-1-({4-[(5-Ethylpyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 85-1

t-Butyl 4-[(5-ethylpyrimidin-2-yl)oxy]piperidine-1-carboxylate

t-Butyl 4-hydroxypiperidine-1-carboxylate (1.04 g, 5.00 mmol) was added to a N,N-dimethylformamide suspension (5.0 ml) of 60% sodium hydride (229 mg, 6.00 mmol), at 0°C, and stirring was carried out at room temperature for 30 minutes. 2-chloro-5-ethylpyrimidine (0.689 ml, 5.50 mmol) was added to the reaction solution, at 0°C, and stirring was carried out for a further 1 hour. Water was added to the reaction solution, followed by extraction with ethyl acetate, and the extract was washed sequentially with water and saline, and dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by silica gel column chromatography to afford t-butyl 4-[(5-ethylpyrimidin-2-yl)oxy]piperidine-1-carboxylate (1.03 g, yield 67%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.33 (2H, s), 5.18-5.12 (1H, m), 3.83-3.77 (2H, m), 3.34-3.27 (2H, m), 2.58 (2H, q, J=7.6 Hz), 2.02-1.97 (2H, m), 1.84-1.76 (2H, m), 1.47 (9H, s), 1.25 (3H, t, J=7.6 Hz).

MS (ESI, m/z): 308 $(M+H)^+$, 252 $(M+H-tBu)^+$, 208 $(M+H-BOC)^+$.

Example 85-2

t-Butyl [(1S)-1-({4-[(5-ethylpyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate

Concentrated hydrochloric acid (3.4 ml) was added to an ethanol solution (6.8 ml) of t-butyl 4-[(5-ethylpyrimidin-2-yl)oxy]piperidine-1-carboxylate (1.03 g, 3.35 mmol), at 0°C, and stirring was carried out at room temperature overnight. The reaction solution was concentrated to afford 5-ethyl-2-(piperidin-4-yloxy)pyrimidine dihydrochloride. This product was used as it is in the next reaction without purification. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (964 mg, 5.03 mmol) was added to a methylene chloride solution (34 ml) of the resulting compound, N-(t-butoxycarbonyl)-L-valine (728 mg, 3.35 mmol), 1-hydroxybenzotriazole monohydrate (543 mg, 4.02 mmol) and N-methylmorpholine (1.11 ml, 10.1 mmol), at room temperature, and stirring

was carried out at room temperature for 6 days. Water was added to the reaction solution, followed by extraction with ethyl acetate, and the extract was washed sequentially with a saturated aqueous sodium hydrogencarbonate solution, water and saline, and dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by silica gel column chromatography to afford t-butyl [(1S)-1-({4-[(5-ethylpyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (1.20 g, yield 88%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.34 (2H, s), 5.38-5.35 (1H, m), 5.29-5.22 (1H, m), 4.53-4.49 (1H, m), 4.00-3.44 (4H, m), 2.59 (2H, q, J=7.6 Hz), 2.10-1.84 (5H, m), 1.44 (9H, s), 1.25 (3H, t, J=7.6 Hz), 0.97 (3H, dd, J=6.8 Hz, 2.2 Hz), 0.90-0.88 (3H, m).

MS (ESI, m/z): 407 $(M+H)^+$.

Example 85-3

(2S)-1-{4-[(5-Ethylpyrimidin-2-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine dihydrochloride

Concentrated hydrochloric acid (3.0 ml) was added to an ethanol solution (6.0 ml) of t-butyl [(1S)-1-({4-[(5-ethylpyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (1.20 g, 2.95 mmol), at 0°C, and stirring was carried out at room temperature overnight. The reaction solution was concentrated to afford (2S)-1-{4-[(5-ethylpyrimidin-2-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine dihydrochloride (1.20 g, yield 100%) as a colorless amorphous substance.

^{1}H-NMR (CD_3OD, 400 MHz) δ: 8.75-8.69 (2H, m), 5.54-5.47 (1H, m), 4.38 (1H, d, J=4.7 Hz), 4.07-3.48 (4H, m), 2.75-2.69 (2H, m), 2.21-1.86 (5H, m), 1.29 (3H, t, J=7.4 Hz), 1.12 (3H, d, J=7.0 Hz), 1.03 (3H, d, J=6.6 Hz).

MS (ESI, m/z): 307 $(M+H)^+$.

Example 85-4

N-[(1S)-1-({4-[(5-Ethylpyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (152 mg, 0.633 mmol) was added to a methylene chloride solution (5.3 ml) of (2S)-1-{4-[(5-ethylpyrimidin-2-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine dihydrochloride (200 mg, 0.527 mmol), 3-hydroxyquinoxaline-2-carboxylic acid (103 mg, 0.527 mmol), 1-hydroxybenzotriazole monohydrate (85.5 mg, 0.633 mmol) and N-methylmorpholine (0.174 ml, 2.11 mmol), at room temperature, and stirring

was carried out at room temperature overnight. Water was added to the reaction solution, followed by extraction with methylene chloride, and the extract was washed sequentially with a saturated aqueous sodium hydrogencarbonate solution, water and saline, and dried over anhydrous sodium sulfate. After the organic layer was concentrated and the resulting residue was purified by silica gel column chromatography, the resulting residue was suspended in a mixed solvent of ethanol-diethyl ether, and subsequently the solid substance was collected by filtration to afford the desired title compound (206 mg, yield 82%) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 12.82-12.64 (1H, m), 10.19 (1H, brs), 8.36 (2H, d, J=6.3 Hz), 8.02 (1H, t, J=9.2 Hz), 7.62-7.27 (3H, m), 5.32-5.07 (2H, m), 4.02-3.68 (4H, m), 2.63-2.56 (2H, m), 2.34-1.96 (5H, m), 1.29-1.24 (3H, m), 1.14-1.09 (6H, m).

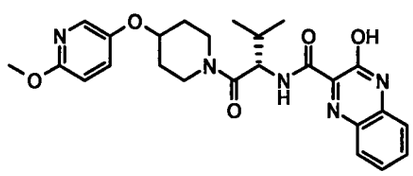
IR (KBr) cm^{-1}: 2965, 1690, 1630, 1525, 1435.

MS (ESI, m/z): 479 $(M+H)^+$.

HRMS (ESI, m/z): 501.2226 (Calcd for $C_{25}H_{30}N_6ONaO_4$: 501.2219).

Anal. Calcd for $C_{25}H_{30}N_6O_4$: C, 62.75; H, 6.32; N, 17.56. Found: C, 62.78; H, 6.30; N, 17.45.

Example 86



3-Hydroxy-N-[(1S)-1-({4-[(6-methoxypyridin-3-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]quinoxaline-2-carboxamide

Example 86-1

t-Butyl [(1S)-1-({4-[(6-methoxypyridin-3-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate

A 40% toluene solution of diisopropyl azodicarboxylate (0.690 ml, 1.31 mmol) was added to a toluene solution (5.0 ml) of t-butyl {(1S)-1-[(4-hydroxypiperidin-1-yl)carbonyl]-2-methylpropyl}carbamate (329 mg, 1.09 mmol), 6-methoxypyridin-3-ol (137 mg, 1.09 mmol) and triphenylphosphine (345 mg, 1.31 mmol), at room temperature, and stirring was carried out at room temperature for 6 days. The reaction solution was concentrated and the resulting residue was diluted with ethyl acetate, followed by sequential washing with a 1N aqueous sodium hydroxide solution, water and saline, and drying over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by

silica gel column chromatography to afford t-butyl [(1S)-1-({4-[(6-methoxypyridin-3-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (273 mg, yield 61%) as a colorless amorphous substance.
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.84 (1H, d, J=2.7 Hz), 7.23 (1H, dd, J=9.0, 2.7 Hz), 6.70 (1H, d, J=9.0 Hz), 5.34 (1H, d, J=9.0 Hz), 4.51-4.38 (2H, m), 3.90 (3H, s), 3.88-3.42 (4H, m), 2.02-1.78 (5H, m), 1.44 (9H, s), 0.98-0.88 (6H, m).
MS (ESI, m/z): 408 $(M+H)^+$.

Example 86-2
(2S)-1-{4-[(6-Methoxypyridin-3-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine dihydrochloride

Concentrated hydrochloric acid (1.0 ml) was added to an ethanol solution (2.0 ml) of t-butyl [(1S)-1-({4-[(6-methoxypyridin-3-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (273 mg, 0.669 mmol), at 0°C, and stirring was carried out at room temperature overnight. The reaction solution was concentrated to afford (2S)-1-{4-[(6-methoxypyridin-3-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine dihydrochloride (270 mg, yield 100%) as a colorless amorphous substance.
^{1}H-NMR (CD_3OD, 400 MHz) δ: 8.19-8.13 (2H, m), 7.51-7.48 (1H, m), 4.82-4.73 (1H, m), 4.37 (1H, d, J=5.1 Hz), 4.16 (3H, s), 4.09-3.43 (4H, m), 2.21-1.75 (5H, m), 1.11 (3H, d, J=7.0 Hz), 1.02 (3H, d, J=6.6 Hz).
MS (ESI, m/z): 308 $(M+H)^+$.

Example 86-3
3-Hydroxy-N-[(1S)-1-({4-[(6-methoxypyridin-3-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]quinoxaline-2-carboxamide

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (193 mg, 1.00 mmol) was added to a methylene chloride solution (6.7 ml) of (2S)-1-{4-[(6-methoxypyridin-3-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine dihydrochloride (255 mg, 0.669 mmol), 3-hydroxyquinoxaline-2-carboxylic acid (131 mg, 0.669 mmol), 1-hydroxybenzotriazole monohydrate (109 mg, 0.803 mmol) and N-methylmorpholine (0.221 ml, 2.68 mmol), at room temperature, and stirring was carried out at room temperature for 3 days. Water was added to the reaction solution, followed by extraction with methylene chloride, and the extract was washed sequentially with a saturated aqueous sodium hydrogencarbonate solution, water and saline, and dried over anhydrous sodium sulfate. After the organic layer was concentrated and the resulting residue was purified by silica gel column chromatography, the

resulting residue was suspended in a mixed solvent of ethanol-diethyl ether, and subsequently the solid substance was collected by filtration to afford the desired title compound (253 mg, yield 79%) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 12.54 (1H, brs), 10.16 (1H, brs), 8.02-7.98 (1H, m), 7.86 (1H, dd, J=7.4 Hz, 2.7 Hz), 7.61-7.22 (4H, m), 6.71 (1H, dd, J=8.8 Hz, 5.3 Hz), 5.10-5.05 (1H, m), 4.49-4.44 (1H, m), 3.91-3.74 (7H, m), 2.36-1.90 (5H, m), 1.26-1.09 (6H, m).

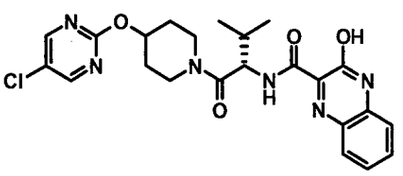
IR (KBr) cm^{-1}: 3430, 2945, 1685, 1640, 1490.

MS (ESI, m/z): 480 $(M+H)^+$.

HRMS (ESI, m/z): 502.2078 (Calcd for $C_{25}H_{29}N_5NaO_5$: 502.2066).

Anal. Calcd for $C_{25}H_{29}N_5O_5$: C, 62.62; H, 6.10; N, 14.60. Found: C, 62.42; H, 6.07; N, 14.58.

Example 87



N-[(1S)-1-({4-[(5-Chloropyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 87-1

t-Butyl [(1S)-1-({4-[(5-chloropyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate

A 40% toluene solution of diisopropyl azodicarboxylate (2.10 ml, 3.99 mmol) was added to a toluene solution (15 ml) of t-butyl {(1S)-1-[(4-hydroxypiperidin-1-yl)carbonyl]-2-methylpropyl}carbamate (1.00 g, 3.33 mmol), 5-chloro-2-hydroxypyrimidine hydrochloride (612 mg, 3.66 mmol) and triphenylphosphine (1.05 g, 3.99 mmol), at room temperature, and stirring was carried out at room temperature for 2 days. The reaction solution was concentrated and the resulting residue was diluted with ethyl acetate, and then the organic layer was washed sequentially with a 1N aqueous sodium hydroxide solution, water and saline, and dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by silica gel column chromatography to afford t-butyl [(1S)-1-({4-[(5-chloropyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (517 mg, yield 38%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.45 (2H, s), 5.36-5.18 (2H, m), 4.52-4.48 (1H, m), 3.98-3.50 (4H, m), 2.10-1.83 (5H, m), 1.44 (9H, s), 0.97 (3H, d,

J=6.3 Hz), 0.89 (3H, dd, J=6.6 Hz, 2.7 Hz).
MS (ESI, m/z): 413 $(M+H)^+$.

Example 87-2
(2S)-1-{4-[(5-Chloropyrimidin-2-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine dihydrochloride

Concentrated hydrochloric acid (1.3 ml) was added to an ethanol solution (2.6 ml) of t-butyl [(1S)-1-({4-[(5-chloropyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (517 mg, 1.25 mmol), at 0°C, and stirring was carried out at room temperature overnight. The reaction solution was concentrated to afford (2S)-1-{4-[(5-chloropyrimidin-2-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine dihydrochloride (456 mg, yield 94%) as a colorless amorphous substance.
^{1}H-NMR (CD_3OD, 400 MHz) δ: 8.59 (2H, d, J=1.6 Hz), 5.36-5.28 (1H, m), 4.35 (1H, d, J=5.1 Hz), 4.07-3.46 (4H, m), 2.23-1.77 (5H, m), 1.11 (3H, d, J=7.0 Hz), 1.02 (3H, d, J=7.0 Hz).
MS (ESI, m/z): 313 $(M+H)^+$.

Example 87-3
N-[(1S)-1-({4-[(5-Chloropyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (149 mg, 0.778 mmol) was added to a methylene chloride solution (5.2 ml) of (2S)-1-{4-[(5-chloropyrimidin-2-yl)oxy]piperidin-1-yl}-3-methyl-1-oxobutan-2-amine dihydrochloride (200 mg, 0.519 mmol), 3-hydroxyquinoxaline-2-carboxylic acid (102 mg, 0.519 mmol), 1-hydroxybenzotriazole monohydrate (84.1 mg, 0.622 mmol) and N-methylmorpholine (0.285 ml, 2.59 mmol), at room temperature, and stirring was carried out at room temperature overnight. Water was added to the reaction solution, followed by extraction with methylene chloride, and the extract was washed sequentially with a saturated aqueous sodium hydrogencarbonate solution, water and saline, and dried over anhydrous sodium sulfate. After the organic layer was concentrated and the resulting residue was purified by silica gel column chromatography, the resulting residue was suspended in a mixed solvent of ethanol-diethyl ether, and then the solid substance was collected by filtration to afford the desired title compound (198 mg, yield 79%) as a yellow solid.
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 12.52 (1H, brs), 10.17 (1H, brs), 8.47-8.46 (2H, m), 8.05-8.00 (1H, m), 7.63-7.26 (3H, m), 5.30-5.06 (2H, m), 4.08-3.63 (4H, m), 2.35-1.91 (5H, m), 1.14-1.09 (6H, m).

IR (KBr) cm^{-1}: 2965, 1690, 1630, 1425.

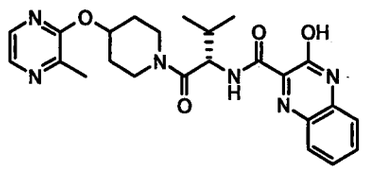
MS (ESI, m/z): 485 $(M+H)^+$.

HRMS (ESI, m/z): 507.1532 (Calcd for $C_{23}H_{25}ClN_6NaO_4$: 507.1524).

Anal. Calcd for $C_{23}H_{25}ClN_6O_4 \cdot 0.1H_2O$: C, 56.76; H, 5.22; N, 17.27; F, 7.28.

Found: C, 56.56; H, 5.07; N, 17.20; F, 7.65.

Example 88



3-Hydroxy-N-[(1S)-2-methyl-1-({4-[(3-methylpyrazin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Example 88-1

t-Butyl [(1S)-2-methyl-1-({4-[(3-methylpyrazin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate

A 40% toluene solution of diisopropyl azodicarboxylate (2.10 ml, 3.99 mmol) was added to a toluene solution (15 ml) of t-butyl {(1S)-1-[(4-hydroxypiperidin-1-yl)carbonyl]-2-methylpropyl}carbamate (1.00 g, 3.33 mmol), 3-methylpyrazin-2-ol (403 mg, 3.66 mmol) and triphenylphosphine (1.05 g, 3.99 mmol), at room temperature, and stirring was carried out at the same temperature overnight. After the reaction solution was concentrated and the resulting residue was diluted with ethyl acetate, the organic layer was washed sequentially with a 1N aqueous sodium hydroxide solution, water and saline, and dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by silica gel column chromatography to afford t-butyl [(1S)-2-methyl-1-({4-[(3-methylpyrazin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate (933 mg, yield 71%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.00 (1H, d, J=2.7 Hz), 7.90-7.88 (1H, m), 5.37-5.30 (2H, m), 4.54-4.50 (1H, m), 3.93-3.48 (4H, m), 2.47 (3H, d, J=6.3 Hz), 2.11-1.79 (5H, m), 1.44 (9H, s), 0.99 (3H, d, J=6.6 Hz), 0.90 (3H, d, J=6.6 Hz).

MS (ESI, m/z): 293 $(M+H)^+$.

Example 88-2

(2S)-3-Methyl-1-{4-[(3-methylpyrazin-2-yl)oxy]piperidin-1-yl}-1-oxobutan-2-amine dihydrochloride

Concentrated hydrochloric acid (2.4 ml) was added to an ethanol

solution (4.8 ml) of t-butyl [(1S)-2-methyl-1-({4-[(3-methylpyrazin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate (933 mg, 2.38 mmol), at 0°C, and stirring was carried out at room temperature overnight. The reaction solution was concentrated to afford (2S)-3-methyl-1-{4-[(3-methylpyrazin-2-yl)oxy]piperidin-1-yl}-1-oxobutan-2-amine dihydrochloride (920 mg, yield 100%) as a colorless amorphous substance.

^{1}H-NMR (CD_3OD, 400 MHz) δ: 8.49-8.47 (1H, m), 8.18-8.16 (1H, m), 5.58-5.49 (1H, m), 4.39 (1H, d, J=4.7 Hz), 4.08-3.53 (4H, m), 2.66 and 2.63 (3H, s), 2.26-1.84 (5H, m), 1.12 (3H, d, J=7.0 Hz), 1.03 (3H, dd, J=7.0, 1.2 Hz).

MS (ESI, m/z): 293 $(M+H)^+$.

Example 88-3

3-Hydroxy-N-[(1S)-2-methyl-1-({4-[(3-methylpyrazin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (157 mg, 0.821 mmol) was added to a methylene chloride solution (5.5 ml) of (2S)-3-methyl-1-{4-[(3-methylpyrazin-2-yl)oxy]piperidin-1-yl}-1-oxobutan-2-amine dihydrochloride (200 mg, 0.547 mmol), 3-hydroxyquinoxaline-2-carboxylic acid (107 mg, 0.547 mmol), 1-hydroxybenzotriazole monohydrate (88.8 mg, 0.657 mmol) and N-methylmorpholine (0.301 ml, 2.74 mmol), at room temperature, and stirring was carried out at room temperature overnight. Water was added to the reaction solution, followed by extraction with methylene chloride, and the extract was washed sequentially with a saturated aqueous sodium hydrogencarbonate solution, water and saline, and dried over anhydrous sodium sulfate. After the organic layer was concentrated and the resulting residue was purified by silica gel column chromatography, the resulting residue was suspended in a mixed solvent of ethanol-diethyl ether, and subsequently the solid substance was collected by filtration to afford the desired title compound (181 mg, yield 71%) as a yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 12.64 (1H, brs), 10.17 (1H, brs), 8.02-8.00 (2H, m), 7.91 (1H, dd, J=6.3 Hz, 2.7 Hz), 7.63-7.38 (3H, m), 5.41-5.34 (1H, m), 5.13-5.08 (1H, m), 4.06-3.68 (4H, m), 2.51 and 2.47 (3H, s), 2.36-1.92 (5H, m), 1.16-1.11 (6H, m).

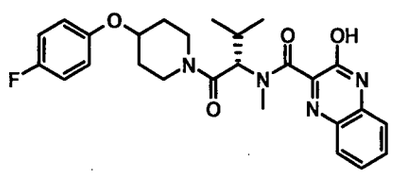
IR (KBr) cm^{-1}: 2960, 1690, 1640, 1540, 1415.

MS (ESI, m/z): 465 $(M+H)^+$.

HRMS (ESI, m/z): 465.2251 (Calcd for $C_{24}H_{29}N_6O_4$: 465.2250).

Anal. Calcd for $C_{24}H_{28}N_6O_4$: C, 62.06; H, 6.08; N, 18.09. Found: C, 61.70; H, 6.05; N, 17.90.

Example 89



N-[(1S)-1-{[4-(4-Fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxy-N-methylquinoxaline-2-carboxamide

Example 89-1

t-Butyl [(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]methylcarbamate

Analogously to Example 2-1, t-butyl [(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]methylcarbamate (530 mg, yield 100%) was obtained from 4-(4-fluorophenoxy)piperidine hydrochloride (300 mg, 1.29 mmol) and N-(t-butoxycarbonyl)-N-methyl-L-valine (300 mg, 1.29 mmol) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.01-6.95 (2H, m), 6.88-6.83 (2H, m), 4.62 (1H, dd, J=10.8 Hz, 4.4 Hz), 4.52-4.35 (1H, m), 4.08-3.92 (1H, m), 3.84-3.75 (1H, m), 3.71-3.60 (1H, m), 3.55-3.31 (1H, m), 2.77 and 2.75 (3H, d, J=2.4 Hz), 2 42-2 31 (1H, m), 1.95-1.61 (4H, m), 1.48 and 1.46 (9H, s), 0.91-0.84 (6H, m).

MS (ESI, m/z): 409 $(M+H)^+$.

Example 89-2

N-[(1S)-1-{[4-(4-Fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxy-N-methylquinoxaline-2-carboxamide

Analogously to Example 2-2, (2S)-1-[4-(4-fluorophenoxy)piperidin-1-yl]-N,3-dimethyl-1-oxobutan-2-amine hydrochloride (400 mg, 100%) was obtained from t-butyl [(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]methylcarbamate (530 mg, 1.29 mmol) as a colorless oil. The resulting compound (100 mg, 0.290 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (60.0 mg, 0.290 mmol) to afford N-[(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxy-N-methylquinoxaline-2-carboxamide (88.0 mg, yield 63%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.74 (1H, brs), 7.81 (1H, d, J=7.8 Hz), 7.67 (1H, d, J=7.3 Hz), 7.61 (1H, d, J=11.2 Hz, 7.3 Hz), 7.38-7.32 (1H, m), 7.15 -7.10 (2H, m), 7.05-7.02 (2H, m), 5.08 (1H, d, J=11.5 Hz), 4.65-4.55 (1H, m), 4.12-4.06 (2H, m), 3.96-3.79 (2H, m), 2.77 and 2.76 (3H, s), 2.07-1.24 (5H, m), 0.97 (3H, dd, J=6.4 Hz, 2.4 Hz), 0.92 (3H, dd, J=6.4

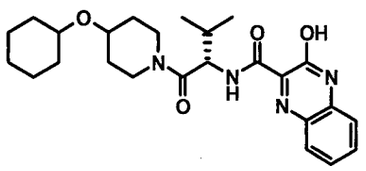
Hz, 3.2 Hz).

IR (ATR) cm^{-1}, 3460, 2960, 1685, 1640, 1505, 1455, 1205, 1055.

MS (ESI, m/z): 503 $(M+Na)^+$.

Anal. Calcd for $C_{26}H_{29}FN_4O_4$: C, 64.99; H, 6.08; F, 3.95; N, 11.66. Found: C, 64.69; H, 6.16; F, 4.14; N, 11.38.

Example 90



N-[(1S)-1-{[4-(Cyclohexyloxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 90-1

t-Butyl 4-(2-cyclohexen-1-yloxy)piperidine-1-carboxylate

Silver oxide (1.48 g) was added to a tetrahydrofuran solution (10 ml) of t-butyl 4-hydroxypiperidine-1-carboxylate (1.00 g, 4.97 mmol) and 3-bromocyclohexene (300 mg, 1.29 mmol), at room temperature, and stirring was carried out at 40°C overnight. After the catalyst was filtered out, the mother liquor was concentrated and the resulting residual material was purified by a medium-pressure preparative liquid chromatograph (manufactured by Yamazen Corporation, W-Prep 2XY) to afford the title compound (467 mg, yield 36%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 5.86-5.82 (1H, m), 5.70 (1H, d, J=7.8 Hz), 4.00-3.95 (1H, m), 3.84-3.76 (2H, m), 3.62-3.56 (1H, m), 3.09-3.02 (2H, m), 2.07-1.50 (10H, m), 1.46 and 1.45 (9H, s).

MS (ESI, m/z): 262 $(M+H)^+$.

Example 90-2

t-Butyl 4-(cyclohexyloxy)piperidine-1-carboxylate

5% Palladium carbon catalyst (60.0 mg) was added to an ethanol solution (10 ml) of t-butyl 4-(2-cyclohexen-1-yloxy)piperidine-1-carboxylate (360 mg, 1.29 mmol), at room temperature, and stirring was carried out at room temperature for 5 hours under hydrogen atmosphere. After the catalyst was filtered out, the mother liquor was concentrated, and the resulting residual material was purified by a medium-pressure preparative liquid chromatograph (manufactured by Yamazen Corporation, W-Prep 2XY) to afford t-butyl 4-(cyclohexyloxy)piperidine-1-carboxylate (211 mg, yield 58%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 3.82-3.75 (2H, m), 3.58-3.52 (1H, m), 3.36-3.30

(1H, m), 3.07-3.01 (2H, m), 1.88-1.70 (8H, m), 1.46 and 1.45 (9H, s), 1.32-1.15 (6H, m).
MS (ESI, m/z): 306 $(M+Na)^+$.

Example 90-3
t-Butyl [(1S)-1-{[4-(cyclohexyloxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate

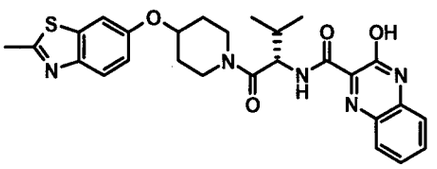
Analogously to Example 23-2, 4-(cyclohexyloxy)piperidine hydrochloride (160 mg, 100%) was obtained from t-butyl 4-(cyclohexyloxy)piperidine-1- (210 mg, 0.740 mmol) as a colorless oil. The resulting compound (160 mg, 0.730 mmol) was condensed with N-(t-butoxycarbonyl)-L-valine (160 mg, 0.730 mmol) to afford t-butyl [(1S)-1-{[4-(cyclohexyloxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate (280 mg, yield 100%) as a colorless amorphous substance.
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 5.36(1H, t, J=9.1 Hz), 4.50-4.46 (1H, m), 3.98-3.89 (1H, m), 3.80-3.71 (1H, m), 3.69-3.63 (1H, m), 3.34-3.28 (3H, m), 1.94-1.71 (7H, m), 1.63 -1.48 (4H, s), 1.43 (9H, s), 1.32-1.18 (4H, m), 0.96 (3H, dd, J=6.4 Hz, 2.4 Hz), 0.86 (3H, dd, J=6.4 Hz, 2.4 Hz).
IR (ATR) cm^{-1}: 2930, 1690, 1420, 1365, 1275, 1230, 1170, 1080.
MS (ESI, m/z): 383 $(M+H)^+$.

Example 90-4
N-[(1S)-1-{[4-(Cyclohexyloxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 2-2, (2S)-1-[4-(cyclohexyloxy)piperidin-1-yl]-3-methyl-1-oxobutan-2-amine hydrochloride (194 mg, 83%) was obtained from t-butyl [(1S)-1-{[4-(cyclohexyloxy)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate (280 mg, 0.730 mmol) as an amorphous substance. The resulting compound (190 mg, 0.600 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (110 mg, 0.600 mmol) to afford N-[(1S)-1-{[4-(cyclohexyloxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide (219 mg, yield 81%) as a pale yellow solid.
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.81 (1H, brs), 9.45 (1H, t, J=8.3 Hz), 7.86 (1H, d, J=8.3 Hz), 7.63 (1H, t, J=7.5 Hz), 7.39-7.36 (1H, m), 4.86 (1H, dd, J=16.1 Hz, 9.3 Hz), 3.95-3.88 (2H, m), 3.70-3.63 (1H, m), 3.39-3.27 (3H, m), 3.19-3.06 (1H, m), 2.51-2.49 (4H, m), 1.92-1.11 (11H, m), 0.95-0.92 (6H, m).
IR (ATR) cm^{-1}: 2930, 1690, 1640, 1530, 1475, 1450, 1090.
MS (ESI, m/z): 455 $(M+H)^+$.

Anal. Calcd for $C_{25}H_{34}N_4O_4$: C, 66.06; H, 7.54; N, 12.33. Found: C, 65.77; H, 7.47; N, 12.33.

Example 91



3-Hydroxy-N-[(1S)-2-methyl-1-({4-[(2-methyl-1,3-benzothiazol-6-yl)oxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Example 91-1

2-Methyl-1,3-benzothiazol-6-ol

A 1N boron bromide methylene chloride solution (8.4 ml, 8.40 mmol) was added to a methylene chloride solution (10 ml) of 6-methoxy-2-methylbenzothiazole (500 mg, 2.79 mmol), at -78°C, under nitrogen stream, and stirring was carried out at 0°C for 1 hour. Water was added to the reaction solution, followed by extraction with methylene chloride. The extract was washed sequentially with a saturated aqueous sodium hydrogencarbonate solution and water, and then dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Yamazen Corporation, W-Prep 2XY) to afford 2-methyl-1,3-benzothiazol-6-ol (103 mg, yield 22%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.66 (1H, d, J=8.8 Hz), 7.23 (1H, d, J=2.4 Hz), 6.94 (1H, dd, J=8.8 Hz, 2.4 Hz), 2.74 (3H, s).

MS (ESI, m/z): 166 $(M+H)^+$.

Example 91-2

t-Butyl [(1S)-2-methyl-1-({4-[(2-methyl-1,3-benzothiazol-6-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate

Analogously to Example 1-2, t-butyl [(1S)-2-methyl-1-({4-[(2-methyl-1,3-benzothiazol-6-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate (214 mg, yield 79%) was obtained from 2-methyl-1,3-benzothiazol-6-ol (100 mg, 0.610 mmol) and t-butyl {(1S)-1-[(4-hydroxypiperidin-1-yl)carbonyl]-2-methylpropyl}carbamate (200 mg, 0.670 mmol) as a colorless amorphous substance.

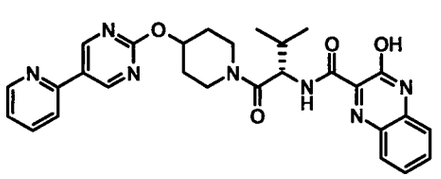
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.83 (1H, d, J=8.8 Hz), 7.32 (1H, d, J=2.0 Hz), 7.05 (1H, dd, J=8.8 Hz, 2.0 Hz), 5.40-5.36 (1H, m), 4.61-4.50 (2H, m), 3.81-3.67 (2H, m), 3.59-3.47 (2H, m), 2.80 (3H, s), 1.99-1.86 (5H, m), 1.44 (9H, s), 0.98 (3H, d, J=6.4 Hz), 0.90 (3H, dd, J=6.4 Hz, 1.5 Hz).

IR (ATR) cm^{-1}: 2965, 1705, 1635, 1450, 1365, 1210, 1165.
MS (ESI, m/z): 448 $(M+H)^+$.

Example 91-3
3-Hydroxy-N-[(1S)-2-methyl-1-({4-[(2-methyl-1,3-benzothiazol-6-yl)oxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Analogously to Example 2-2, (2S)-3-methyl-1-{4-[(2-methyl-1,3-benzothiazol-6-yl)oxy]piperidin-1-yl}-1-oxobutan-2-amine hydrochloride (180 mg, 100%) was obtained from t-butyl [(1S)-2-methyl-1-({4-[(2-methyl-1,3-benzothiazol-6-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate (210 mg, 0.470 mmol) as a colorless oil. The resulting compound (180 mg, 0.470 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (90.0 mg, 0.470 mmol) to afford 3-hydroxy-N-[(1S)-2-methyl-1-({4-[(2-methyl-1,3-benzothiazol-6-yl)oxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide (181 mg, yield 74%) as a yellow solid.
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.78 (1H, brs), 10.20 (1H, brs), 7.99 (1H, s), 7.85 (1H, dd, J=8.8 Hz, 5.9 Hz), 7.61 (1H, brs), 7.51 (1H, brs), 7.34 (2H, dd, J=5.9 Hz, 2.0 Hz), 7.07 (1H, dt, J=9.1 Hz, 2.0 Hz), 5.09 (1H, t, J=7.3 Hz), 4.68-4.61 (1H, m), 4.02-3.73 (4H, m), 2.81 (3H, d, J=2.0 Hz), 2.40-2.17 (2H, m), 2.07-1.91 (3H, m), 1.16-1.09 (6H, m).
IR (KBr) cm^{-1}: 2960, 1690, 1640, 1530, 1455, 1210.
MS (ESI, m/z): 520 $(M+H)^+$.
Anal. Calcd for $C_{27}H_{29}N_5O_4S$: C, 62.41; H, 5.63; N, 13.48. Found: C, 62.17; H, 5.79; N, 13.17.

Example 92



3-Hydroxy-N-[(1S)-2-methyl-1-({4-[(5-pyridin-2-ylpyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide
Example 92-1
t-Butyl 4-[(5-pyridin-2-ylpyrimidin-2-yl)oxy]piperidine-1-carboxylate

Tetrakis(triphenylphosphine)palladium (116 mg, 0.100 mmol) was added to a toluene solution (6.0 ml) of t-butyl 4-[(5-bromopyrimidin-2-yl)oxy]piperidine-1-carboxylate (360 mg, 1.00 mmol) and 2-(tributylstannyl)pyridine (555 mg, 1.51 mmol), under nitrogen stream, and stirring was carried out for 7 hours under heating to reflux. After completion of the reaction, the reaction solution was cooled to room

temperature, and poured into ice water, followed by extraction with ethyl acetate. The extract was washed sequentially with water and saline, and then dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., 25+M) to afford t-butyl 4-[(5-pyridin-2-ylpyrimidin-2-yl)oxy]piperidine-1-carboxylate (183 mg, yield 52%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 9.07 (2H, s), 8.67-8.66 (1H, m), 7.77-7.74 (1H, m), 7.63 (1H, d, J=7.2 Hz), 7.27-7.25 (1H, m), 5.27-5.21 (1H, m), 3.80-3.78 (2H, m), 3.33-3.27 (2H, m), 2.01-1.98 (2H, m), 1.83-1.80 (2H, m), 1.45 (9H, s).

MS (FAB, m/z): 357 $(M+H)^+$.

Example 92-2

t-Butyl [(1S)-2-methyl-1-({4-[(5-pyridin-2-ylpyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate

Analogously to Example 23-2, 2-(piperidin-4-yloxy)-5-pyridin-2-ylpyrimidine dihydrochloride (169 mg) was obtained from t-butyl 4-[(5-pyridin-2-ylpyrimidin-2-yl)oxy]piperidine-1-carboxylate (183 mg, 0.513 mmol) as a white solid. The resulting compound (169 mg, 0.513 mmol) was condensed with N-(t-butoxycarbonyl)-L-valine (167 mg, 0.770 mmol) to afford t-butyl [(1S)-2-methyl-1-({4-[(5-pyridin-2-ylpyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate (212 mg, yield 91%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 9.15 (2H, s), 8.74 (1H, d, J=4.8 Hz), 7.85-7.82 (1H, m), 7.71 (1H, d, J=7.6 Hz), 7.34-7.32 (1H, m), 5.42-5.39 (2H, m), 4.56-4.54 (1H, m), 4.06-3.51 (4H, m), 2.19-1.91 (5H, m), 1.47 (9H, s), 1.01 (3H, d, J=6.8 Hz), 0.93 (3H, d, J=6.8 Hz).

MS (FAB, m/z): 456 $(M+H)^+$.

Example 92-3

3-Hydroxy-N-[(1S)-2-methyl-1-({4-[(5-pyridin-2-ylpyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Analogously to Example 23-3, (2S)-3-methyl-1-oxy-1-{4-[(5-pyridin-2-ylpyrimidin-2-yl)oxy]piperidin-1-yl}butan-2-amine dihydrochloride (200 mg) was obtained from t-butyl [(1S)-2-methyl-1-({4-[(5-pyridin-2-ylpyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate (212 mg, 0.465 mmol) as a white solid.

The resulting compound (100 mg, 0.247 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (71.0 mg, 0.371 mmol) under nitrogen

stream to afford the desired title compound (70.0 mg, yield 54%) as a pale yellow solid.

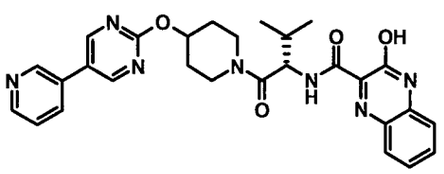
^{1}H-NMR (DMSO-d_6, 500 MHz) δ: 12.86 (1H, br s), 9.56 (1H, br s), 9.29 (2H, d, J=4.0 Hz), 8.72 (1H, d, J=4.4 Hz), 8.07 (1H, d, J=7.6 Hz), 7.96 (1H, t, J=7.6 Hz), 7.90 (1H, dd, J=8.0 Hz, 2.0 Hz), 7.67 (1H, t, J=7.6 Hz), 7.45-7.42 (3H, m), 5.37-5.35 (1H, m), 4.96 (1H, q, J=7.6 Hz), 4.08-4.00 (2H, m), 3.66-3.29 (2H, m), 2.09-1.75 (5H, m), 1.01-0.97 (6H, m).

IR (KBr) cm^{-1}: 2965, 1685, 1630, 1425, 1335.

MS (ESI, m/z): 528 $(M+H)^+$.

HRMS (ESI, m/z): 528.2371 (Calcd for $C_{28}H_{30}N_7O_4$: 528.2359).

Example 93



3-Hydroxy-N-[(1S)-2-methyl-1-({4-[(5-pyridin-3-ylpyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Example 93-1

t-Butyl 4-[(5-pyridin-3-ylpyrimidin-2-yl)oxy]piperidine-1-carboxylate

Analogously to Example 80-2, t-butyl 4-[(5-pyridin-3-ylpyrimidin-2-yl)oxy]piperidine-1-carboxylate (243 mg, yield 68%) was obtained from t-butyl [4-[(5-bromopyrimidin-2-yl)oxy]piperidine-1-carboxylate (360 mg, 1.00 mmol) and 2-pyridineboronic acid (186 mg, 1.51 mmol) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.77 (1H, d, J=1.6 Hz), 8.69 (2H, s), 8.65-8.62 (1H, m), 7.81-7.78 (1H, m), 7.40-7.38 (1H, m), 5.22-5.21 (1H, m), 3.79-3.77 (2H, m), 3.33-3.26 (2H, m), 2.02-1.99 (2H, m), 1.86-1.80 (2H, m), 1.45 (9H, s).

Example 93-2

t-Butyl [(1S)-2-methyl-1-({4-[(5-pyridin-3-ylpyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate

Analogously to Example 23-2, 2-(piperidin-4-yloxy)-5-pyridin-3-ylpyrimidine dihydrochloride (225 mg) was obtained from t-butyl 4-[(5-pyridin-3-ylpyrimidin-2-yl)oxy]piperidine-1-carboxylate (243 mg, 0.682 mmol) as a white solid. The resulting compound (225 mg, 0.682 mmol) was condensed with N-(t-butoxycarbonyl)-L-valine (222 mg, 1.02 mmol) to afford t-butyl [(1S)-2-methyl-1-({4-[(5-pyridin-3-ylpyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate (227 mg, yield 73%) as a

colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.79 (1H, d, J=2.4 Hz), 8.72 (2H, s), 8.66 (1H, d, J=4.8 Hz), 7.83 (1H, dt, J=7.6 Hz, 2.0 Hz), 7.42 (1H, dd, J=8.0 Hz, 4.8 Hz), 5.38-5.29 (2H, m), 4.50 (1H, dd, J=8.8 Hz, 5.8 Hz), 4.03-3.43 (4H, m), 2.13-1.86 (5H, m), 1.42 (9H, s), 0.96 (3H, d, J=6.8 Hz), 0.88 (3H, d, J=6.8 Hz).

MS (FAB, m/z): 456 $(M+H)^+$.

Example 93-3

3-Hydroxy-N-[(1S)-2-methyl-1-({4-[(5-pyridin-3-ylpyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Analogously to Example 23-3, (2S)-3-methyl-1-oxy-1-{4-[(5-pyridin-3-ylpyrimidin-2-yl)oxy]piperidin-1-yl}butan-2-amine dihydrochloride (213 mg) was obtained from t-butyl [(1S)-2-methyl-1-({4-[(5-pyridin-3-ylpyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate (227 mg, 0.498 mmol) as a white solid. The resulting compound (106 mg, 0.249 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (72.0 mg, 0.374 mmol) to afford the desired title compound (55.0 mg, yield 42%) as a pale yellow solid.

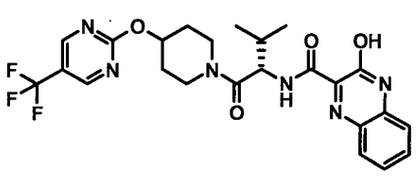
^{1}H-NMR (DMSO-d_6, 500 MHz) δ: 12.83 (1H, brs), 9.58 (1H, brs), 9.02 (2H, d, J=4.4 Hz), 8.96 (1H, s), 8.62 (1H, d, J=4.4 Hz), 8.17 (1H, dd, J=8.0 Hz, 2.0 Hz), 7.86 (1H, d, J=8.0 Hz), 7.63 (1H, t, J=7.6 Hz), 7.53 (1H, dd, J=7.6 Hz, 4.8 Hz), 7.37 (2H, t, J=7.6 Hz), 5.30-5.29 (1H, m), 4.93-4.90 (1H, m), 4.06-3.97 (2H, m), 3.62-3.25 (2H, m), 1.98-1.82 (5H, m), 0.98-0.92 (6H, m).

IR (KBr) cm^{-1}: 2965, 1690, 1640, 1525, 1440, 1335.

MS (ESI, m/z): 550 $(M+Na)^+$.

HRMS (ESI, m/z): 550.2174 (Calcd for $C_{28}H_{29}N_7NaO_4$: 550.2179).

Example 94



3-Hydroxy-N-{(1S)-2-methyl-1-[(4-{[5-(trifluoromethyl)pyrimidin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide

Example 94-1

t-Butyl 4-[(5-iodopyrimidin-2-yl)oxy]piperidine-1-carboxylate

Sodium iodide (336 mg, 2.24 mmol), copper iodide (213 mg, 1.12 mmol) and N,N-dimethylethylenediamine (0.241 ml, 2.24 mmol) were added

sequentially to a 1,4-dioxane solution (8.0 ml) of t-butyl 4-[(5-bromopyrimidin-2-yl)oxy]piperidine-1-carboxylate (400 mg, 1.12 mmol), under nitrogen stream, and stirring was carried out for 5 hours under heating to reflux. After completion of the reaction, the reaction solution was cooled to room temperature, and poured into ice water, followed by extraction with ethyl acetate. The extract was washed sequentially with water and saline, and then dried over anhydrous sodium sulfate. The resulting organic layer was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., 25+M) to afford t-butyl 4-[(5-iodopyrimidin-2-yl)oxy]piperidine-1-carboxylate (212 mg, yield 47%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.59 (2H, s), 5.10-5.06 (1H, m), 3.76-3.75 (2H, m), 3.29-3.23 (2H, m), 1.94-1.94 (2H, m), 1.77-1.74 (2H, m), 1.43 (9H, s).

MS (FAB, m/z): 406 $(M+H)^+$.

Example 94-2

t-Butyl 4-{[5-(trifluoromethyl)pyrimidin-2-yl]oxy}piperidine-1-carboxylate

Potassium fluoride (86.0 mg, 1.48 mmol), copper iodide (282 mg, 1.48 mmol) and (trifluoromethyl)trimethylsilane (0.219 ml, 1.48 mmol) were added sequentially to a N,N'-dimethylformamide solution (2.0 ml) of t-butyl 4-[(5-iodopyrimidin-2-yl)oxy]piperidine-1-carboxylate (120 mg, 0.296 mmol), under nitrogen stream, and stirring was carried out at 60°C overnight. After completion of the reaction, the reaction solution was cooled to room temperature, and poured into ice water, followed by extraction with ethyl acetate. The extract was washed sequentially with water and saline, and then dried over anhydrous sodium sulfate. The resulting organic layer was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., 25+M) to afford t-butyl 4-{[5-(trifluoromethyl)pyrimidin-2-yl]oxy}piperidine-1-carboxylate (60.0 mg, yield 54%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.74 (2H, s), 5.29-5.21 (1H, m), 3.80-3.77 (2H, m), 3.31-3.27 (2H, m), 2.03-2.00 (2H, m), 1.82-1.77 (2H, m), 1.46 (9H, s).

MS (FAB, m/z): 347 $(M+H)^+$.

Example 94-3

t-Butyl {(1S)-2-methyl-1-[(4-{[5-(trifluoromethyl)pyrimidin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}carbamate

Analogously to Example 23-2, 2-(piperidin-4-yloxy)-5-(trifluoromethyl)pyrimidine hydrochloride (159 mg) was obtained from t-butyl 4-{[5-(trifluoromethyl)pyrimidin-2-yl]oxy}piperidine-1-carboxylate (195 mg, 0.561 mmol) as a white solid. The resulting compound (159 mg, 0.561 mmol) was condensed with N-(t-butoxycarbonyl)-L-valine (183 mg, 0.842 mmol) to afford t-butyl {(1S)-2-methyl-1-[(4-{[5-(trifluoromethyl)pyrimidin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}carbamate (217 mg, yield 87%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.73 (2H, s), 5.35-5.32 (2H, m), 4.47 (1H, dd, J=9.0 Hz, 5.6 Hz), 4.00-3.42 (4H, m), 2.03-1.88 (5H, m), 1.40 (9H, s), 0.94 (3H, d, J=6.8 Hz), 0.86 (3H, d, J=6.8 Hz).

MS (FAB, m/z): 447 $(M+H)^+$.

Example 94-4

3-Hydroxy-N-{(1S)-2-methyl-1-[(4-{[5-(trifluoromethyl)pyrimidin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide

Analogously to Example 23-3, (2S)-3-methyl-1-oxo-1-(4-{[5-(trifluoromethyl)pyrimidin-2-yl]oxy}piperidin-1-yl)butan-2-amine hydrochloride (186 mg) was obtained from t-butyl [{(1S)-2-methyl-1-[(4-{[5-(trifluoromethyl)pyrimidin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}carbamate (217 mg, 0.486 mmol) as a white solid. The resulting compound (93.0 mg, 0.243 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (70.0 mg, 0.365 mmol) to afford the desired title compound (60.0 mg, yield 48%) as a pale yellow solid.

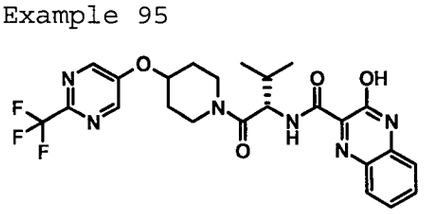
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.78 (1H, brs), 10.21 (1H, brs), 8.78 (2H, d, J=7.6 Hz), 8.01 (1H, t, J=9.2 Hz), 7.63-7.54 (2H, m), 7.38 (1H, brs), 5.44-5.38 (1H, m), 5.12-5.08 (1H, m), 4.01-3.69 (4H, m), 2.26-2.09 (5H, m), 1.14-1.11 (6H, m).

IR (KBr) cm^{-1}: 2965, 1690, 1630, 1455, 1320, 1135.

MS (ESI, m/z): 541 $(M+Na)^+$.

HRMS (ESI, m/z): 541.1786 (Calcd for $C_{24}H_{25}F_3N_6NaO_4$: 541.1787).

Example 95



3-Hydroxy-N-{(1S)-2-methyl-1-[(4-{[2-(trifluoromethyl)pyrimidin-5-yl]oxy}piperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide

Example 95-1

5-Bromo-2-(trifluoromethyl)pyrimidine

Sodium iodide (3.75 g, 25.0 mmol) and a 55 wt% aqueous hydriodic acid solution (1.48 g) were added sequentially to a chloroform solution (8.0 ml) of 5-bromo-2-chloropyrimidine (2.90 g, 15.0 mmol), at 0°C, and stirring was carried out at room temperature for 20 hours. After completion of the reaction, the reaction solution was poured into ice water, followed by extraction with ethyl acetate. The extract was washed sequentially with water and saline, and then dried over anhydrous sodium sulfate. The resulting organic layer was concentrated to afford 5-bromo-2-iodopyrimidine (3.00 g) as a colorless amorphous substance. This product was used in the next reaction without purification.

Potassium fluoride (1.22 g, 21.1 mmol), copper iodide (4.01 mg, 21.1 mmol) and (trifluoromethyl)trimethylsilane (3.13 ml, 21.1 mmol) were added sequentially to a N,N-dimethylformamide solution (20 ml) of the resulting compound (3.00 g, 10.5 mmol), and stirring was carried out at 70°C for 2 hours. After completion of the reaction, the reaction solution was cooled to room temperature, and poured into ice water, followed by extraction with ethyl acetate. The extract was washed sequentially with water and saline, and then dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., 25+M) to afford 5-bromo-2-(trifluoromethyl)pyrimidine (278 mg, yield 12%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.94 (2H, s).

MS (EI, m/z): 226 (M^+).

Example 95-2

2-(Trifluoromethyl)pyrimidin-5-ol

palladium acetate (27.0 mg, 0.122 mmol), bis(pinacolato)diboron (342 mg, 1.35 mmol) and potassium acetate (359 mg, 3.66 mmol) were added sequentially to a N,N-dimethylformamide solution (3.0 ml) of 5-bromo-2-(trifluoromethyl)pyrimidine (278 mg, 1.22 mmol), under nitrogen stream, and stirring was carried out at 90°C for 3 hours. After completion of the reaction, the reaction solution was cooled to room temperature, and poured into ice water, followed by extraction with ethyl acetate. The extract was washed sequentially with water and saline, and then the resulting organic layer was dried over anhydrous sodium sulfate. The

organic layer was concentrated and the resulting residue was dissolved in a mixed solution of tetrahydrofuran-water (8.0 ml, 1:1, v/v), followed by addition of sodium perborate tetrahydrate and stirring overnight. After completion of the reaction, the reaction solution was cooled to room temperature, and poured into ice water, followed by extraction with ethyl acetate. The extract was washed sequentially with water and saline, and then dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., 25+M) to afford 2-(trifluoromethyl)pyrimidin-5-ol (220 mg, 100%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.46 (2H, s).

MS (EI, m/z): 164 (M^+).

Example 95-3

t-Butyl {(1S)-2-methyl-1-[(4-{[2-(trifluoromethyl)pyrimidin-5-yl]oxy}piperidin-1-yl)carbonyl]propyl}carbamate

Analogously to Example 1-2, t-butyl {(1S)-2-methyl-1-[(4-{[2-(trifluoromethyl)pyrimidin-5-yl]oxy}piperidin-1-yl)carbonyl]propyl}carbamate (320 mg, 49%) was obtained from 2-(trifluoromethyl)pyrimidin-5-ol (240 mg, 1.46 mmol) and t-butyl {(1S)-1-[(4-hydroxypiperidin-1-yl)carbonyl]-2-methylpropyl}carbamate (527 mg, 1.76 mmol) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.50 (2H, s), 5.35 (1H, d, J=9.2 Hz), 4.80-4.72 (1H, m), 4.47 (1H, dd, J=9.2 Hz, 6.0 Hz), 3.91-3.50 (4H, m), 2.12-1.84 (5H, m), 1.41 (9H, s), 0.95 (3H, d, J=6.8 Hz), 0.89 (3H, d, J=6.8 Hz).

MS (FAB, m/z): 447 $(M+H)^+$.

Example 95-4

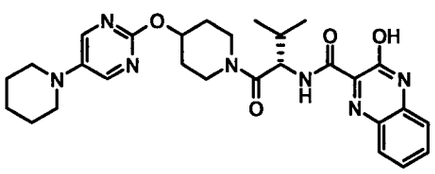
3-Hydroxy-N-{(1S)-2-methyl-1-[(4-{[2-(trifluoromethyl)pyrimidin-5-yl]oxy}piperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide

Analogously to Example 23-3, (2S)-3-methyl-1-oxo-1-(4-{[2-(trifluoromethyl)pyrimidin-5-yl]oxy}piperidin-1-yl)butan-2-amine hydrochloride (274 mg) was obtained from t-butyl {(1S)-2-methyl-1-[(4-{[2-(trifluoromethyl)pyrimidin-5-yl]oxy}piperidin-1-yl)carbonyl]propyl}carbamate (320 mg, 0.717 mmol) as a white solid.

The resulting compound (137 mg, 0.360 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (103 mg, 0.538 mmol) under nitrogen stream to afford the desired title compound (70.0 mg, yield 38%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.84 (1H, brs), 9.55 (1H, brs), 8.85 (2H, d, J=3.6 Hz), 7.86 (1H, t, J=6.8 Hz), 7.64 (1H, t, J=8.0 Hz), 7.39-7.38 (2H, m), 5.04-5.02 (1H, m), 4.93-4.89 (1H, m), 4.01-3.99 (2H, m), 3.44-3.27 (2H, m), 2.08-2.04 (3H, m), 1.61 (2H, s), 0.96-0.95 (6H, m).
IR (KBr) cm^{-1}: 2965, 1685, 1640, 1535, 1350.
MS (ESI, m/z): 519 $(M+H)^+$.
HRMS (ESI, m/z): 519.1966 (Calcd for $C_{24}H_{26}F_3N_6O_4$: 519.1968).

Example 96



3-Hydroxy-N-[(1S)-2-methyl-1-({4-[(5-piperidin-1-ylpyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Example 96-1

t-Butyl 4-[(5-piperidin-1-ylpyrimidin-2-yl)oxy]piperidine-1-carboxylate

Tris(dibenzylideneacetone)dipalladium (96.0 mg, 0.167 mmol), 1,1'-bi-2-naphthol (312 mg, 0.501 mmol), piperidine (0.332 ml, 3.35 mmol) and sodium t-butoxide (324 mg, 3.35 mmol) were added sequentially to a toluene solution (10 ml) of t-butyl 4-[(5-bromopyrimidin-2-yl)oxy]piperidine-1-carboxylate (600 mg, 1.67 mmol), under nitrogen stream, and stirring was carried out for 5 hours under heating to reflux. After completion of the reaction, the reaction solution was cooled to room temperature, and poured into ice water, followed by extraction with ethyl acetate. The extract was washed sequentially with water and saline, and then dried over anhydrous sodium sulfate. The resulting organic layer was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., 25+M) to afford t-butyl 4-[(5-piperidin-1-ylpyrimidin-2-yl)oxy]piperidine-1-carboxylate (600 mg, yield 98%) as a white solid.
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.14 (2H, s), 5.06-5.01 (1H, m), 3.77-3.73 (2H, m), 3.29-3.23 (2H, m), 3.02-3.01 (4H, m), 1.94 (2H, brs), 1.79-1.67 (6H, m), 1.57-1.51 (2H, m), 1.43 (9H, s).
MS (FAB, m/z): 363 $(M+H)^+$.

Example 96-2

t-Butyl [(1S)-2-methyl-1-({4-[(5-piperidin-1-ylpyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate

Analogously to Example 23-2, 5-piperidin-1-yl-2-(piperidin-4-

yloxy)pyrimidine dihydrochloride (556 mg) was obtained from t-butyl 4-[(5-piperidin-1-ylpyrimidin-2-yl)oxy]piperidine-1-carboxylate (600 mg, 1.66 mmol) as a white solid. The resulting compound (556 mg, 1.66 mmol) was condensed with N-(t-butoxycarbonyl)-L-valine (539 mg, 2.48 mmol) to afford t-butyl [(1S)-2-methyl-1-({4-[(5-piperidin-1-ylpyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate (567 mg, yield 74%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.15 (2H, s), 5.35-5.33 (1H, m), 5.15-5.11 (1H, m), 4.47 (1H, dd, J=8.8 Hz, 5.6 Hz), 3.91-3.40 (4H, m), 3.03 (4H, t, J=5.6 Hz), 2.04-1.78 (5H, m), 1.73-1.67 (4H, m), 1.57-1.51 (2H, m), 1.40 (9H, s), 0.93 (3H, dd, J=6.8 Hz, 2.4 Hz), 0.85 (3H, dd, J=6.8 Hz, 4.0 Hz).

MS (FAB, m/z): 462 $(M+H)^+$.

Example 96-3

3-Hydroxy-N-[(1S)-2-methyl-1-({4-[(5-piperidin-1-ylpyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Analogously to Example 23-3, (2S)-3-methyl-1-oxo-1-{4-[(5-piperidin-1-ylpyrimidin-2-yl)oxy]piperidin-1-yl}butan-2-amine dihydrochloride (534 mg) was obtained from t-butyl [(1S)-2-methyl-1-({4-[(5-piperidin-1-ylpyrimidin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate (567 mg, 1.23 mmol) as a white solid. The resulting compound (283 mg, 0.614 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (175 mg, 0.921 mmol) to afford the desired title compound (105 mg, yield 32%) as a pale yellow solid.

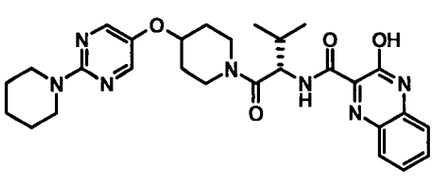
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.84 (1H, brs), 9.56 (1H, brs), 8.32 (2H, d, J=3.6 Hz), 7.87 (1H, d, J=8.0 Hz), 7.64 (1H, t, J=8.0 Hz), 7.39-7.37 (2H, m), 5.10-5.09 (1H, m), 4.95-4.92 (1H, m), 4.00-3.95 (2H, m), 3.55-3.23 (2H, m), 3.07 (4H, t, J=5.2 Hz), 2.06-2.04 (3H, m), 1.62-1.52 (8H, m), 0.96-0.94 (6H, m).

IR (KBr) cm^{-1}: 2940, 1690, 1640, 1525, 1440, 1320.

MS (ESI, m/z): 556 $(M+Na)^+$.

HRMS (ESI, m/z): 556.2641 (Calcd for $C_{28}H_{35}N_7NaO_4$: 556.2648).

Example 97



3-Hydroxy-N-[(1S)-2-methyl-1-({4-[(2-piperidin-1-ylpyrimidin-5-

yl)oxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Example 97-1

t-Butyl [(1S)-2-methyl-1-({4-[(2-piperidin-1-ylpyrimidin-5-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate

Piperidine (0.284 ml, 2.83 mmol) and potassium carbonate (330 mg, 4.78 mmol) were added sequentially to a N,N-dimethylformamide solution (4.0 ml) of t-butyl (1S)-1-({4-[(2-chloropyrimidin-5-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]carbamate (300 mg, 0.956 mmol), under nitrogen stream, and stirring was carried out at 100°C for 3 hours. After completion of the reaction, the reaction solution was cooled to room temperature, and poured into ice water, followed by extraction with ethyl acetate. The extract was washed sequentially with water and saline, and then dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., 25+M) to afford t-butyl [(1S)-2-methyl-1-({4-[(2-piperidin-1-ylpyrimidin-5-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate (400 mg, yield 91%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.04 (2H, s), 5.32 (1H, d, J=9.2 Hz), 4.46-4.44 (1H, m), 4.26-4.18 (1H, m), 3.89-3.59 (6H, m), 3.49-3.34 (2H, m), 1.97-1.49 (11H, m), 1.40 (9H, s), 0.93 (3H, dd, J=6.8 Hz, 5.2 Hz), 0.85 (3H, dd, J=6.8 Hz, 2.8 Hz).

Example 97-2

3-Hydroxy-N-[(1S)-2-methyl-1-({4-[(2-piperidin-1-ylpyrimidin-5-yl)oxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide

Analogously to Example 23-3, (2S)-3-methyl-1-oxo-1-{4-[(2-piperidin-1-ylpyrimidin-5-yl)oxy]piperidin-1-yl}butan-2-amine dihydrochloride (376 mg) was obtained from t-butyl [(1S)-2-methyl-1-({4-[(2-piperidin-1-ylpyrimidin-5-yl)oxy]piperidin-1-yl}carbonyl)propyl]carbamate (400 mg, 0.867 mmol) as a white solid. The resulting compound (188 mg, 0.433 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (125 mg, 0.650 mmol) to afford the desired title compound (70.0 mg, yield 30%) as a pale yellow solid.

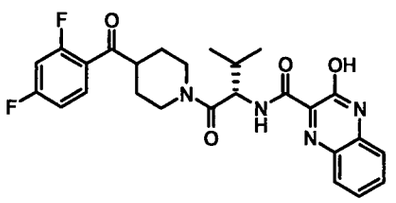
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.84 (1H, brs), 9.52 (1H, brs), 8.23 (2H, d, J=6.4 Hz), 7.87 (1H, d, J=7.6 Hz), 7.64 (1H, t, J=7.6 Hz), 7.39-7.38 (2H, m), 4.92-4.89 (1H, m), 4.45-4.43 (1H, m), 3.93-3.88 (2H, m), 3.66 (4H, t, J=4.8 Hz), 3.47-3.22 (2H, m), 2.02-1.92 (3H, m), 1.60-1.51 (8H, m), 0.95 (6H, t, J=6.8 Hz).

IR (KBr) cm^{-1}: 2935, 1690, 1635, 1495, 1445, 1255.

MS (ESI, m/z): 556 $(M+Na)^+$.

HRMS (ESI, m/z): 556.2651 (Calcd for $C_{28}H_{35}N_7NaO_4$: 556.2648).

Example 98



N-[(1S)-1-{[4-(2,4-Difluorobenzoyl)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Example 98-1

t-Butyl [(1S)-1-{[4-(2,4-difluorobenzoyl)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate

Analogously to Example 2-1, 4-(2,4-difluorobenzoyl)piperidine hydrochloride (1.00 g, 3.82 mmol) was condensed with N-(t-butoxycarbonyl)-L-valine (1.25 g, 5.73 mmol) to afford N-[(1S)-1-{[4-(2,4-difluorobenzoyl)piperidin-1-yl]carbonyl}-2-methylpropyl]-3,4-difluoro-2-hydroxybenzamide (1.45 g, yield 90%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.87-7.84 (1H, m), 6.97 (1H, t, J=8.0 Hz), 6.91-6.84 (1H, m), 5.33 (1H, t, J=8.0 Hz), 4.53-4.48 (2H, m), 4.02-3.98 (1H, m), 3.37-3.32 (1H, m), 3.26-3.16 (1H, m), 2.87-2.83 (1H, m), 2.01-1.85 (3H, m), 1.75-1.51 (2H, m), 1.41 (9H, s), 0.94 (3H, t, J=6.8 Hz), 0.86 (3H, d, J=6.8 Hz).

MS (FAB, m/z): 425 $(M+H)^+$.

Example 98-2

N-[(1S)-1-{[4-(2,4-Difluorobenzoyl)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Analogously to Example 23-3, (2,4-difluorophenyl)(1-L-valylpiperidin-4-yl)methanone hydrochloride (1.29 g) was obtained from t-butyl [(1S)-1-{[4-(2,4-difluorobenzoyl)piperidin-1-yl]carbonyl}-2-methylpropyl]carbamate (1.45 g, 3.44 mmol) as a white solid. The resulting compound (300 mg, 0.831 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (238 mg, 1.25 mmol) to afford the desired title compound (362 mg, yield 88%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6, 500 MHz) δ: 12.82 (1H, brs), 9.51 (1H, brs), 7.95-7.79 (2H, m), 7.63 (1H, t, J=8.0 Hz), 7.47-7.33 (3H, m), 7.28-7.24 (1H, m),

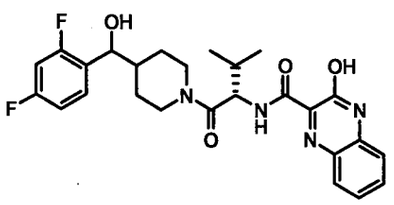
4.92-4.86 (1H, m), 4.44-4.40 (1H, m), 4.18-4.16 (1H, m), 3.39-3.26 (2H, m), 2.84-2.81 (1H, m), 2.00-1.83 (3H, m), 1.61-1.31 (2H, m), 0.95-0.93 (6H, m).

IR (KBr) cm^{-1}: 2965, 1685, 1610, 1530, 1270.

MS (ESI, m/z): 519 $(M+Na)^+$.

HRMS (ESI, m/z): 519.1812 (Calcd for $C_{26}H_{26}F_2N_4NaO_4$: 519.1820).

Example 99



N-[(1S)-1-({4-[(2,4-Difluorophenyl)(hydroxy)methyl]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide

Sodium borohydride (183 mg, 0.483 mmol) was added to a methanol solution (2.0 ml) of N-[(1S)-1-{[4-(2,4-difluorobenzoyl)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide (218 mg, 0.439 mmol), at 0°C, and stirring was carried out at the same temperature for 1 hour. After completion of the reaction, the reaction solution was poured into ice water, followed by extraction with ethyl acetate. The extract was washed sequentially with water and saline, and then dried over anhydrous sodium sulfate. The resulting organic layer was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., 25+M) to afford the desired title compound (85.0 mg, yield 39%) as a pale yellow solid.

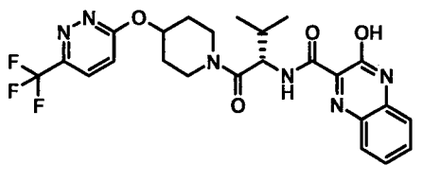
^{1}H-NMR (DMSO-d_6, 500 MHz) δ: 12.83 (1H, brs), 9.55 (1H, brs), 7.87-7.85 (1H, m), 7.63 (1H, q, J=8.0 Hz), 7.50-7.47 (1H, m), 7.38-7.36 (2H, m), 7.15-7.09 (2H, m), 5.44-5.42 (1H, m), 4.92-4.85 (1H, m), 4.60-4.55 (1H, m), 4.45-4.42 (1H, m), 4.16-4.01 (1H, m), 3.38-3.33 (1H, m), 3.03-3.01 (1H, m), 2.02-2.00 (1H, m), 1.86-1.79 (2H, m), 1.44-1.06 (2H, m), 0.93-0.89 (6H, m).

IR (KBr) cm^{-1}: 3425, 2965, 1685, 1620, 1525, 1455.

MS (ESI, m/z): 521 $(M+Na)^+$.

HRMS (ESI, m/z): 521.1965 (Calcd for $C_{26}H_{28}F_2N_4NaO_4$: 521.1976).

Example 100



3-Hydroxy-N-{(1S)-2-methyl-1-[(4-{[6-(trifluoromethyl)pyridazin-3-yl]oxy}piperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide

Example 100-1

3-Chloro-6-(trifluoromethyl)pyridazine

Sodium iodide (1.31 g, 8.72 mmol) and a 55 wt% aqueous hydriodic acid solution (1.25 g) were added sequentially to a chloroform solution (4.0 ml) of 3,6-dichloropyridazine (1.00 g, 6.71 mmol), at 0°C, and stirring was carried out at 40°C for 5 hours. After completion of the reaction, at 0°C, 2N sodium hydroxide was added for neutralization, followed by extraction with ethyl acetate. The extract was washed sequentially with water and saline, and then dried over anhydrous sodium sulfate. The resulting organic layer was concentrated to afford 3-chloro-6-iodopyridazine (1.23 g) as a white solid. This product was used as it is in the next reaction without purification.

Potassium fluoride (889 mg, 15.3 mmol), copper iodide (2.92 g, 15.3 mmol) and (trifluoromethyl)trimethylsilane (2.27 ml, 15.3 mmol) were added sequentially to a N,N-dimethylformamide solution (10 ml) of the resulting compound (1.23 g, 5.11 mmol), and stirring was carried out at 60°C for 2.5 hours. After completion of the reaction, the reaction solution was cooled to room temperature, and poured into ice water, followed by extraction with ethyl acetate. The extract was washed sequentially with water and saline, and then dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue was purified by a medium-pressure preparative liquid chromatograph (manufactured by Biotage, Inc., 25+M) to afford 3-chloro-6-(trifluoromethyl)pyridazine (350 mg, yield 38%) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.83 (1H, d, J=9.2 Hz), 7.76 (1H, d, J=9.2 Hz).

MS (EI, m/z): 182 (M^+).

Example 100-2

t-Butyl {(1S)-2-methyl-1-[(4-{[6-(trifluoromethyl)pyridazin-3-yl]oxy}piperidin-1-yl)carbonyl]propyl}carbamate

Analogously to Example 64-1, t-butyl {(1S)-2-methyl-1-[(4-{[6-(trifluoromethyl)pyridazin-3-yl]oxy}piperidin-1-yl)carbonyl]propyl}carbamate (380 mg, yield 44%) was obtained from 3-chloro-6-(trifluoromethyl)pyridazine (350 mg, 1.92 mmol) and t-butyl

{(1S)-1-[(4-hydroxypiperidin-1-yl)carbonyl]-2-methylpropyl}carbamate (634 mg, 2.11 mmol) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 7.71 (1H, d, J=9.2 Hz), 7.11 (1H, dd, J=9.2 Hz, 3.2 Hz), 5.68-5.65 (1H, m), 5.34 (1H, t, J=9.2 Hz), 4.52-4.50 (1H, m), 4.13-3.79 (2H, m), 3.61-3.40 (2H, m), 2.21-2.13 (2H, m), 1.94-1.84 (3H, m), 1.44 (9H, s), 0.98 (3H, d, J=6.8 Hz), 0.90 (3H, t, J=6.0 Hz).

MS (FAB, m/z): 447 $(M+H)^+$.

Example 100-3

3-Hydroxy-N-{(1S)-2-methyl-1-[(4-{[6-(trifluoromethyl)pyridazin-3-yl]oxy}piperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide

Analogously to Example 23-3, (2S)-3-methyl-1-oxo-1-{4-{[6-(trifluoromethyl)pyridazin-3-yl]oxy}piperidin-1-yl}butan-2-amine hydrochloride (299 mg) was obtained from t-butyl {(1S)-2-methyl-1-[(4-{[6-(trifluoromethyl)pyridazin-3-yl]oxy}piperidin-1-yl)carbonyl]propyl}carbamate (350 mg, 0.784 mmol) as a white solid. The resulting compound (150 mg, 0.392 mmol) was condensed with 3-hydroxyquinoxaline-2-carboxylic acid (112 mg, 0.588 mmol) to afford the desired title compound (85.0 mg, yield 42%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.79 (1H, brs), 9.57 (1H, brs), 8.17 (1H, dd, J=9.2 Hz, 4.0 Hz), 7.87-7.86 (1H, m), 7.66-7.62 (1H, m), 7.51 (1H, dd, J=9.2 Hz, 5.6 Hz), 7.39-7.37 (2H, m), 5.60-5.59 (1H, m), 4.95-4.93 (1H, m), 4.03-3.95 (2H, m), 3.63-3.32 (2H, m), 2.07-1.77 (5H, m), 0.96 (6H, t, J=6.0 Hz).

IR (KBr) cm^{-1}: 2960, 1690, 1630, 1525, 1450, 1300.

MS (ESI, m/z): 541 $(M+Na)^+$.

HRMS (ESI, m/z): 541.1788 (Calcd for $C_{24}H_{25}F_3N_6NaO_4$: 541.1787).

[Preparation Examples]

Preparation Example 1

Injection Solution

1.5% by weight of the compound of Example 8 is stirred in 10% by volume of propylene glycol followed by adjusting to a fixed volume with water for injection and sterilizing to obtain an injection solution.

Preparation Example 2

Hard Capsule

50 mg of the compound of Example 12 in powder form, 128.7 mg of lactose, 70 mg of cellulose and 1.3 mg of magnesium stearate are mixed and filtered with a 60 mesh sieve followed by filling the powder into a 250 mg No. 3 gelatin capsule to obtain a capsule.

Preparation Example 3

Tablet

50 mg of the compound of Example 16 in powder form, 124 mg of lactose, 25 mg of cellulose and 1 mg of magnesium stearate are mixed and tableted with a tablet making machine to obtain a 200 mg tablet. This tablet can be sugar-coated as necessary.

[Test Examples]

(Test Example 1) Measurement of Inhibitory Action on γ-Glutamyl Carboxylation Reaction

Cells were used that expressed Gas6 excreted outside the cells when subjected to γ-glutamyl carboxylation, and inhibitory action on γ-glutamyl carboxylation reaction was assessed by measuring the secreted amount of extracellular Gas6 by ELISA method.

(A) Preparation for Assay Plate Containing Solid-Phase Anti-human Gas6 Antibody

Goat anti-human Gas6 antibody (R&D Systems, Inc.) was diluted to 1 μg/ml with Dulbecco's phosphate-buffered saline, and 40 μl aliquots thereof were dispensed into each well of a 384-well microplate. After immobilizing the antibody to the solid phase by allowing it to stand at 4°C overnight or at room temperature for 2 hours or more, each well was washed three times with wash buffer (10 mM Tris-HCl pH 7.4, 150 mM sodium chloride, 0.05% Tween20). After removing the supernatant, 80 μl aliquots of a 1% aqueous solution of Block Ace (Dainippon Sumitomo Pharma) were dispensed into each well and allowed to react at room temperature for 1 hour or more.

(B) Exposure of Test Compounds to Cells Stably Expressing Human Gas6

Cells that stably express human Gas6 (Gas6-HEK293), which were prepared by inserting human Gas6 gene (inserted between SalI and NotI within multiple cloning sites of pCIneo expression vector) into HEK293 cells, were grown and sub-cultured using Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal calf serum (FCS). On the day before ELISA measurement, the Gas6-HEK293 cells were detached with trypsin-EDTA, dispersed in DMEM containing 10% FCS, and disseminated into each well of a 384-well, collagen type I-coated plate (Becton-Dickinson) in 30 μl aliquots containing 1.0×10^4 cells each, followed by culturing for 3 to 4 hours at 5% CO_2 and 37°C. 30 μL aliquots of DMEM containing test compound solutions, prepared at various concentrations by dissolving in DMSO, and vitamin K_2 at 0.1% and 100 nM, respectively (indicating final

concentrations in both cases) were added to each well followed by additionally culturing for 18 to 20 hours.

(C) Quantification of γ-Glutamyl Carboxylated Gas6 by ELISA and Calculation of 50% Inhibitory Concentrations of γ-Glutamyl Carboxylation Reaction

After removing the 1% Block Ace aqueous solution from the preliminarily prepared assay plates containing solid phase anti-human Gas6 antibody, the culture supernatant of Gas6-HEK293 cells exposed to the test compounds was collected and 40 µl aliquots were dispensed into each well followed by allowing to react at room temperature for 2 hours (Step 1). The culture supernatant was removed and each well was washed three times with wash buffer. Thereafter, the same washing procedure was carried out between Steps 2 and 3 and Steps 3 and 4. Subsequently, 40 µl aliquots of mouse anti-human γ-glutamyl carboxylase antibody (American Diagnostica inc.), adjusted to 0.5 µg/ml with immunoreaction buffer (100 mM Tris-HCl pH 7.4, 0.05% Tween20, 0.1% Block Ace), were dispensed into each well and allowed to react at room temperature for 1 hour (Step 2). Next, 40 µl aliquots of alkaline phosphatase-conjugated anti-mouse IgG antibody adjusted to 1.0 µg/ml with immunoreaction buffer were dispensed into each well and allowed to react at room temperature for 1 hour (Step 3). 40 µl aliquots of BluePhos Microwell (KPL) were dispensed into each well, and after incubating at room temperature for 10 minutes (Step 4), 20 µl aliquots of 5% EDTA were added to each well to stop the color development reaction, followed by measurement of absorbance at 620 nm (Step 5). The γ-glutamyl carboxylation reaction inhibition rate of each test compound was calculated by assigning a value of 100% for the γ-glutamyl carboxylation reaction to the absorbance of wells in which the cells were only exposed to vitamin K_2 and DMSO in the absence of test compound, and assigning a value of 0% for the γ-glutamyl carboxylation reaction to the absorbance of wells in which cells were exposed to 10 µM warfarin in the absence of vitamin K_2. 50% inhibitory concentration (IC_{50}) values for the γ-glutamyl carboxylation reaction were calculated from the γ-glutamyl carboxylation reaction inhibition rates of the test compounds at each concentration.

The results are shown in Table 1.

(Table 1)

Example No. of Test Compound	IC_{50} (nM)

Example 1	8.4
Example 2	6.6
Example 3	3.5
Example 4	4.7
Example 6	74
Example 7	1.7
Example 8	1.8
Example 9	<0.6
Example 10	<0.6
Example 11	6.5
Example 12	4.2
Example 13	5.8
Example 14	25
Example 15	18
Example 16	7.0
Example 18	2.9
Example 19	4.7
Example 21	0.89
Example 23	<0.6
Example 29	7.2
Example 30	1.7
Example 34	12
Example 35	<0.6
Example 36	1.8
Example 37	5.4
Example 45	1.3
Example 49	4.3
Example 61	5.1
Example 62	3.6
Example 65	20
Example 67	0.75
Example 69	3.4
Example 74	5.5
Example 80	7.1
Example 81	4.6
Example 82	4.6
Example 84	5.5
Example 86	0.7
Example 91	3.8

Example 94	2.7
Example 96	9.6
Example 97	4.5
Example 98	3.5
Example 99	4.9
Example 100	10.4

(Test Example 2) Measurement of Ex Vivo Anticoagulatory Activity

(A) Dosing and Collection of Blood Samples

Dosing solutions (1 mg/ml), in which the test compounds were dissolved or suspended in 0.5% methyl cellulose (MC), were orally administered to rats (3 mg/kg). 18 hours after administration, 0.5 ml of blood (containing aqueous citric acid solution) were sampled from the jugular vein using a syringe injected with 50 µl of a 3.13% (w/v) aqueous trisodium citrate dihydrate solution. The citrated blood was centrifuged for 10 minutes at 1500 x g to separate the plasma. Blood was also sampled from rats not dosed with test compounds and plasma was obtained therefrom for use as a control.

(B) Measurement of Prothrombin Time and Calculation of Prolongation Rate

Prothrombin time (PT) was measured using Amelung KC-10A Micro Coagulometer (MC Medical), a coagulation time measurement apparatus. 50 µl of saline were added to 50 µl of plasma followed by pre-incubating at 37°C for 1 minute. The coagulation reaction was started by adding 100 µl of Thromboplastin C Plus (Dade Behring), which was adjusted to 0.5 U/ml by suspending in water for injection, followed by measurement of PT. The PT values of rats not dosed with test compounds were used as a control, and PT prolongation rates of rats dosed with test compounds were expressed as a percentage.

The results are shown in Table 2.

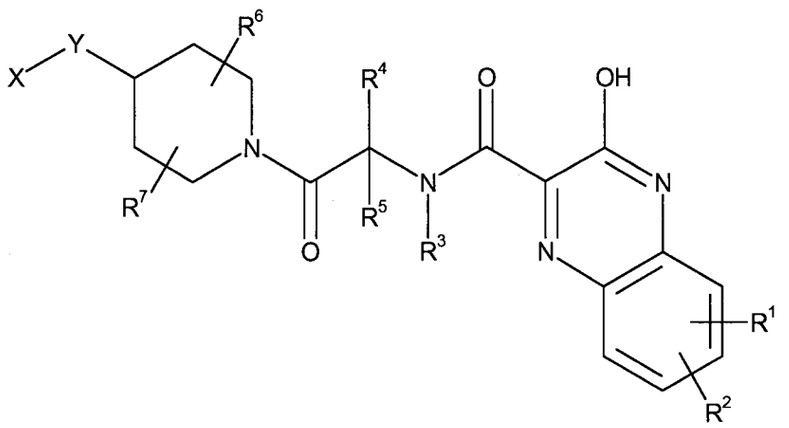
(Table 2)

Example No. of Test Compound	PT (%)
Example 1	731
Example 3	616
Example 4	790
Example 6	557
Example 7	732
Example 8	576
Example 9	751

Example 10	802
Example 12	725
Example 13	580
Example 15	663
Example 16	720
Example 18	709
Example 21	637
Example 23	681
Example 29	707
Example 36	649
Example 37	644
Example 45	609
Example 49	750
Example 65	568
Example 69	798
Example 74	688
Example 80	616
Example 81	706
Example 86	582
Example 94	574
Example 98	623
Example 99	747

Claims

1. A compound represented by the general formula (i):



wherein,

each of R^1 and R^2 independently represents a hydrogen atom, a halogen atom, a cyano group, a C_{1-4} alkyl group or a C_{1-4} alkoxy group,

R^3 represents a hydrogen atom or a C_{1-4} alkyl group,

each of R^4 and R^5 independently represents a hydrogen atom, a halogen atom, a C_{1-4} alkyl group, a C_{2-4} alkenyl group, a C_{2-4} alkynyl group, a C_{3-5} cycloalkyl group or a hydroxy C_{1-4} alkyl group,

each of R^6 and R^7 independently represents a hydrogen atom or a C_{1-4} alkyl group,

X represents a monocyclic or bicyclic C_{3-10} cycloalkyl group, a monocyclic or bicyclic C_{6-10} aryl group or a monocyclic or bicyclic 5- to 10-membered heterocyclic group (in which the heterocyclic group includes aromatic heterocycles and non-aromatic heterocycles and contains 1 to 3 atoms selected from the group consisting of a nitrogen atom, a sulfur atom and an oxygen atom), which may be substituted with 1 to 3 substituents selected from substituent group α,

Y represents -CHRa-, -C(OH)Ra-, -CO-, -O-, -NRa-, -S-, -SO- or -SO_2-,

Ra represents a hydrogen atom, a C_{1-4} alkyl group, a halogeno C_{1-4} alkyl group or a C_{1-4} alkanoyl group,or

in the case where Ra in Y is a C_{1-4} alkyl group, a halogeno C_{1-4} alkyl group or a C_{1-4} alkanoyl group, Ra may form a 5- or 6-membered ring by bonding with an atom that is a component of X,

substituent group α represents:

a halogen atom, a cyano group, a nitro group, a hydroxy group;

a C_{1-4} alkyl group, a C_{2-4} alkenyl group, a C_{2-4} alkynyl group, a C_{3-6} cycloalkyl group, a C_{1-4} alkoxy group or a C_{3-6} cycloalkoxy group, which may be substituted with substituent(s) selected from substituent group β;

-OCORb, -CORb, -COORb, -CONRbRc, -NRbRc, -NRbCORc, -NRbSORc, -$NRbSO_2Rc$, -SRb, -SORb, -SO_2Rb;

a phenyl group, and

a 5- or 6-membered heterocyclic group, which may be substituted with a C_{1-4} alkyl group(s) (in which the heterocyclic group includes aromatic heterocycles and non-aromatic heterocycles and contains 1 to 3 atoms selected from the group consisting of a nitrogen atom, a sulfur atom and an oxygen atom),

each of Rb and Rc independently represents a hydrogen atom, a C_{1-4} alkyl group or a halogeno C_{1-4} alkyl group, and

substituent group β represents a halogen atom, a hydroxy group, a C_{1-4} alkoxy group and a C_{1-4} alkanoyloxy group,

or a pharmacologically acceptable salt thereof.

2. A compound or a pharmacologically acceptable salt thereof, according to claim 1, wherein each of R^1 and R^2 independently represents a hydrogen atom or a halogen atom.

3. A compound or a pharmacologically acceptable salt thereof, according to claim 1, wherein each of R^1 and R^2 independently represents a hydrogen atom or a fluorine atom.

4. A compound or a pharmacologically acceptable salt thereof, according to claim 1, wherein R^1 and R^2 both represent a hydrogen atom.

5. A compound or a pharmacologically acceptable salt thereof, according to any one of claims 1 to 4, wherein R^3 represents a hydrogen atom or a methyl group.

6. A compound or a pharmacologically acceptable salt thereof, according to any one of claims 1 to 4, wherein R^3 represents a hydrogen atom.

7. A compound or a pharmacologically acceptable salt thereof, according to any one of claims 1 to 6, wherein R^4 represents a hydrogen atom, a fluorine atom, a C_{1-4} alkyl group, a C_{2-4} alkenyl group, a C_{2-4} alkynyl group, a C_{3-5} cycloalkyl group or a hydroxy C_{1-4} alkyl group, and R^5 represents a hydrogen atom.

8. A compound or a pharmacologically acceptable salt thereof,

according to any one of claims 1 to 6, wherein R^4 represents a methyl group, an ethyl group, an isopropyl group, an isobutyl group, a t-butyl group, a cyclopropyl group or a 1-hydroxy-1-methylethyl group, and R^5 represents a hydrogen atom.

9. A compound or a pharmacologically acceptable salt thereof, according to any one of claims 1 to 6, wherein R^4 represents a methyl group, an ethyl group, an isopropyl group, a t-butyl group, a cyclopropyl group or a 1-hydroxy-1-methylethyl group, and R^5 represents a hydrogen atom.

10. A compound or a pharmacologically acceptable salt thereof, according to any one of claims 1 to 6, wherein R^4 represents an ethyl group, an isopropyl group, a cyclopropyl group or a 1-hydroxy-1-methylethyl group, and R^5 represents a hydrogen atom.

11. A compound or a pharmacologically acceptable salt thereof, according to any one of claims 1 to 6, wherein each of R^4 and R^5 independently represents a hydrogen atom, a halogen atom, a C_{1-4} alkyl group, a C_{2-4} alkenyl group, a C_{2-4} alkynyl group or a C_{3-5} cycloalkyl group.

12. A compound or a pharmacologically acceptable salt thereof, according to any one of claims 1 to 6, wherein R^4 represents a hydrogen atom, a methyl group, an ethyl group, an isopropyl group, an isobutyl group, a t-butyl group or a cyclopropyl group, and R^5 represents a hydrogen atom.

13. A compound or a pharmacologically acceptable salt thereof, according to any one of claims 1 to 12, wherein each of R^6 and R^7 independently represents a hydrogen atom or a methyl group.

14. A compound or or pharmacologically acceptable salt thereof, according to any one of claims 1 to 12, wherein R^6 and R^7 both represent a hydrogen atom.

15. A compound or a pharmacologically acceptable salt thereof, according to any one of claims 1 to 14, wherein X represents a phenyl group, a naphthyl group, a pyridyl group, a pyridazinyl group, a pyrimidinyl group, a pyrazinyl group, a quinolyl group, an isoquinolyl

group, a benzimidazolyl group, a benzoxazolyl group or a benzothiazolyl group, which may be substituted with 1 or 2 substituents selected from substituent group α, and

substituent group α represents a halogen atom, a cyano group, a nitro group, a hydroxy group, a methyl group, an ethyl group, a propyl group, an isopropyl group, a t-butyl group, a hydroxymethyl group, a fluoromethyl group, a difluoromethyl group, a trifluoromethyl group, a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, an acetoxy group, a trifluoromethoxy group, an acetyl group, a methoxycarbonyl group, an ethoxycarbonyl group, a dimethylcarbamoyl group, a piperidyl group, a pyrrolidyl group, a morpholino group, a pyrazolyl group, a methylpyrazolyl group, an oxadiazolyl group, a methyloxadiazolyl group, a phenyl group and a pyridyl group.

16. A compound or a pharmacologically acceptable salt thereof, according to any one of claims 1 to 14, wherein X represents a phenyl group, a naphthyl group, a pyridyl group, a pyridazinyl group, a pyrimidinyl group, a pyrazinyl group, a quinolyl group or an isoquinolyl group, which may be substituted with 1 or 2 substituents selected from substituent group α, and

substituent group α represents a fluorine atom, a chlorine atom, a bromine atom, a cyano group, a hydroxy group, a methyl group, an ethyl group, a propyl group, an isopropyl group, a t-butyl group, a hydroxymethyl group, a fluoromethyl group, a difluoromethyl group, a trifluoromethyl group, a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, a trifluoromethoxy group, a piperidyl group, a pyrrolidyl group, a phenyl group and a pyridyl group.

17. A compound or a pharmacologically acceptable salt thereof, according to any one of claims 1 to 14, wherein X represents a phenyl group, a 2-pyridyl group, a 3-pyridyl group, a 3-pyridazinyl group, a 2-pyrimidinyl group or a 5-pyrimidinyl group, which may be substituted with 1 or 2 substituents selected from substituent group α, and

substituent group α represents a fluorine atom, a chlorine atom, a bromine atom, a cyano group, a hydroxy group, a methyl group, an ethyl group, a t-butyl group, a trifluoromethyl group, a methoxy group, an ethoxy group, a trifluoromethoxy group, a phenyl group and a pyridyl group.

18. A compound or a pharmacologically acceptable salt thereof,

according to any one of claims 1 to 14, wherein X represents a phenyl group or a 2-pyridyl group, which may be substituted with 1 or 2 substituents selected from substituent group α, and
substituent group α represents a fluorine atom, a chlorine atom, a trifluoromethyl group, a methoxy group and a trifluoromethoxy group.

19. A compound or a pharmacologically acceptable salt thereof, according to any one of claims 1 to 14, wherein X represents 4-fluorophenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 4-chlorophenyl, 2,4-dichlorophenyl, 4-trifluoromethylphenyl, 4-trifluoromethoxyphenyl, 5-fluoropyridin-2-yl, 5-chloropyridin-2-yl, 5-trifluoromethylpyridin-2-yl or 6-methoxypyridin-3-yl.

20. A compound or a pharmacologically acceptable salt thereof, according to any one of claims 1 to 14, wherein X represents a phenyl group, a naphthyl group, a pyridyl group, a pyridazinyl group, a pyrimidinyl group, a pyrazinyl group, a quinolyl group or an isoquinolyl group, which may be substituted with 1 or 2 substituents selected from substituent group α, and
substituent group α represents a fluorine atom, a chlorine atom, a bromine atom, a cyano group, a hydroxy group, a methyl group, an ethyl group, a propyl group, an isopropyl group, a t-butyl group, a hydroxymethyl group, a fluoromethyl group, a difluoromethyl group, a trifluoromethyl group, a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, a trifluoromethoxy group, a phenyl group and a pyridyl group.

21. A compound or a pharmacologically acceptable salt thereof, according to any one of claims 1 to 14, wherein X represents a phenyl group, a naphthyl group, a pyridyl group, a pyridazinyl group or a pyrimidinyl group, which may be substituted with 1 or 2 substituents selected from substituent group α, and
substituent group α represents a fluorine atom, a chlorine atom, a bromine atom, a cyano group, a hydroxy group, a methyl group, a trifluoromethyl group, a methoxy group, a trifluoromethoxy group and a phenyl group.

22. A compound or a pharmacologically acceptable salt thereof, according to any one of claims 1 to 14, wherein X represents a phenyl group or a pyridyl group, which may be substituted with 1 or 2

substituents selected from substituent group α, and
substituent group α represents a fluorine atom, a chlorine atom, a cyano group, a trifluoromethyl group and a trifluoromethoxy group.

23. A compound or a pharmacologically acceptable salt thereof, according to any one of claims 1 to 22, wherein Y represents -CO-, -O- or -NRa-, Ra represents a hydrogen atom, a methyl group or an ethyl group, and Ra may form a 5-membered ring by bonding with an atom that is a component of X in the case where Ra is an ethyl group in Y.

24. A compound or a pharmacologically acceptable salt thereof, according to any one of claims 1 to 22, wherein Y represents -O- or -NRa-, and Ra represents a hydrogen atom, a methyl group or an ethyl group.

25. A compound or a pharmacologically acceptable salt thereof, according to any one of claims 1 to 22, wherein Y represents -O-.

26. A compound or a pharmacologically acceptable salt thereof, according to claim 1, which is selected from the following:
N-{(1S)-2-[4-(2-fluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(3-fluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(4-fluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(4-chlorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-[(1S)-1-methyl-2-oxo-2-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}ethyl]quinoxaline-2-carboxamide,
N-{(1S)-2-[4-(4-cyanophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(2,4-difluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(3,4-difluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2-{4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}-1-methyl-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2-{4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}-1-methyl-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-[(1S)-1-methyl-2-oxo-2-(4-{[5-(trifluoromethyl)pyridin-2-

yl]oxy}piperidin-1-yl)ethyl]quinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(2-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(3-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-chlorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-[(1S)-1-({4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-cyanophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(2,4-difluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(3,4-difluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-{(1S)-1-[(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(2-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(3-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-chlorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-[(1S)-2-methyl-1-({4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-cyanophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(2,4-difluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(3,4-difluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-

methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-{(1S)-2-methyl-1-[(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide,
3-hydroxy-N-[(1S)-1-({4-[(6-methoxypyridin-3-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]quinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(2,4-difluorobenzoyl)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(2,4-difluorophenyl)(hydroxy)methyl]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-hydroxy-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-1-cyclopropyl-2-[4-(2-fluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-1-cyclopropyl-2-[4-(3-fluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-1-cyclopropyl-2-[4-(4-fluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(4-chlorophenoxy)piperidin-1-yl]-1-cyclopropyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-cyclopropyl-2-oxo-2-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}ethyl]-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(4-cyanophenoxy)piperidin-1-yl]-1-cyclopropyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-1-cyclopropyl-2-[4-(2,4-difluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-1-cyclopropyl-2-[4-(3,4-difluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-cyclopropyl-2-{4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2-{4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}-1-cyclopropyl-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-cyclopropyl-2-oxo-2-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)ethyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2,2-dimethyl-1-{[4-(2-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2,2-dimethyl-1-{[4-(3-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2,2-dimethyl-1-{[4-(4-fluorophenoxy)piperidin-1-

yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-chlorophenoxy)piperidin-1-yl]carbonyl}-2,2-dimethylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2,2-dimethyl-1-({4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}carbonyl)propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-cyanophenoxy)piperidin-1-yl]carbonyl}-2,2-dimethylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(2,4-difluorophenoxy)piperidin-1-yl]carbonyl}-2,2-dimethylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(3,4-difluorophenoxy)piperidin-1-yl]carbonyl}-2,2-dimethylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2,2-dimethyl-1-({4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2,2-dimethylpropyl]-3-hydroxyquinoxaline-2-carboxamide, and
N-{(1S)-2,2-dimethyl-1-[(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}-3-hydroxyquinoxaline-2-carboxamide.

27. A compound or a pharmacologically acceptable salt thereof, according to claim 1, which is selected from the following:
N-{(1S)-2-[4-(2-fluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(3-fluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(4-fluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(4-chlorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-[(1S)-1-methyl-2-oxo-2-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}ethyl]quinoxaline-2-carboxamide,
N-{(1S)-2-[4-(4-cyanophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(2,4-difluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(3,4-difluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2-{4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}-1-methyl-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2-{4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}-1-methyl-2-

oxoethyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-[(1S)-1-methyl-2-oxo-2-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)ethyl]quinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(2-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(3-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-chlorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-[(1S)-1-({4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-cyanophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(2,4-difluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(3,4-difluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-{(1S)-1-[(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(2-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(3-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-chlorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-[(1S)-2-methyl-1-({4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}carbonyl)propyl]quinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-cyanophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(2,4-difluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(3,4-difluorophenoxy)piperidin-1-yl]carbonyl}-2-methyl-

propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-{(1S)-2-methyl-1-[(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide,
N-{(1S)-1-cyclopropyl-2-[4-(2-fluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-1-cyclopropyl-2-[4-(3-fluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-1-cyclopropyl-2-[4-(4-fluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(4-chlorophenoxy)piperidin-1-yl]-1-cyclopropyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-cyclopropyl-2-oxo-2-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}ethyl]-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(4-cyanophenoxy)piperidin-1-yl]-1-cyclopropyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-1-cyclopropyl-2-[4-(2,4-difluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-1-cyclopropyl-2-[4-(3,4-difluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-cyclopropyl-2-{4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2-{4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}-1-cyclopropyl-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-cyclopropyl-2-oxo-2-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)ethyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2,2-dimethyl-1-{[4-(2-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2,2-dimethyl-1-{[4-(3-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2,2-dimethyl-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-chlorophenoxy)piperidin-1-yl]carbonyl}-2,2-dimethylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2,2-dimethyl-1-({4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}carbonyl)propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-cyanophenoxy)piperidin-1-yl]carbonyl}-2,2-dimethyl-

propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(2,4-difluorophenoxy)piperidin-1-yl]carbonyl}-2,2-dimethylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(3,4-difluorophenoxy)piperidin-1-yl]carbonyl}-2,2-dimethylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2,2-dimethyl-1-({4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2,2-dimethylpropyl]-3-hydroxyquinoxaline-2-carboxamide, and
N-{(1S)-2,2-dimethyl-1-[(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}-3-hydroxyquinoxaline-2-carboxamide.

28. A compound or a pharmacologically acceptable salt thereof, according to claim 1, which is selected from the following:
N-{(1S)-2-[4-(4-chlorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(2,4-difluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-{(1S)-2-[4-(3,4-difluorophenoxy)piperidin-1-yl]-1-methyl-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2-{4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}-1-methyl-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-2-{4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}-1-methyl-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-[(1S)-1-methyl-2-oxo-2-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)ethyl]quinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-chlorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)propyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-{(1S)-1-[(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide,
N-[(1S)-1-{[4-(4-fluorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-[(1S)-2-methyl-1-({4-[4-(trifluoromethoxy)phenoxy]piperidin-

1-yl}carbonyl)propyl]quinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-fluoropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
N-[(1S)-1-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}carbonyl)-2-methylpropyl]-3-hydroxyquinoxaline-2-carboxamide,
3-hydroxy-N-{(1S)-2-methyl-1-[(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)carbonyl]propyl}quinoxaline-2-carboxamide, and
N-{(1S)-1-cyclopropyl-2-[4-(4-fluorophenoxy)piperidin-1-yl]-2-oxoethyl}-3-hydroxyquinoxaline-2-carboxamide.

29. A pharmaceutical composition comprising as an active ingredient a compound or a pharmacologically acceptable salt thereof according to any one of claims 1 to 28.

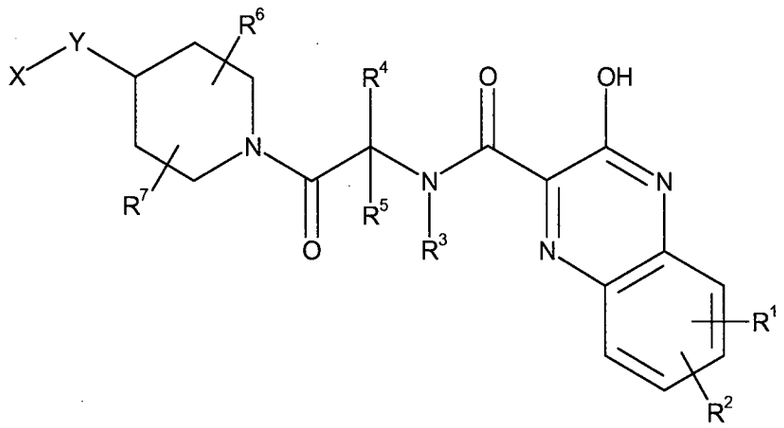
30. A pharmaceutical composition for preventing and/or treating a blood coagulation disorder, comprising as an active ingredient a compound or a pharmacologically acceptable salt thereof according to any one of claims 1 to 28.

31. A pharmaceutical composition for preventing and/or treating thromboembolism, congenital anticoagulant factor deficiency or plasminogen abnormality, comprising as an active ingredient a compound or a pharmacologically acceptable salt thereof according to any one of claims 1 to 28.

32. A pharmaceutical composition for preventing thrombogenesis following artificial valve replacement surgery, or thrombogenesis caused by nonvalvular atrial fibrillation or atrial fibrillation accompanying valvular heart disease, comprising as an active ingredient a compound or a pharmacologically acceptable salt thereof according to any one of claims 1 to 28.

ABSTRACT

The present invention provides a novel hydroxyquinoxaline carboxamide derivative that is useful for preventing and/or treating blood coagulation disorders. A compound represented by formula (i), or a pharmacologically acceptable salt thereof:



wherein, each of R^1 and R^2 independently represents a group such as a hydrogen atom or a halogen atom; R^3 represents a group such as a hydrogen atom; each of R^4 and R^5 independently represents a group such as a hydrogen atom, a halogen atom or a C_{1-4} alkyl group; each of R^6 and R^7 independently represents a hydrogen atom or a C_{1-4} alkyl group; X represents a group such as a C_{3-10} cycloalkyl group, C_{6-10} aryl group or a 5- to 10-membered heterocyclic group, which may be substituted with substituent(s) selected from substituent group α; Y represents a group such as -CO-, -O- or -NRa-, and Ra represents a group such as a hydrogen atom or a C_{1-4} alkyl group.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2009/055741

A. CLASSIFICATION OF SUBJECT MATTER
C07D401/12(2006.01)i, *A61K31/498*(2006.01)i, *A61K31/501*(2006.01)i, *A61K31/506*(2006.01)i, *A61K31/5377*(2006.01)i, *A61P7/02*(2006.01)i, *A61P9/00*(2006.01)i, *C07D401/14*(2006.01)i, *C07D417/14*(2006.01)i
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)
C07D401/12, A61K31/498, A61K31/501, A61K31/506, A61K31/5377, A61P7/02, A61P9/00, C07D401/14, C07D417/14

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)
CA/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	WO 2007/092681 A2 (BRISTOL-MYERS SQUIBB CO.), 16 August, 2007 (16.08.07), Example 561 & US 2007/0208056 A1 & KR 2008095890 A	1-32
A	JP 2003-502314 A (Eli Lilly and Co.), 21 January, 2003 (21.01.03), Example 245 & US 2002/0055522 A1 & EP 1192132 A & WO 2000/076971 A2 & CN 1438999 A	1-32

☐ 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
21 April, 2009 (21.04.09)	12 May, 2009 (12.05.09)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

DERIVADO DE HIDROXI-QUINOXALIN-CARBOXAMIDA

CAMPO TÉCNICO

La presente invención se refiere a un derivado de hidroxi-quinoxalin-carboxamida, y a las sales farmacológicamente aceptables del mismo, que son útiles como productos farmacéuticos. De una manera más particular, la presente invención se refiere a un derivado de hidroxi-quinoxalin-carboxamida, y a las sales farmacológicamente aceptables del mismo, que demuestran una acción anticoagulante.

TÉCNICA ANTECEDENTE

En los años recientes, el plazo de vida promedio ha llegado a ser más largo y el tamaño de la población de ancianos ha aumentado debido al progreso en el cuidado médico. En adición, la proporción de las personas que sufren de enfermedades cardiovasculares ha aumentado debido a los cambios en los hábitos en el comer y en el estilo de vida. En particular, no solamente las enfermedades trombóticas, tales como infarto cerebral, infarto de miocardio, o alteración circulatoria periférica demuestran altos índices de mortalidad, sino que las serias restricciones vitales causadas por las secuelas presentan una enorme carga para los pacientes. La inhibición de la formación de trombos es importante para prevenir y tratar estas enfermedades.

El aumento de la coagulación sanguínea ha sido convencionalmente una de las causas de angina inestable, infarto

cerebral, embolia cerebral, infarto de miocardio, infarto pulmonar, embolia pulmonar, enfermedad de Buerger, trombosis de venas profundas, síndrome de coagulación intravascular generalizada, trombosis en seguida de reemplazo de válvula protésica, reoclusión en seguida de reconstrucción vascular, y trombosis durante la circulación extracorpórea. De conformidad con lo anterior, existe una necesidad de un anticoagulante oral que tenga una respuesta superior a la dosis, sustantividad, bajo riesgo de hemorragia y pocos efectos secundarios (Documento No Patentado 1).

Los anticoagulantes orales que se encuentran actualmente en el mercado son fármacos basados en cumarina, como es representado por la warfarina (Documento de Patente 1). Este fármaco inhibe el suministro de vitamina K reducida mediante la inhibición del ciclo metabólico de la vitamina K, e inhibe la modificación mediante γ-carboxilación (modificación de Gla) de los residuos de ácido glutámico mediante la γ-carboxilasa. Esto conduce al fármaco para inhibir la activación de los factores de coagulación sanguínea dependientes de la vitamina K (tales como FII, FVII, FIX o FX), y demuestra una potente acción anticoagulante. Sin embargo, aunque la warfarina demuestra efectos farmacológicos potentes y estables, tiene un estrecho rango terapéutico efectivo, y requiere del monitoreo mediante un muestreo frecuente de sangre con el objeto de acomodar las diferencias individuales en la dosis efectiva. En adición, el riesgo de desviarse del rango terapéutico debido a las interacciones de los fármacos, también se ha señalado la influencia

de la vitamina K de la dieta. Por consiguiente, existe un deseo de un anticoagulante oral que permita controlar fácilmente los efectos farmacológicos con un monitoreo de baja frecuencia, que tenga una seguridad superior, y que tenga una alta versatilidad general.

En los años recientes, se ha reportado un derivado de cumarina ATI-5923 (Documento de Patente 2) que está diseñado para evitar la interacción de la warfarina con los fármacos, y actualmente se está sometiendo a estudios clínicos. En adición, se ha reportado la sulfaquinoxalina como un compuesto diferente de un derivado de cumarina (Documento No Patentado 2). Sin embargo, la estructura de hidroxi-quinoxalina que tienen los compuestos de la presente solicitud como una estructura parcial de los mismos, no se da a conocer ni se sugiere en estos documentos de la técnica anterior.

[Documento de Patente 1] Patente de los Estados Unidos de Norteamérica Número 2,642,441.

[Documento de Patente 2] Solicitud Internacional Número WO 2005/100336.

[Documento No Patentado 1] Thrombosis Research, Volumen 68, páginas 507-512, 1992.

[Documento No Patentado 2] Archive of Biochemistry and Biophysics, Volumen 269, páginas 18-24, 1989.

DESCRIPCIÓN DE LA INVENCIÓN

[Problemas que serán resueltos por la invención]

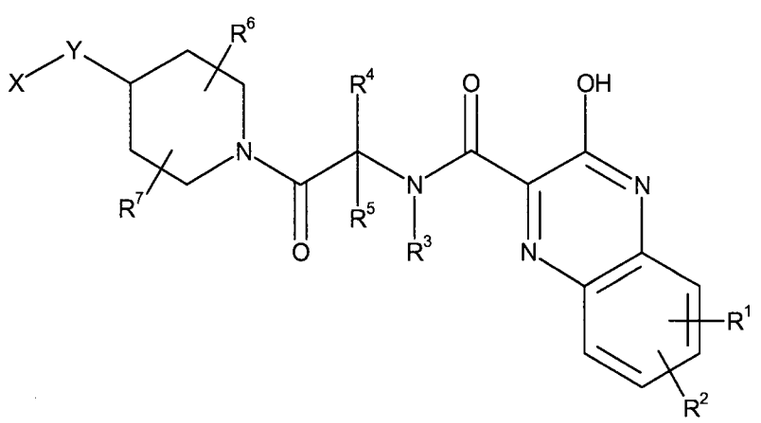
Como un resultado de la conducción de estudios sobre la

síntesis de compuestos que sean capaces de inhibir la activación de los factores de coagulación sanguínea, como se describe anteriormente, junto con la acción farmacológica de los mismos, los inventores de la presente invención encontraron que un grupo de compuestos que tienen, para su estructura básica, un derivado de hidroxi-quinoxalin-carboxamida, tienen una acción anticoagulante superior, conduciendo de esta manera a la realización de la presente invención.

[Medios para resolver los problemas]

La presente invención se refiere a:

(1) un compuesto representado por la siguiente fórmula general (i):



en donde:

cada uno de R^1 y R^2 representa independientemente un átomo de hidrógeno, un átomo de halógeno, un grupo ciano, un grupo alquilo de 1 a 4 átomos de carbono, o un grupo alcoxilo de 1 a 4 átomos de carbono,

R^3 representa un átomo de hidrógeno o un grupo alquilo

de 1 a 4 átomos de carbono,

cada uno de R^4 y R^5 representa independientemente un átomo de hidrógeno, un átomo de halógeno, un grupo alquilo de 1 a 4 átomos de carbono, un grupo alquenilo de 2 a 4 átomos de carbono, un grupo alquinilo de 2 a 4 átomos de carbono, un grupo cicloalquilo de 3 a 5 átomos de carbono, o un grupo hidroxi-alquilo de 1 a 4 átomos de carbono,

cada uno de R^6 y R^7 representa independientemente un átomo de hidrógeno o un grupo alquilo de 1 a 4 átomos de carbono,

X representa un grupo cicloalquilo de 3 a 10 átomos de carbono monocíclico o bicíclico, un grupo arilo de 6 a 10 átomos de carbono monocíclico o bicíclico, o un grupo heterocíclico de 5 a 10 miembros monocíclico o bicíclico (en donde el grupo heterocíclico incluye heterociclos aromáticos y heterociclos no aromáticos, y contiene de 1 a 3 átomos seleccionados a partir del grupo que consiste en un átomo de nitrógeno, un átomo de azufre, y un átomo de oxígeno), el cual puede estar sustituido con 1 a 3 sustituyentes seleccionados a partir del grupo sustituyente α,

Y representa -CHRa-, -C(OH)Ra-, -CO-, -O-, -NRa-, -S-, -SO- o $-SO_2-$,

Ra representa un átomo de hidrógeno, un grupo alquilo de 1 a 4 átomos de carbono, un grupo halo-alquilo de 1 a 4 átomos de carbono, o un grupo alcanoílo de 1 a 4 átomos de carbono, o

en el caso en donde Ra en Y es un grupo alquilo de 1 a 4 átomos de carbono, un grupo halo-alquilo de 1 a 4 átomos de

carbono, o un grupo alcanoílo de 1 a 4 átomos de carbono, Ra puede formar un anillo de 5 ó 6 miembros mediante su enlace con un átomo que sea un componente de X,

el grupo sustituyente α representa:

un átomo de halógeno, un grupo ciano, un grupo nitro, un grupo hidroxilo;

un grupo alquilo de 1 a 4 átomos de carbono, un grupo alquenilo de 2 a 4 átomos de carbono, un grupo alquinilo de 2 a 4 átomos de carbono, un grupo cicloalquilo de 3 a 6 átomos de carbono, un grupo alcoxilo de 1 a 4 átomos de carbono, o un grupo cicloalcoxilo de 3 a 6 átomos de carbono, el cual puede estar sustituido con sustituyente(s) seleccionado(s) a partir del grupo sustituyente ß;

-OCORb, -CORb, -COORb, -CONRbRc, -NRbRc, -NRbCORc, -NRbSORc, -NRbSO$_2$Rc, -SRb, -SORb, -SO$_2$Rb;

un grupo fenilo, y

un grupo heterocíclico de 5 ó 6 miembros, el cual puede estar sustituido con un grupo alquilo de 1 a 4 átomos de carbono (en donde el grupo heterocíclico incluye heterociclos aromáticos y heterociclos no aromáticos, y contiene de 1 a 3 átomos seleccionados a partir del grupo que consiste en un átomo de nitrógeno, un átomo de azufre, y un átomo de oxígeno),

cada uno de Rb y Rc representa independientemente un átomo de hidrógeno, un grupo alquilo de 1 a 4 átomos de carbono o un grupo halo-alquilo de 1 a 4 átomos de carbono, y

el grupo sustituyente ß representa un átomo de halógeno, un grupo hidroxilo, un grupo alcoxilo de 1 a 4 átomos de carbono, y un grupo alcanoiloxilo de 1 a 4 átomos de carbono,

o una sal farmacológicamente aceptable del mismo,

(2) un compuesto o una sal farmacológicamente aceptable del mismo, descrito en (1) anterior, en donde cada uno de R^1 y R^2 representa independientemente un átomo de hidrógeno o un átomo de halógeno,

(3) un compuesto o una sal farmacológicamente aceptable del mismo, descrito en (1) anterior, en donde cada uno de R^1 y R^2 representa independientemente un átomo de hidrógeno o un átomo de flúor,

(4) un compuesto o una sal farmacológicamente aceptable del mismo, descrito en (1) anterior, en donde R^1 y R^2 representan ambos un átomo de hidrógeno,

(5) un compuesto o una sal farmacológicamente aceptable del mismo, descrito en cualquiera de (1) a (4) anteriores, en donde R^3 representa un átomo de hidrógeno o un grupo metilo,

(6) un compuesto o una sal farmacológicamente aceptable del mismo, descrito en cualquiera de (1) a (4) anteriores, en donde R^3 representa un átomo de hidrógeno,

(7) un compuesto o una sal farmacológicamente aceptable del mismo, descrito en cualquiera de (1) a (6) anteriores, en donde R^4 representa un átomo de hidrógeno, un átomo de flúor, un grupo alquilo de 1 a 4 átomos de carbono, un grupo alquenilo de 2 a 4

átomos de carbono, un grupo alquinilo de 2 a 4 átomos de carbono, un grupo cicloalquilo de 3 a 5 átomos de carbono, o un grupo hidroxi-alquilo de 1 a 4 átomos de carbono, y R^5 representa un átomo de hidrógeno,

(8) un compuesto o una sal farmacológicamente aceptable del mismo, descrito en cualquiera de (1) a (6) anteriores, en donde R^4 representa un grupo metilo, un grupo etilo, un grupo isopropilo, un grupo isobutilo, un grupo terbutilo, un grupo ciclopropilo, o un grupo 1-hidroxi-1-metil-etilo, y R^5 representa un átomo de hidrógeno,

(9) un compuesto o una sal farmacológicamente aceptable del mismo, descrito en cualquiera de (1) a (6) anteriores, en donde R^4 representa un grupo metilo, un grupo etilo, un grupo isopropilo, un grupo terbutilo, un grupo ciclopropilo, o un grupo 1-hidroxi-1-metil-etilo, y R^5 representa un átomo de hidrógeno,

(10) un compuesto o una sal farmacológicamente aceptable del mismo, descrito en cualquiera de (1) a (6) anteriores, en donde R^4 representa un grupo etilo, un grupo isopropilo, un grupo ciclopropilo, o un grupo 1-hidroxi-1-metil-etilo, y R^5 representa un átomo de hidrógeno,

(11) un compuesto o una sal farmacológicamente aceptable del mismo, descrito en cualquiera de (1) a (6) anteriores, en donde cada uno de R^4 y R^5 representa independientemente un átomo de hidrógeno, un átomo de halógeno, un grupo alquilo de 1 a 4 átomos de carbono, un grupo alquenilo de 2 a 4 átomos de carbono, un grupo alquinilo de 2 a 4 átomos de carbono, o un grupo cicloalquilo

de 3 a 5 átomos de carbono,

(12) un compuesto o una sal farmacológicamente aceptable del mismo, descrito en cualquiera de (1) a (6) anteriores, en donde R^4 representa un átomo de hidrógeno, un grupo metilo, un grupo etilo, un grupo isopropilo, un grupo isobutilo, un grupo terbutilo o un grupo ciclopropilo, y R^5 representa un átomo de hidrógeno,

(13) un compuesto o una sal farmacológicamente aceptable del mismo, descrito en cualquiera de (1) a (12) anteriores, en donde cada uno de R^6 y R^7 representa independientemente un átomo de hidrógeno o un grupo metilo,

(14) un compuesto o una sal farmacológicamente aceptable del mismo, descrito en cualquiera de (1) a (12) anteriores, en donde R^6 y R^7 representan ambos un átomo de hidrógeno,

(15) un compuesto o una sal farmacológicamente aceptable del mismo, descrito en cualquiera de (1) a (14) anteriores, en donde X representa un grupo fenilo, un grupo naftilo, un grupo piridilo, un grupo piridazinilo, un grupo pirimidinilo, un grupo pirazinilo, un grupo quinolilo, un grupo isoquinolilo, un grupo bencimidazolilo, un grupo benzoxazolilo, o un grupo benzotiazolilo, el cual puede estar sustituido con 1 ó 2 sustituyentes seleccionados a partir del grupo sustituyente α, y

el grupo sustituyente α representa un átomo de halógeno, un grupo ciano, un grupo nitro, un grupo hidroxilo, un grupo metilo, un grupo etilo, un grupo propilo, un grupo isopropilo, un grupo terbutilo, un grupo hidroxi-metilo, un grupo fluoro-metilo, un grupo

difluoro-metilo, un grupo trifluoro-metilo, un grupo metoxilo, un grupo etoxilo, un grupo propoxilo, un grupo isopropoxilo, un grupo acetoxilo, un grupo trifluoro-metoxilo, un grupo acetilo, un grupo metoxi-carbonilo, un grupo etoxi-carbonilo, un grupo dimetil-carbamoílo, un grupo piperidilo, un grupo pirrolidilo, un grupo morfolino, un grupo pirazolilo, un grupo metil-pirazolilo, un grupo oxadiazolilo, un grupo metil-oxadiazolilo, un grupo fenilo, y un grupo piridilo,

(16) un compuesto o una sal farmacológicamente aceptable del mismo, descrito en cualquiera de (1) a (14) anteriores, en donde X representa un grupo fenilo, un grupo naftilo, un grupo piridilo, un grupo piridazinilo, un grupo pirimidinilo, un grupo pirazinilo, un grupo quinolilo, o un grupo isoquinolilo, el cual puede estar sustituido con 1 ó 2 sustituyentes seleccionados a partir del grupo sustituyente α, y

el grupo sustituyente α representa un átomo de flúor, un átomo de cloro, un átomo de bromo, un grupo ciano, un grupo hidroxilo, un grupo metilo, un grupo etilo, un grupo propilo, un grupo isopropilo, un grupo terbutilo, un grupo hidroxi-metilo, un grupo fluoro-metilo, un grupo difluoro-metilo, un grupo trifluoro-metilo, un grupo metoxilo, un grupo etoxilo, un grupo propoxilo, un grupo isopropoxilo, un grupo trifluoro-metoxilo, un grupo piperidilo, un grupo pirrolidilo, un grupo fenilo, y un grupo piridilo,

(17) un compuesto o una sal farmacológicamente aceptable del mismo, descrito en cualquiera de (1) a (14) anteriores, en donde X representa un grupo fenilo, un grupo 2-piridilo, un grupo 3-piridilo,

un grupo 3-piridazinilo, un grupo 2-pirimidinilo, o un grupo 5-pirimidinilo, el cual puede estar sustituido con 1 ó 2 sustituyentes seleccionados a partir del grupo sustituyente α, y

el grupo sustituyente α representa un átomo de flúor, un átomo de cloro, un átomo de bromo, un grupo ciano, un grupo hidroxilo, un grupo metilo, un grupo etilo, un grupo terbutilo, un grupo trifluoro-metilo, un grupo metoxilo, un grupo etoxilo, un grupo trifluoro-metoxilo, un grupo fenilo, y un grupo piridilo,

(18) un compuesto o una sal farmacológicamente aceptable del mismo, descrito en cualquiera de (1) a (14) anteriores, en donde X representa un grupo fenilo o un grupo 2-piridilo, el cual puede estar sustituido con 1 ó 2 sustituyentes seleccionados a partir del grupo sustituyente α, y el grupo sustituyente α representa un átomo de flúor, un átomo de cloro, un grupo trifluoro-metilo, un grupo metoxilo, y un grupo trifluoro-metoxilo,

(19) un compuesto o una sal farmacológicamente aceptable del mismo, descrito en cualquiera de (1) a (14) anteriores, en donde X representa 4-fluoro-fenilo, 2,4-difluoro-fenilo, 3,4-difluoro-fenilo, 4-cloro-fenilo, 2,4-dicloro-fenilo, 4-trifluoro-metil-fenilo, 4-trifluoro-metoxi-fenilo, 5-fluoro-piridin-2-ilo, 5-cloro-piridin-2-ilo, 5-trifluoro-metil-piridin-2-ilo o 6-metoxi-piridin-3-ilo,

(20) un compuesto o una sal farmacológicamente aceptable del mismo, descrito en cualquiera de (1) a (14) anteriores, en donde X representa un grupo fenilo, un grupo naftilo, un grupo piridilo, un grupo piridazinilo, un grupo pirimidinilo, un grupo pirazinilo, un grupo

quinolilo, o un grupo isoquinolilo, el cual puede estar sustituido con 1 ó 2 sustituyentes seleccionados a partir del grupo sustituyente α, y el grupo sustituyente α representa un átomo de flúor, un átomo de cloro, un átomo de bromo, un grupo ciano, un grupo hidroxilo, un grupo metilo, un grupo etilo, un grupo propilo, un grupo isopropilo, un grupo terbutilo, un grupo hidroxi-metilo, un grupo fluoro-metilo, un grupo difluoro-metilo, un grupo trifluoro-metilo, un grupo metoxilo, un grupo etoxilo, un grupo propoxilo, un grupo isopropoxilo, un grupo trifluoro-metoxilo, un grupo fenilo, y un grupo piridilo,

(21) un compuesto o una sal farmacológicamente aceptable del mismo, descrito en cualquiera de (1) a (14) anteriores, en donde X representa un grupo fenilo, un grupo naftilo, un grupo piridilo, un grupo piridazinilo, o un grupo pirimidinilo, el cual puede estar sustituido con 1 ó 2 sustituyentes seleccionados a partir del grupo sustituyente α, y el grupo sustituyente α representa un átomo de flúor, un átomo de cloro, un átomo de bromo, un grupo ciano, un grupo hidroxilo, un grupo metilo, un grupo trifluoro-metilo, un grupo metoxilo, un grupo trifluoro-metoxilo y un grupo fenilo,

(22) un compuesto o una sal farmacológicamente aceptable del mismo, descrito en cualquiera de (1) a (14) anteriores, en donde X representa un grupo fenilo o un grupo piridilo, el cual puede estar sustituido con 1 ó 2 sustituyentes seleccionados a partir del grupo sustituyente α, y el grupo sustituyente α representa un átomo de flúor, un átomo de cloro, un grupo ciano, un grupo trifluoro-metilo, y un grupo trifluoro-metoxilo,

(23) un compuesto o una sal farmacológicamente aceptable del mismo, descrito en cualquiera de (1) a (22) anteriores, en donde Y representa -CO-, -O- o -NRa-, Ra representa un átomo de hidrógeno, un grupo metilo, o un grupo etilo, y Ra puede formar un anillo de 5 miembros mediante su enlace con un átomo que sea un componente de X en el caso en donde Ra sea un grupo etilo en Y,

(24) un compuesto o una sal farmacológicamente aceptable del mismo, descrito en cualquiera de (1) a (22) anteriores, en donde Y representa -O- o -NRa-, y Ra representa un átomo de hidrógeno, un grupo metilo, o un grupo etilo,

(25) un compuesto o una sal farmacológicamente aceptable del mismo, descrito en cualquiera de (1) a (22) anteriores, en donde Y representa -O-,

(26) un compuesto o una sal farmacológicamente aceptable del mismo, descrito en (1) anterior, el cual se selecciona a partir de los siguientes:

N-{(1S)-2-[4-(2-fluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(3-fluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(4-fluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(4-cloro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-[(1S)-1-metil-2-oxo-2-{4-[4-(trifluoro-metoxi)-

fenoxi]-piperidin-1-il}-etil]-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(4-ciano-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2-{4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-1-metil-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2-{4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-1-metil-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-[(1S)-1-metil-2-oxo-2-(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-etil]-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(2-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(3-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-cloro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-[(1S)-1-({4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-ciano-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-{(1S)-1-[(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(2-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(3-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-cloro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-[(1S)-2-metil-1-({4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-ciano-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-

2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-{(1S)-2-metil-1-[(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida,

3-hidroxi-N-[(1S)-1-({4-[(6-metoxi-piridin-3-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(2,4-difluoro-benzoil)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(2,4-difluoro-fenil)-(hidroxi)-metil]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-hidroxi-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-1-ciclopropil-2-[4-(2-fluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-1-ciclopropil-2-[4-(3-fluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-1-ciclopropil-2-[4-(4-fluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(4-cloro-fenoxi)-piperidin-1-il]-1-ciclopropil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-ciclopropil-2-oxo-2-{4-[4-(trifluoro-metoxi)-

fenoxi]-piperidin-1-il}-etil]-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(4-ciano-fenoxi)-piperidin-1-il]-1-ciclopropil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-1-ciclopropil-2-[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-1-ciclopropil-2-[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-ciclopropil-2-{4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2-{4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-1-ciclopropil-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-ciclopropil-2-oxo-2-(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-etil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2,2-dimetil-1-{[4-(2-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2,2-dimetil-1-{[4-(3-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2,2-dimetil-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-cloro-fenoxi)-piperidin-1-il]-carbonil}-2,2-dimetil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2,2-dimetil-1-({4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-carbonil)-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-ciano-fenoxi)-piperidin-1-il]-carbonil}-2,2-

dimetil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-2,2-dimetil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-2,2-dimetil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2,2-dimetil-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2,2-dimetil-propil]-3-hidroxi-quinoxalin-2-carboxamida, y

N-{(1S)-2,2-dimetil-1-[(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-3-hidroxi-quinoxalin-2-carboxamida,

(27) un compuesto o una sal farmacológicamente aceptable del mismo, descrito en (1) anterior, el cual se selecciona a partir de los siguientes:

N-{(1S)-2-[4-(2-fluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(3-fluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(4-fluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(4-cloro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-[(1S)-1-metil-2-oxo-2-{4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-etil]-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(4-ciano-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2-{4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-1-metil-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2-{4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-1-metil-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-[(1S)-1-metil-2-oxo-2-(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-etil]-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(2-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(3-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-cloro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-[(1S)-1-({4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-ciano-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-

propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-{(1S)-1-[(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(2-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(3-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-cloro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-[(1S)-2-metil-1-({4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-ciano-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-{(1S)-2-metil-1-[(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida,

N-{(1S)-1-ciclopropil-2-[4-(2-fluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-1-ciclopropil-2-[4-(3-fluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-1-ciclopropil-2-[4-(4-fluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(4-cloro-fenoxi)-piperidin-1-il]-1-ciclopropil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-ciclopropil-2-oxo-2-{4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-etil]-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(4-ciano-fenoxi)-piperidin-1-il]-1-ciclopropil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-1-ciclopropil-2-[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-1-ciclopropil-2-[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-ciclopropil-2-{4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2-{4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-1-

ciclopropil-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-ciclopropil-2-oxo-2-(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-etil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2,2-dimetil-1-{[4-(2-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2,2-dimetil-1-{[4-(3-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2,2-dimetil-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-cloro-fenoxi)-piperidin-1-il]-carbonil}-2,2-dimetil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2,2-dimetil-1-({4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-carbonil)-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-ciano-fenoxi)-piperidin-1-il]-carbonil}-2,2-dimetil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-2,2-dimetil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-2,2-dimetil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2,2-dimetil-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2,2-dimetil-propil]-3-hidroxi-quinoxalin-2-carboxamida, y

N-{(1S)-2,2-dimetil-1-[(4-{[5-(trifluoro-metil)-piridin-2-il]-

oxi}-piperidin-1-il)-carbonil]-propil}-3-hidroxi-quinoxalin-2-carboxamida,

(28) un compuesto o una sal farmacológicamente aceptable del mismo, descrito en (1) anterior, el cual se selecciona a partir de los siguientes:

N-{(1S)-2-[4-(4-cloro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2-{4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-1-metil-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2-{4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-1-metil-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-[(1S)-1-metil-2-oxo-2-(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-etil]-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-cloro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-{(1S)-1-[(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-[(1S)-2-metil-1-({4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-{(1S)-2-metil-1-[(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida, y

N-{(1S)-1-ciclopropil-2-[4-(4-fluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida.

(29) Una composición farmacéutica, la cual comprende, como un ingrediente activo, un compuesto o una sal farmacológicamente aceptable del mismo, seleccionado a partir de aquéllos descritos en cualquiera de (1) a (28) anteriores,

(30) una composición farmacéutica para prevenir y/o tratar un trastorno de la coagulación sanguínea, el cual comprende, como un ingrediente activo, un compuesto o una sal farmacológicamente aceptable del mismo, seleccionado a partir de aquéllos descritos en cualquiera de (1) a (28) anteriores,

(31) una composición farmacéutica para prevenir y/o tratar tromboembolismo, deficiencia congénita del factor anticoagulante, o

anormalidad de plasminógeno, la cual comprende, como un ingrediente activo, un compuesto o una sal farmacológicamente aceptable del mismo, seleccionado a partir de aquéllos descritos en cualquiera de (1) a (28) anteriores, y,

(32) una composición farmacéutica para prevenir trombogénesis en seguida de cirugía de reemplazo de válvula artificial, o trombogénesis causada por fibrilación auricular no valvular, o fibrilación auricular que acompaña a cardiopatía valvular, la cual comprende, como un ingrediente activo, un compuesto o una sal farmacológicamente aceptable del mismo, seleccionado a partir de aquéllos descritos en cualquiera de (1) a (28) anteriores.

En adición, la presente invención proporciona un método para prevenir y/o tratar trastornos de la coagulación sanguínea, el cual comprende administrar una cantidad efectiva de un compuesto o de una sal farmacológicamente aceptable del mismo, seleccionado a partir de aquéllos descritos en cualquiera de (1) a (28) anteriores, a un animal de sangre caliente (y de preferencia a un ser humano) (tal como un método para prevenir y/o tratar tromboembolismo, deficiencia congénita del factor anticoagulante, o anormalidad de plasminógeno, o un método para prevenir trombogénesis en seguida de cirugía de reemplazo de válvula artificial, o trombogénesis causada por fibrilación auricular no valvular, o fibrilación auricular que acompaña a cardiopatía valvular).

En la fórmula general (i) anteriormente mencionada, un "átomo de halógeno" en las definiciones de R^1, R^2, R^4, R^5, α y ß, se refiere a

un átomo de flúor, un átomo de cloro, un átomo de bromo, o un átomo de yodo. Es de preferencia un átomo de flúor o un átomo de cloro, y de una manera muy preferible es un átomo de flúor.

Un "grupo alquilo de 1 a 4 átomos de carbono", en las definiciones de R^1, R^2, R^3, R^4, R^5, R^6, R^7, Ra, Rb, Rc y α, se refiere a un grupo alquilo lineal o ramificado que tiene 1 a 4 átomos de carbono, por ejemplo, metilo, etilo, propilo, isopropilo, butilo normal, isobutilo, butilo secundario, o butilo terciario.

Un "grupo halo-alquilo de 1 a 4 átomos de carbono", en las definiciones de Ra, Rb y Rc, se refiere a un grupo en donde uno o dos o más átomos de hidrógeno del "grupo halo-alquilo de 1 a 4 átomos de carbono" anteriormente mencionado están sustituidos por los "átomos de halógeno" anteriormente mencionados. Los ejemplos son fluoro-metilo, difluoro-metilo, trifluoro-metilo y 2,2,2-trifluoro-etilo, y de preferencia trifluoro-metilo.

Un "grupo hidroxi-alquilo de 1 a 4 átomos de carbono" en las definiciones de R^4 y R^5, se refiere a un grupo en donde uno o dos o más átomos de hidrógeno del "grupo alquilo de 1 a 4 átomos de carbono" anteriormente mencionado están sustituidos por grupos hidroxilo. Los ejemplos son hidroxi-metilo, 1-hidroxi-etilo, 2-hidroxi-etilo, 1-hidroxi-1-metil-etilo, 1-hidroxi-2-metil-propilo y 3-hidroxi-butilo. Es de preferencia 1-hidroxi-1-metil-etilo.

Un "grupo alquenilo de 2 a 4 átomos de carbono", en las definiciones de R^4, R^5 y α, se refiere a un grupo alquenilo lineal o ramificado que tiene de 2 a 4 átomos de carbono, por ejemplo, vinilo,

1-propenilo, 2-propenilo, isopropenilo, 1-metil-2-propenilo, 2-metil-2-propenilo, 2-butenilo, 3-butenilo o 1,3-butadienilo. Es de preferencia un grupo alquenilo que tiene 2 ó 3 átomos de carbono.

Un "grupo alquinilo de 2 a 4 átomos de carbono", en las definiciones de R^4 y R^5, se refiere a un grupo alquinilo lineal o ramificado que tiene de 2 a 4 átomos de carbono, por ejemplo, un grupo etinilo, 2-propinilo, 1-metil-2-propinilo, 2-metil-2-propinilo, 2-butinilo o 3-butinilo. Es de preferencia un grupo alquinilo que tiene 2 ó 3 átomos de carbono.

Un "grupo cicloalquilo de 3 a 5 átomos de carbono", en las definiciones de R^4 y R^5, se refiere a un grupo cicloalquilo que tiene de 3 a 5 átomos de carbono, por ejemplo, ciclopropilo, ciclobutilo o ciclopentilo.

Un "grupo cicloalquilo de 3 a 6 átomos de carbono", en la definición de α, se refiere a un grupo cicloalquilo que tiene de 3 a 6 átomos de carbono, por ejemplo, el "grupo cicloalquilo de 3 a 5 átomos de carbono" anteriormente mencionado, o ciclohexilo.

Un "grupo cicloalquilo de 3 a 10 átomos de carbono monocíclico o bicíclico", en la definición de X, se refiere a un grupo hidrocarburo cíclico saturado, monocíclico o bicíclico, que tiene de 3 a 10 átomos de carbono, por ejemplo, el "grupo cicloalquilo de 3 a 6 átomos de carbono" anteriormente mencionado o ciclo-octilo, ciclononilo, o tetrahidro-naftilo.

Un "grupo arilo de 6 a 10 átomos de carbono monocíclico o bicíclico", en la definición de X, se refiere a un grupo hidrocarburo

aromático que tiene de 6 a 10 átomos de carbono, por ejemplo, fenilo o naftilo, y de preferencia fenilo.

Un "grupo heterocíclico de 5 ó 6 miembros", en la definición de α, incluye heterociclos aromáticos y heterociclos no aromáticos monocíclicos de 5 ó 6 miembros, y el grupo heterocíclico contiene de 1 a 3 átomos seleccionados a partir del grupo que consiste en un átomo de nitrógeno, un átomo de azufre, y un átomo de oxígeno.

Los grupos heterocíclicos aromáticos que son un "grupo heterocíclico de 5 ó 6 miembros" incluyen los grupos heterocíclicos aromáticos monocíclicos que contienen de 1 a 3 átomos seleccionados a partir del grupo que consiste en un átomo de nitrógeno, un átomo de azufre, y un átomo de oxígeno, tales como los grupos de anillo de 5 miembros, tales como pirrolilo, tienilo, furilo, pirazolilo, imidazolilo, oxazolilo, isoxazolilo, triazolilo, tetrazolilo o tiadiazolilo, y los grupos de anillo de 6 miembros, tales como los grupos piranilo, piridilo, piridazinilo, pirimidinilo o pirazinilo. Los ejemplos preferidos incluyen 2-piridilo, 3-piridilo, 3-piridazinilo, 2-pirimidinilo y 5-pirimidinilo, mientras que los ejemplos más preferidos incluyen 2-piridilo, 3-piridilo, 3-piridazinilo y 2-pirimidinilo.

Entre los "grupos heterocíclicos de 5 ó 6 miembros", un grupo heterocíclico no aromático se refiere a un grupo en donde 1 a 3 átomos de carbono de un grupo cicloalquilo monocíclico o de un grupo cicloalquenilo monocíclico que tiene 5 ó 6 átomos de carbono, están sustituidos con un átomo seleccionado a partir del grupo que consiste en un átomo de nitrógeno, un átomo de azufre, y un átomo

de oxígeno.

Los grupos heterocíclicos no aromáticos que son "grupos heterocíclicos de 5 ó 6 miembros" incluyen grupos heterocíclicos no aromáticos monocíclicos como un anillo del grupo de 5 miembros, tales como pirrolidinilo, pirrolinilo, imidazolidinilo, imidazolinilo, pirazolidinilo, pirazolinilo, oxazolidinilo o tiazolidinilo; y un grupo de anillo de 6 miembros, tal como piperidilo, tetrahidro-piridilo, dihidro-piridilo, piperazinilo, morfolinilo o tiomorfolinilo.

Un "grupo heterocíclico de 5 a 10 miembros monocíclico o bicíclico", en la definición de X, incluye heterociclos aromáticos y heterociclos no aromáticos de 5 a 10 miembros monocíclicos o bicíclicos, y el grupo heterocíclico contiene de 1 a 3 átomos seleccionados a partir del grupo que consiste en un átomo de nitrógeno, un átomo de azufre, y un átomo de oxígeno.

Los heterociclos aromáticos de 5 a 10 miembros monocíclicos o bicíclicos incluyen, por ejemplo, los grupos heterocíclicos aromáticos en los "grupos heterocíclicos de 5 ó 6 miembros" anteriormente mencionados, y los grupos heterocíclicos aromáticos bicíclicos que contienen de 1 a 3 átomos seleccionados a partir del grupo que consiste en un átomo de nitrógeno, un átomo de azufre, y un átomo de oxígeno, tales como indolilo, isoindolilo, benzo-tiofenilo, isobenzo-tiofenilo, benzo-furanilo, isobenzo-furanilo, indazolilo, bencimidazolilo, imidazopiridilo, benzoxazolilo, benzotiazolilo, quinolilo o isoquinolilo. Los ejemplos preferidos incluyen piridilo, piridazinilo, pirimidinilo, pirazinilo, quinolilo, isoquinolilo,

bencimidazolilo, benzoxazolilo y benzotiazolilo; los ejemplos más preferidos incluyen piridilo, piridazinilo, pirimidinilo, quinolilo e isoquinolilo, y los ejemplos todavía más preferidos incluyen 2-piridilo, 3-piridilo, 3-piridazinilo, 2-pirimidinilo y 5-pirimidinilo, siendo todavía muy preferido el 2-piridilo.

Un grupo heterocíclico no aromático monocíclico o bicíclico de 5 a 10 miembros se refiere a un grupo en donde 1 a 3 átomos de carbono de un grupo cicloalquilo o cicloalquenilo monocíclico que tiene de 5 a 10 átomos de carbono, están sustituidos con un átomo seleccionado a partir del grupo que consiste en un átomo de nitrógeno, un átomo de azufre, y un átomo de oxígeno, o un grupo en donde 1 a 3 átomos de carbono de un grupo bicicloalquilo o bicicloalquenilo que tiene de 7 a 10 átomos de carbono, están sustituidos con un átomo seleccionado a partir del grupo que consiste en un átomo de nitrógeno, un átomo de azufre, o un átomo de oxígeno. Los ejemplos incluyen un grupo heterocíclico no aromático entre los "grupos heterocíclicos de 5 ó 6 miembros" anteriormente mencionados, y los grupos heterocíclicos bicíclicos no aromáticos, tales como un grupo indolinilo, isoindolinilo, tiocromanilo, o cromanilo.

Un "grupo alcoxilo de 1 a 4 átomos de carbono", en las definiciones de R^1, R^2, α y ß, se refiere a un grupo en donde un átomo de oxígeno está enlazado al "grupo alquilo de 1 a 4 átomos de carbono" anteriormente mencionado. Los ejemplos incluyen metoxilo, etoxilo, propoxilo, isopropoxilo, butoxilo, isobutoxilo y terbutoxilo,

mientras que los ejemplos preferidos incluyen metoxilo, etoxilo, propoxilo, e isopropoxilo, siendo más preferido el metoxilo.

Un "grupo cicloalcoxilo de 3 a 6 átomos de carbono", en la definición de α, se refiere a un grupo en donde un átomo de oxígeno está enlazado al "grupo cicloalquilo de 3 a 6 átomos de carbono" anteriormente mencionado. Los ejemplos incluyen ciclopropoxilo, ciclobutoxilo, ciclopentoxilo, y ciclohexiloxilo.

Un "grupo alcanoílo de 1 a 4 átomos de carbono", en la definición de Ra, se refiere, por ejemplo, a formilo, acetilo, propionilo, butirilo, o isobutirilo.

Un "grupo alcanoiloxilo de 1 a 4 átomos de carbono", en la definición de ß, se refiere a un grupo en donde un átomo de oxígeno está enlazado al "grupo alcanoílo de 1 a 4 átomos de carbono" anteriormente mencionado. Los ejemplos incluyen formiloxilo, acetiloxilo, propioniloxilo, butiriloxilo, e isobutiriloxilo.

R^1 y R^2 del compuesto (i) de la presente invención, son cada uno independientemente, de preferencia, un átomo de hidrógeno o un átomo de halógeno, más preferiblemente un átomo de hidrógeno o un átomo de flúor, y todavía más preferiblemente ambos R^1 y R^2 son átomos de hidrógeno.

Las posiciones de sustitución de R^1 y R^2 son de preferencia las posiciones 6 ó 7, y es más preferiblemente la posición 7.

R^3 del compuesto (i) de la presente invención, es de preferencia un átomo de hidrógeno o un grupo metilo, y de una manera muy preferible, es un átomo de hidrógeno.

R^4 y R^5 en el compuesto (i) de la presente invención, son de preferencia de tal manera que R^4 es un átomo de hidrógeno, un átomo de flúor, un grupo alquilo de 1 a 4 átomos de carbono, un grupo alquenilo de 2 a 4 átomos de carbono, un grupo alquinilo de 2 a 4 átomos de carbono, un grupo cicloalquilo de 3 a 5 átomos de carbono, o un grupo hidroxi-alquilo de 1 a 4 átomos de carbono, y R^5 es un átomo de hidrógeno. Más preferiblemente, R^4 es un grupo metilo, un grupo etilo, un grupo isopropilo, un grupo isobutilo, un grupo terbutilo, un grupo ciclopropilo, o un grupo 1-hidroxi-1-metil-etilo, y R^5 es un átomo de hidrógeno. Todavía más preferiblemente, R^4 es un grupo metilo, un grupo etilo, un grupo isopropilo, un grupo terbutilo, un grupo ciclopropilo, o un grupo 1-hidroxi-1-metil-etilo, y R^5 es un átomo de hidrógeno. Todavía más preferiblemente, R^4 es un grupo etilo, un grupo isopropilo, un grupo ciclopropilo, o un grupo 1-hidroxi-1-metil-etilo, y R^5 es un átomo de hidrógeno.

R^6 y R^7 del compuesto (i) de la presente invención, son cada uno independientemente, de preferencia, un átomo de hidrógeno o un grupo metilo, y de una manera muy preferible, R^6 y R^7 son ambos átomos de hidrógeno.

Las posiciones de sustitución de R^6 y R^7 son de preferencia la posición 3 o la posición 5.

X del compuesto (i) de la presente invención, es de preferencia un grupo fenilo, un grupo naftilo, un grupo piridilo, un grupo piridazinilo, un grupo pirimidinilo, un grupo pirazinilo, un grupo quinolilo, un grupo isoquinolilo, un grupo bencimidazolilo, un grupo

benzoxazolilo, o un grupo benzotiazolilo que puede estar sustituido con 1 ó 2 sustituyentes seleccionados a partir del grupo sustituyente α, y el grupo sustituyente α consiste en un átomo de halógeno, un grupo ciano, un grupo nitro, un grupo hidroxilo, un grupo metilo, un grupo etilo, un grupo propilo, un grupo isopropilo, un grupo terbutilo, un grupo hidroxi-metilo, un grupo fluoro-metilo, un grupo difluoro-metilo, un grupo trifluoro-metilo, un grupo metoxilo, un grupo etoxilo, un grupo propoxilo, un grupo isopropoxilo, un grupo acetoxilo, un grupo trifluoro-metoxilo, un grupo acetilo, un grupo metoxi-carbonilo, un grupo etoxi-carbonilo, un grupo dimetil-carbamoílo, un grupo piperidilo, un grupo pirrolidilo, un grupo morfolino, un grupo pirazolilo, un grupo metil-pirazolilo, un grupo oxadiazolilo, un grupo metil-oxadiazolilo, un grupo fenilo, y un grupo piridilo.

Más preferiblemente, X es un grupo fenilo, un grupo naftilo, un grupo piridilo, un grupo piridazinilo, un grupo pirimidinilo, un grupo pirazinilo, un grupo quinolilo, o un grupo isoquinolilo que puede estar sustituido con 1 ó 2 sustituyentes seleccionados a partir del grupo sustituyente α, y el grupo sustituyente α consiste en un átomo de flúor, un átomo de cloro, un átomo de bromo, un grupo ciano, un grupo hidroxilo, un grupo metilo, un grupo etilo, un grupo propilo, un grupo isopropilo, un grupo terbutilo, un grupo hidroxi-metilo, un grupo fluoro-metilo, un grupo difluoro-metilo, un grupo trifluoro-metilo, un grupo metoxilo, un grupo etoxilo, un grupo propoxilo, un grupo isopropoxilo, un grupo trifluoro-metoxilo, un grupo piperidilo, un grupo pirrolidilo, un grupo fenilo, y un grupo piridilo.

Todavía más preferiblemente, X es un grupo fenilo, un grupo naftilo, un grupo piridilo, un grupo piridazinilo, un grupo pirimidinilo, un grupo pirazinilo, un grupo quinolilo, o un grupo isoquinolilo que puede estar sustituido con 1 ó 2 sustituyentes seleccionados a partir del grupo sustituyente α, y el grupo sustituyente α consiste en un átomo de flúor, un átomo de cloro, un átomo de bromo, un grupo ciano, un grupo hidroxilo, un grupo metilo, un grupo etilo, un grupo propilo, un grupo isopropilo, un grupo terbutilo, un grupo hidroxi-metilo, un grupo fluoro-metilo, un grupo difluoro-metilo, un grupo trifluoro-metilo, un grupo metoxilo, un grupo etoxilo, un grupo propoxilo, un grupo isopropoxilo, un grupo trifluoro-metoxilo, un grupo fenilo, y un grupo piridilo.

Todavía más preferiblemente, X es un grupo fenilo, un grupo 2-piridilo, un grupo 3-piridilo, un grupo 3-piridazinilo, un grupo 2-pirimidinilo, o un grupo 5-pirimidinilo que puede estar sustituido con 1 ó 2 sustituyentes seleccionados a partir del grupo sustituyente α, y el grupo sustituyente α consiste en un átomo de flúor, un átomo de cloro, un átomo de bromo, un grupo ciano, un grupo hidroxilo, un grupo metilo, un grupo etilo, un grupo terbutilo, un grupo trifluoro-metilo, un grupo metoxilo, un grupo etoxilo, un grupo trifluoro-metoxilo, un grupo fenilo, y un grupo piridilo.

Todavía más preferiblemente, X es un grupo fenilo o un grupo piridilo que puede estar sustituido con 1 ó 2 sustituyentes seleccionados a partir del grupo sustituyente α, y el grupo sustituyente α consiste en un átomo de flúor, un átomo de cloro, un

grupo ciano, un grupo trifluoro-metilo, un grupo metoxilo, y un grupo trifluoro-metoxilo.

Todavía más preferiblemente, X es un grupo fenilo o un grupo 2-piridilo que puede estar sustituido con 1 ó 2 sustituyentes seleccionados a partir del grupo sustituyente α, y el grupo sustituyente α consiste en un átomo de flúor, un átomo de cloro, un grupo trifluoro-metilo, un grupo metoxilo, y un grupo trifluoro-metoxilo.

Los ejemplos específicos preferibles de X incluyen 2-fluoro-fenilo, 4-fluoro-fenilo, 2,4-difluoro-fenilo, 3,4-difluoro-fenilo, 2-cloro-fenilo, 4-cloro-fenilo, 2,4-dicloro-fenilo, 3,4-dicloro-fenilo, 2-bromo-fenilo, 4-bromo-fenilo, 2-cloro-4-fluoro-fenilo, 4-cloro-2-fluoro-fenilo, 2-bromo-4-fluoro-fenilo, 4-bromo-2-fluoro-fenilo, 2-ciano-fenilo, 4-ciano-fenilo, 2-ciano-4-fluoro-fenilo, 4-ciano-2-fluoro-fenilo, 2-hidroxi-fenilo, 4-hidroxi-fenilo, 2-metil-fenilo, 4-metil-fenilo, 2-trifluoro-metil-fenilo, 4-trifluoro-metil-fenilo, 2-metoxi-fenilo, 4-metoxi-fenilo, 2-trifluoro-metoxi-fenilo, 4-trifluoro-metoxi-fenilo, 2-bifenilo, 4-bifenilo, 5-fluoro-piridin-2-ilo, 6-fluoro-piridin-3-ilo, 5-cloro-piridin-2-ilo, 6-cloro-piridin-3-ilo, 6-metoxi-piridin-3-ilo, 5-ciano-piridin-2-ilo, 5-trifluoro-metil-piridin-2-ilo, 5-trifluoro-metoxi-piridin-2-ilo, 3,5-difluoro-piridin-2-ilo, 6-metoxi-piridazin-3-ilo, 6-isopropoxi-piridazin-3-ilo, 5-fluoro-pirimidin-2-ilo, 5-cloro-pirimidin-2-ilo, 5-bromo-pirimidin-2-ilo, 5-trifluoro-metil-pirimidin-2-ilo, 5-trifluoro-metoxi-pirimidin-2-ilo, o 5-fenil-pirimidin-2-ilo.

Los ejemplos específicos más preferibles de X incluyen 4-

fluoro-fenilo, 2,4-difluoro-fenilo, 3,4-difluoro-fenilo, 4-cloro-fenilo, 2,4-dicloro-fenilo, 4-trifluoro-metil-fenilo, 4-trifluoro-metoxi-fenilo, 5-fluoro-piridin-2-ilo, 5-cloro-piridin-2-ilo, 5-trifluoro-metil-piridin-2-ilo, o 6-metoxi-piridin-3-ilo.

Y del compuesto (i) de la presente invención, es de preferencia -CO-, -O- o -NRa-, y Ra es de preferencia un átomo de hidrógeno, un grupo metilo, o un grupo etilo. En el caso en donde Ra en Y es un grupo etilo, Ra también puede formar de preferencia un anillo de 5 miembros mediante su enlace con átomos que sean componentes de X. Más preferiblemente, Y es -O- o -NRa-, y Ra es un átomo de hidrógeno, un grupo metilo, o un grupo etilo. Y es todavía más preferiblemente -O-.

Debido a que el compuesto (i) de la presente invención puede estar en la forma de una sal mediante la reacción con un ácido en el caso de que tenga un grupo básico, tal como un grupo amino, o mediante la reacción con una base en el caso de que tenga un grupo ácido, tal como un grupo sulfonamido, una "sal farmacológicamente aceptable del mismo" se refiere a esa sal.

Los ejemplos de las sales basadas en grupos básicos incluyen las sales de los ácidos inorgánicos, tales como los haluros de hidrógeno, tales como fluorhidratos, clorhidratos, bromhidratos o yodhidratos; nitratos, percloratos, sulfatos o fosfatos; las sales de los ácidos orgánicos, tales como las sales de ácido alcano inferior-sulfónico, tales como metan-sulfonatos, trifluoro-metan-sulfonatos o etan-sulfonatos; las sales de ácido aril-sulfónico, tales como bencen-

sulfonatos o p-toluen-sulfonatos; acetatos, malatos, fumaratos, succinatos, citratos, ascorbatos, tartratos, oxalatos o maleatos; y las sales de aminoácidos, tales como las sales de glicina, las sales de lisina, las sales de arginina, las sales de ornitina, los glutamatos o aspartatos.

Por otra parte, los ejemplos de las sales basadas en grupos ácidos incluyen las sales de metales, tales como las sales de metales alcalinos, tales como las sales de sodio, las sales de potasio o las sales de litio, las sales de metales alcalinotérreos, tales como las sales de calcio o las sales de magnesio, las sales de aluminio o las sales de hierro; las sales inorgánicas, tales como las sales de amonio, las sales de amina, tales como las sales orgánicas, tales como las sales de teroctil-amina, las sales de dibencil-amina, las sales de morfolina, las sales de glucosamina, las sales de alquil-éster de fenil-glicina, las sales de etilen-diamina, las sales de N-metil-glucamina, las sales de guanidina, las sales de dietil-amina, las sales de trietil-amina, las sales de diciclohexil-amina, las sales de N,N'-dibencil-etilen-diamina, las sales de cloro-procaína, las sales de procaína, las sales de dietanolamina, las sales de N-bencil-fenetil-amina, las sales de piperazina, las sales de tetrametil-amonio o las sales de tris-(hidroxi-metil)-amino-metano; y las sales de aminoácidos, tales como las sales de glicina, las sales de lisina, las sales de arginina, las sales de ornitina las sales de, los glutamatos o aspartatos.

Un compuesto representado por la fórmula general (i) de la

presente invención, o una sal farmacológicamente aceptable del mismo, puede absorber humedad y formar un hidrato como un resultado de permitirle reposar al aire, y estos hidratos también se incluyen en la presente invención.

Un compuesto representado por la fórmula general (i) de la presente invención, o una sal farmacológicamente aceptable del mismo, puede formar un solvato como un resultado de permitirle reposar en un solvente, y estos solvatos también se incluyen en la presente invención.

Un compuesto representado por la fórmula general (i) de la presente invención, o una sal farmacológicamente aceptable del mismo, tiene isómeros ópticos basados en un centro asimétrico de una molécula de los mismos. En los compuestos de la presente invención, estos isómeros y las mezclas de estos isómeros están todos representados por una sola fórmula, es decir, la fórmula general (i). Por consiguiente, la presente invención incluye todos estos isómeros y las mezclas de estos isómeros.

Aunque los ejemplos de los compuestos típicos representados por la fórmula general (i) de la presente invención incluyen los compuestos enlistados en seguida, la presente invención no está limitada a estos compuestos.

Los ejemplos de estos compuestos incluyen:

N-{(1S)-2-[4-(2-fluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(3-fluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-

3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(4-fluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(4-cloro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-[(1S)-1-metil-2-oxo-2-{4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-etil]-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(4-ciano-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2-{4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-1-metil-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2-{4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-1-metil-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-[(1S)-1-metil-2-oxo-2-(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-etil]-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(2-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(3-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-cloro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-[(1S)-1-({4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-ciano-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-{(1S)-1-[(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(2-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(3-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-cloro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-[(1S)-2-metil-1-({4-[4-(trifluoro-metoxi)-fenoxi]-

piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-ciano-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-{(1S)-2-metil-1-[(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida,

3-hidroxi-N-[(1S)-1-({4-[(6-metoxi-piridin-3-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(2,4-difluoro-benzoil)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(2,4-difluoro-fenil)-(hidroxi)-metil]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-hidroxi-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-1-ciclopropil-2-[4-(2-fluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-1-ciclopropil-2-[4-(3-fluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-1-ciclopropil-2-[4-(4-fluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(4-cloro-fenoxi)-piperidin-1-il]-1-ciclopropil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-ciclopropil-2-oxo-2-{4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-etil]-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(4-ciano-fenoxi)-piperidin-1-il]-1-ciclopropil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-1-ciclopropil-2-[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-1-ciclopropil-2-[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-ciclopropil-2-{4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2-{4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-1-ciclopropil-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-ciclopropil-2-oxo-2-(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-etil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2,2-dimetil-1-{[4-(2-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2,2-dimetil-1-{[4-(3-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2,2-dimetil-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-cloro-fenoxi)-piperidin-1-il]-carbonil}-2,2-

dimetil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2,2-dimetil-1-({4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-carbonil)-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-ciano-fenoxi)-piperidin-1-il]-carbonil}-2,2-dimetil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-2,2-dimetil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-2,2-dimetil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2,2-dimetil-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2,2-dimetil-propil]-3-hidroxi-quinoxalin-2-carboxamida, y

N-{(1S)-2,2-dimetil-1-[(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-3-hidroxi-quinoxalin-2-carboxamida,

Entre estos compuestos, los preferidos son:

N-{(1S)-2-[4-(2-fluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(3-fluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(4-fluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(4-cloro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-[(1S)-1-metil-2-oxo-2-{4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-etil]-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(4-ciano-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2-{4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-1-metil-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2-{4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-1-metil-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-[(1S)-1-metil-2-oxo-2-(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-etil]-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(2-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(3-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-cloro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-[(1S)-1-({4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-ciano-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-

hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-{(1S)-1-[(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(2-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(3-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-cloro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-[(1S)-2-metil-1-({4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-ciano-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-{(1S)-2-metil-1-[(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida,

N-{(1S)-1-ciclopropil-2-[4-(2-fluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-1-ciclopropil-2-[4-(3-fluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-1-ciclopropil-2-[4-(4-fluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(4-cloro-fenoxi)-piperidin-1-il]-1-ciclopropil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-ciclopropil-2-oxo-2-{4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-etil]-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(4-ciano-fenoxi)-piperidin-1-il]-1-ciclopropil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-1-ciclopropil-2-[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-1-ciclopropil-2-[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-ciclopropil-2-{4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-

il}-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2-{4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-1-ciclopropil-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-ciclopropil-2-oxo-2-(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-etil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2,2-dimetil-1-{[4-(2-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2,2-dimetil-1-{[4-(3-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2,2-dimetil-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-cloro-fenoxi)-piperidin-1-il]-carbonil}-2,2-dimetil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2,2-dimetil-1-({4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-carbonil)-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-ciano-fenoxi)-piperidin-1-il]-carbonil}-2,2-dimetil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-2,2-dimetil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-2,2-dimetil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2,2-dimetil-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2,2-dimetil-propil]-3-hidroxi-quinoxalin-2-carboxamida, y

N-{(1S)-2,2-dimetil-1-[(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-3-hidroxi-quinoxalin-2-carboxamida,

Entre estos compuestos, los más preferidos son:

N-{(1S)-2-[4-(4-cloro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2-{4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-1-metil-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2-{4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-1-metil-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-[(1S)-1-metil-2-oxo-2-(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-etil]-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-cloro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-{(1S)-1-[(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-

piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-[(1S)-2-metil-1-({4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-{(1S)-2-metil-1-[(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida, y

N-{(1S)-1-ciclopropil-2-[4-(4-fluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida.

[Efecto de la invención]

Un compuesto representado por la fórmula general (i) de la presente invención, o una sal farmacológicamente aceptable del mismo, tiene una acción anticoagulante superior. De conformidad con lo anterior, es útil como un ingrediente activo de una preparación preventiva y/o terapéutica para los trastornos de la coagulación sanguínea (tales como un agente preventivo y/o terapéutico para tromboembolismos, deficiencias congénitas del factor anticoagulante o anormalidades de plasminógeno, o agentes preventivos para trombogénesis en seguida de cirugía de reemplazo de válvula artificial, o trombogénesis causada por fibrilación auricular no valvular, o fibrilación auricular que acompaña a cardiopatía valvular).

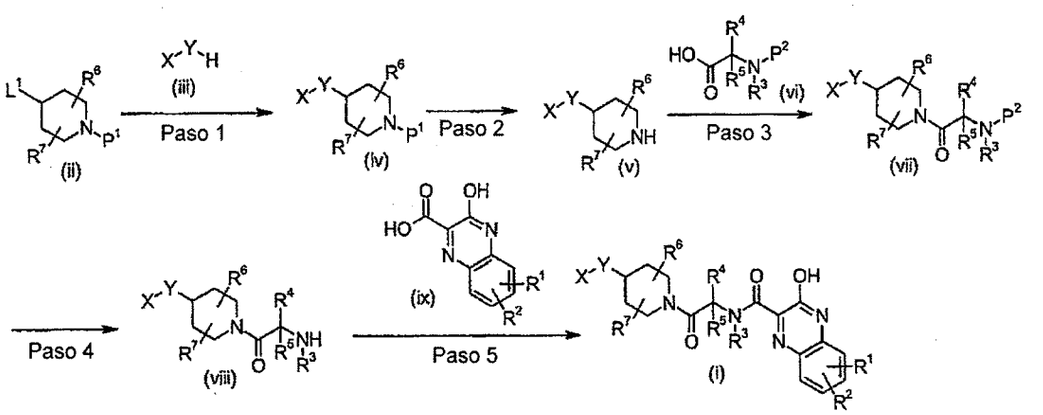
Mejor modo para llevar a cabo la invención

Un compuesto representado por la fórmula general (i) de la presente invención se puede elaborar de acuerdo con un método de elaboración indicado en <Método de elaboración 1> a <Método de elaboración 5>.

<Método de elaboración 1>

Este método de elaboración es un método para obtener un compuesto de la presente invención representado por la fórmula general (i) a partir de un compuesto representado por la fórmula general (ii).

(Esquema 1)



En la fórmula anterior, R^1, R^2, R^3, R^4, R^5, R^6, R^7, X e Y son iguales a como se definen anteriormente.

L^1 representa un grupo saliente. Los ejemplos de los grupos salientes (L^1) incluyen átomos de halógeno, tales como un grupo cloro o un grupo bromo, y grupos sulfoniloxilo, tales como un grupo metan-sulfoniloxilo, un grupo p-toluen-sulfoniloxilo o un grupo trifluoro-metan-sulfoniloxilo.

P^1 y P^2 representan los grupos protectores de un grupo amino. Los ejemplos de los grupos protectores (P^1 y P^2) incluyen los grupos alcoxi-carbonilo, tales como un grupo metoxi-carbonilo, un grupo etoxi-carbonilo, un grupo terbutoxi-carbonilo o un grupo aliloxi-carbonilo, los grupos ariloxi-carbonilo, tales como un grupo benciloxi-carbonilo o un grupo para-metoxi-benciloxi-carbonilo; y los grupos aril-metilo, tales como un grupo bencilo o un grupo trifenil-metilo.

Paso 1

Este paso es un paso para sintetizar un compuesto representado por la fórmula general (iv), mediante la reacción de un derivado de piperidina representado por la fórmula general (ii), que tiene un grupo saliente (L^1) en la posición 4, y en donde el grupo amino está protegido por un grupo protector (P^1), y un compuesto representado por la fórmula general (iii) en un solvente inerte en la presencia de una base.

Los ejemplos de los solventes inertes incluyen los solventes basados en halógeno, tales como cloruro de metileno, cloroformo, dicloro-etano o tetracloruro de carbono, los solventes basados en éter, tales como tetrahidrofurano, 1,2-dimetoxi-etano o dioxano, los solventes basados en aromáticos, tales como benceno o tolueno, y los solventes basados en amida, tales como N,N-dimetil-formamida o N-metil-pirrolidona.

Los ejemplos de las bases incluyen las bases orgánicas, tales como piridina, trietil-amina, N,N-di-isopropil-etil-amina, 4-(dimetil-

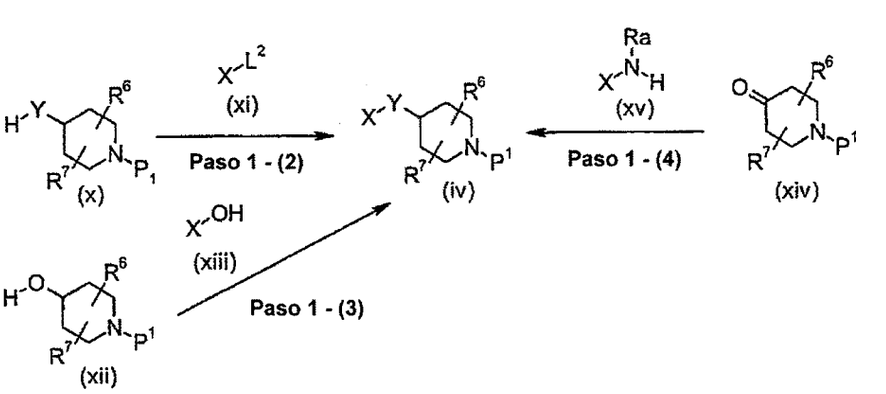
amino)-piridina, N-metil-morfolina, 2,6-lutidina o colidina, y carbonatos, alcóxidos e hidróxidos de metales alcalinos o de metales alcalinotérreos, tales como carbonato de sodio, carbonato de potasio, carbonato de cesio, fluoruro de cerio, carbonato ácido de sodio, etóxido de sodio, butóxido de potasio o hidróxido de sodio.

La temperatura de reacción es desde el enfriamiento hasta el calentamiento a reflujo (la temperatura a la cual el solvente se calienta y se pone a reflujo varía dependiendo del solvente), y específicamente es de 0°C a 200°C, y de preferencia es de 0°C a 150°C.

El tiempo de reacción varía dependiendo de la temperatura de reacción, de los compuestos de la materia prima, de los reactivos de la reacción, del solvente utilizado en la reacción, y similares. Normalmente es de 30 minutos a 48 horas, y de preferencia es de 1 a 8 horas.

Un compuesto representado por la fórmula general (iv) obtenido en este paso, se puede sintetizar utilizando un método diferente, como se indica en seguida.

(Esquema 2)



En la fórmula anterior, R^6, R^7, Ra, P^1, X e Y son iguales a como se definen anteriormente.

L^2 representa un grupo saliente. Los ejemplos de los grupos salientes (L^2) incluyen átomos de halógeno, tales como un grupo cloro o un grupo bromo, y un grupo metan-sulfoniloxilo, un grupo p-toluen-sulfoniloxilo, o un grupo trifluoro-metan-sulfoniloxilo.

Paso 1-(2)

Este paso es un paso para sintetizar un compuesto representado por la fórmula (iv) anterior, a partir de un compuesto representado por la fórmula general (x), y un compuesto representado por la fórmula general (xi).

Esta reacción se puede lograr mediante un método que cumple con la condiciones de reacción empleadas en el Paso 1.

Paso 1-(3)

Entre los compuestos representados por la fórmula (iv), un compuesto en donde Y representa un átomo de oxígeno se puede sintetizar a partir de un compuesto representado por la fórmula general (xii) anterior, empleando una reacción de Mitsunobu llevada a cabo en un solvente.

Los ejemplos de los solventes utilizados en esta reacción incluyen los solventes que son inertes en la reacción, incluyendo los solventes basados en aromáticos, tales como benceno, tolueno o xileno, y los solventes basados en éter, tales como dietil-éter, tetrahidrofurano, o dioxano.

Los ejemplos de los reactivos de la reacción incluyen los

reactivos de fósforo orgánico, tales como trifenil-fosfina y los reactivos diazoicos, tales como azodicarboxilato de dietilo, azodicarboxilato de di-isopropilo, o azodicarboxilato de dipiperidin-amida, y de preferencia se utilizan azodicarboxilato de trifenil-fosfina y de di-isopropilo.

La temperatura de reacción es desde el enfriamiento hasta el calentamiento a reflujo (la temperatura a la cual el solvente se calienta y se pone a reflujo varía dependiendo del solvente), y específicamente es de 0°C a 200°C, y de preferencia es de 0°C a 150°C.

El tiempo de reacción varía dependiendo de la temperatura de reacción, de los compuestos de la materia prima, de los reactivos de la reacción, del solvente utilizado en la reacción, y similares. Normalmente es de 30 minutos a 48 horas, y de preferencia es de 1 a 8 horas.

Paso 1-(4)

Entre los compuestos representados por la fórmula (iv), un compuesto en donde Y representa un átomo de nitrógeno se puede sintetizar a partir de un derivado de 4-piperidinona representado por la fórmula (xiv) anterior, en donde el grupo amino está protegido con un grupo protector (P^1), utilizando un método de aminación reductiva llevado a cabo en un solvente.

Los ejemplos de los solventes utilizados en esta reacción incluyen los solventes que son inertes en la reacción, incluyendo los solventes basados en aromáticos, tales como benceno, tolueno o

xileno, los solventes basados en éter, tales como dietil-éter, tetrahidrofurano o dioxano, y alcoholes tal como metanol, etanol o isopropanol.

Como los reactivos de la reacción, se utilizan agentes de reducción, tales como borohidruro de sodio, ciano-borohidruro de sodio o triacetoxi-borohidruro de sodio, y de preferencia se utiliza ciano-borohidruro de sodio.

La temperatura de reacción es desde el enfriamiento hasta el calentamiento a reflujo (la temperatura a la cual el solvente se calienta y se pone a reflujo varía dependiendo del solvente), y específicamente es de 0°C a 200°C, y de preferencia es de 0°C a 150°C.

Aunque el tiempo de reacción varía dependiendo de la temperatura de reacción, de los compuestos de la materia prima, de los reactivos de la reacción, del solvente utilizado en la reacción, y similares, normalmente es de 30 minutos a 48 horas, y de preferencia es de 1 a 8 horas.

Paso 2

Este paso es un paso para obtener un compuesto representado por la fórmula general (v), o una sal del mismo, mediante la remoción de un grupo protector (P^1) de un compuesto representado por la fórmula general (iv) mediante un método adecuado.

El método empleado para remover el grupo protector varía dependiendo de las propiedades químicas del grupo protector utilizado, y en el caso de un grupo protector de tipo acilo, tal como

un grupo alcanoílo, un grupo alcoxi-carbonilo o un grupo aroílo, el grupo protector se puede remover mediante hidrólisis utilizando una base, tal como un hidróxido de metal alcalino, tal como hidróxido de litio, hidróxido de sodio o hidróxido de potasio.

En adición, en el caso de un grupo protector de tipo metoxi-carbonilo sustituido, tal como un grupo terbutil-carbonilo o un grupo para-metoxi-benciloxi-carbonilo, el grupo protector se puede remover mediante un ácido adecuado, tal como ácido acético, ácido clorhídrico, ácido sulfúrico, ácido bromhídrico, ácido fosfórico, ácido trifluoro-acético, ácido trifluoro-metan-sulfónico, o una combinación de los mismos.

En adición, un grupo aril-metoxi-carbonilo, tal como un grupo benciloxi-carbonilo, un grupo para-metoxi-benciloxi-carbonilo o un grupo para-nitro-benciloxi-carbonilo, y un grupo aril-metilo, tal como un grupo bencilo, se puede remover mediante hidrólisis utilizando un catalizador de paladio-carbón.

Un grupo trifenil-metilo se puede remover, por ejemplo, con ácido fórmico, ácido acético, ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido fosfórico, ácido trifluoro-acético, ácido trifluoro-metan-sulfónico, o una combinación de los mismos, y se puede remover mediante hidrólisis utilizando un catalizador de paladio-carbón.

Este paso de preferencia se lleva a cabo en agua, en un solvente orgánico adecuado, o en un solvente mixto de los mismos, y los ejemplos de los solventes orgánicos adecuados utilizados

incluyen los solventes que son inertes en la reacción, incluyendo los solventes basados en halógeno, tales como cloruro de metileno, cloroformo, dicloro-etano o tetracloruro de carbono, los éteres, tales como tetrahidrofurano, 1,2-dimetoxi-etano o dioxano, y los alcoholes, tales como metanol o etanol.

La temperatura de reacción es desde el enfriamiento hasta el calentamiento a reflujo (la temperatura a la cual el solvente se calienta y se pone a reflujo varía dependiendo del solvente), y específicamente es de 0°C a 200°C, y de preferencia es de 0°C a 150°C.

Aunque el tiempo de reacción varía dependiendo de la temperatura de reacción, de los compuestos de la materia prima, de los reactivos de la reacción, del solvente utilizado en la reacción, y similares, normalmente es de 30 minutos a 48 horas, y de preferencia es de 1 a 8 horas.

Paso 3

Este paso es un paso para obtener los compuestos representados por la fórmula general (vii), mediante la reacción de los compuestos representados por la fórmula general (v), o una sal de los mismos, con derivados de aminoácidos representados por la fórmula general (vi).

En esta reacción, después de convertir el derivado de aminoácido representado por la fórmula general (vi) hasta un compuesto activador, el derivado de aminoácido se condensa con un compuesto representado por la fórmula general (v). Aunque los

ejemplos de los compuestos activadores incluyen los haluros de ácido producidos utilizando un haluro de ácido, tal como cloruro de tionilo, los ésteres activos obtenidos mediante la reacción con un fenol, tal como para-nitro-fenol, las amidas activas obtenidas mediante la reacción, por ejemplo, con 1,1-carbonil-di-imidazol, y los productos de reacción con hexafluorofosfito de 1-benzotriazoliloxi-pirrolidino-fosfonio o clorhidrato de N,N-diciclohexil-carbodi-imida, los cuales se utilizan usualmente en la síntesis de péptidos a partir de aminoácidos. De preferencia se utilizan los productos de reacción con clorhidrato de N,N-diciclohexil-carbodi-imida. En esta reacción, también se puede agregar el 1-hidroxi-benzotriazol, y similares, como sea necesario.

Un compuesto representado por la fórmula general (vii) se puede obtener mediante la reacción de un compuesto activador de un derivado de aminoácido obtenido de esta manera, y un compuesto representado por la fórmula general (v), o una sal del mismo, en un solvente inerte, y normalmente en la presencia de una base.

Los ejemplos de los solventes inertes utilizados incluyen los solventes que son inertes en la reacción, incluyendo los solventes basados en halógeno, tales como cloruro de metileno, cloroformo, dicloro-etano o tetracloruro de carbono, los solventes basados en éter, tales como tetrahidrofurano, 1,2-dimetoxi-etano o dioxano, los solventes basados en aromáticos, tales como benceno o tolueno, y los solventes basados en amida, tales como N,N-dimetil-formamida o N-metil-pirrolidona.

Los ejemplos de las bases utilizadas incluyen las bases orgánicas, tales como piridina, trietil-amina, N,N-di-isopropil-etil-amina, 4-(dimetil-amino)-piridina, N-metil-morfolina, 2,6-lutidina o colidina, y los carbonatos, alcóxidos e hidróxidos de metales alcalinos o de metales alcalinotérreos, tales como carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, etóxido de sodio, butóxido de potasio, hidróxido de sodio, o hidruro de potasio. De preferencia se utilizan trietil-amina y N-metil-morfolina.

La temperatura de reacción es desde el enfriamiento hasta el calentamiento a reflujo (la temperatura a la cual el solvente se calienta y se pone a reflujo varía dependiendo del solvente), y específicamente es de 0°C a 200°C, y de preferencia es de 0°C a 150°C.

El tiempo de reacción varía dependiendo de la temperatura de reacción, de los compuestos de la materia prima, de los reactivos de la reacción, del solvente utilizado en la reacción, y similares. Normalmente es de 30 minutos a 48 horas, y de preferencia es de 1 a 8 horas.

Paso 4

Este paso es un paso para obtener un compuesto representado por la fórmula general (viii), o una sal del mismo, mediante la remoción de un grupo protector (P^2) de un grupo amino de un compuesto representado por la fórmula general (vii).

Esta reacción se puede lograr mediante un método que cumple con la condiciones de reacción empleadas en el Paso 2.

Paso 5

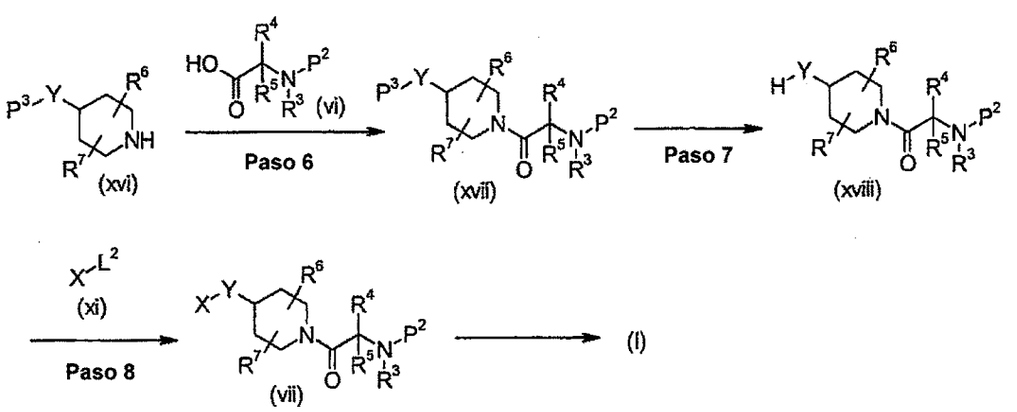
Este paso es un paso para obtener un compuesto representado por la fórmula general (i), llevando a cabo una reacción de condensación entre una amina representada por la fórmula general (viii), o una sal de la misma, y un ácido carboxílico representado por la fórmula general (ix).

Esta reacción se puede lograr mediante un método que cumple con la condiciones de reacción empleadas en el Paso 3.

<Método de elaboración 2>

Este método de elaboración es un método para obtener un compuesto de la presente invención representado por la fórmula general (i) mediante la síntesis de un compuesto representado por la fórmula general (vii) a partir de un compuesto representado por la fórmula general (xvi).

(Esquema 3)



En la fórmula anterior, R^3, R^4, R^5, R^6, R^7, P^2, L^2, X e Y son iguales a como se definen anteriormente.

P^3 representa un grupo amino, o un grupo protector de un

grupo hidroxilo. Como los ejemplos de los grupos protectores, P^2 y P^3 son ambos los grupos protectores de un grupo amino en el caso en donde Y está representado por la fórmula NRa. En otros casos, estos grupos protectores indican diferentes grupos a partir de unos y otros, y se seleccionan respectivamente los grupos para los cuales P^3 es estable bajo las condiciones para remover P^2.

En el caso en donde Y es un átomo de oxígeno, los ejemplos de los grupos protectores incluyen los grupos protectores de tipo acilo, tales como un grupo acetilo, un grupo alcanoílo o un grupo benzoílo, los grupos aril-metilo, tales como un grupo bencilo, los grupos silil-éter, tales como un grupo terbutil-difenil-silílo o un grupo terbutil-dimetil-silílo, un grupo metoxi-metilo y un grupo tetrahidro-piranilo, y de preferencia se utiliza un grupo terbutil-difenil-silílo.

Paso 6

Este paso es un paso para obtener un compuesto representado por la fórmula (xvii) anteriormente mencionada, mediante una reacción de un derivado de piperidina representado por la fórmula (xvi) anteriormente mencionada, y un aminoácido representado por la fórmula (vi) anteriormente mencionada.

Esta reacción se puede lograr mediante un método que cumple con la condiciones de reacción empleadas en el Paso 3.

Paso 7

Este paso es un paso para obtener un compuesto representado por la fórmula (xviii) anteriormente mencionada, o una sal del mismo, mediante la remoción de un grupo protector (P^3) de un compuesto

representado por la fórmula (xvii) anteriormente mencionada.

En el caso en donde Y en la fórmula (xvii) es un grupo representado por la fórmula NRa, este paso se puede lograr mediante un método que cumple con la condiciones de reacción empleadas en el Paso 2.

En el caso en donde Y en la fórmula (xvii) es un átomo de oxígeno, el método empleado para remover el grupo protector (P^3) varía dependiendo de las propiedades químicas del grupo protector utilizado, y por ejemplo, un grupo acilo, tal como un grupo alcanoílo o un grupo aroílo, se puede remover mediante hidrólisis con una base adecuada, tal como un hidróxido de metal alcalino, tal como hidróxido de litio, hidróxido de sodio o hidróxido de potasio. En el caso de un grupo aril-metilo, el grupo protector se puede remover mediante hidrólisis utilizando un catalizador de paladio-carbón. Un grupo sililo, tal como un grupo terbutil-dimetil-sililo o un grupo terbutil-difenil-sililo, se puede remover mediante un hidrofluoruro, tal como fluoruro de tetrabutil-amonio. En adición, un grupo metoxi-metilo o un grupo tetrahidro-piranilo se puede remover mediante ácido acético o ácido clorhídrico, y similares.

Los ejemplos de los solventes utilizados en esta reacción incluyen los solventes que son inertes en la reacción, incluyendo los solventes basados en halógeno, tales como cloruro de metileno, cloroformo, dicloro-etano o tetracloruro de carbono, los solventes basados en éter, tales como tetrahidrofurano, 1,2-dimetoxi-etano o dioxano, los solventes basados en aromáticos, tales como benceno o

tolueno, los solventes basados en alcohol, tales como metanol, etanol o isopropanol, y los solventes basados en amida, tales como N,N-dimetil-formamida y N-metil-pirrolidona.

La temperatura de reacción es desde el enfriamiento hasta el calentamiento a reflujo (la temperatura a la cual el solvente se calienta y se pone a reflujo varía dependiendo del solvente), y específicamente es de 0°C a 200°C, y de preferencia es de 0°C a 150°C.

Aunque el tiempo de reacción varía dependiendo de la temperatura de reacción, de los compuestos de la materia prima, de los reactivos de la reacción, del solvente utilizado en la reacción, y similares, normalmente es de 30 minutos a 48 horas, y de preferencia es de 1 a 8 horas.

Paso 8

Este paso es un paso para sintetizar un compuesto representado por la fórmula (vii) anteriormente mencionada, mediante la reacción de un compuesto representado por la fórmula (xviii) anteriormente mencionada, o una sal del mismo, con un compuesto representado por la fórmula (xi) anteriormente mencionada.

Esta reacción se puede lograr mediante un método que cumple con la condiciones de reacción empleadas en el Paso 1.

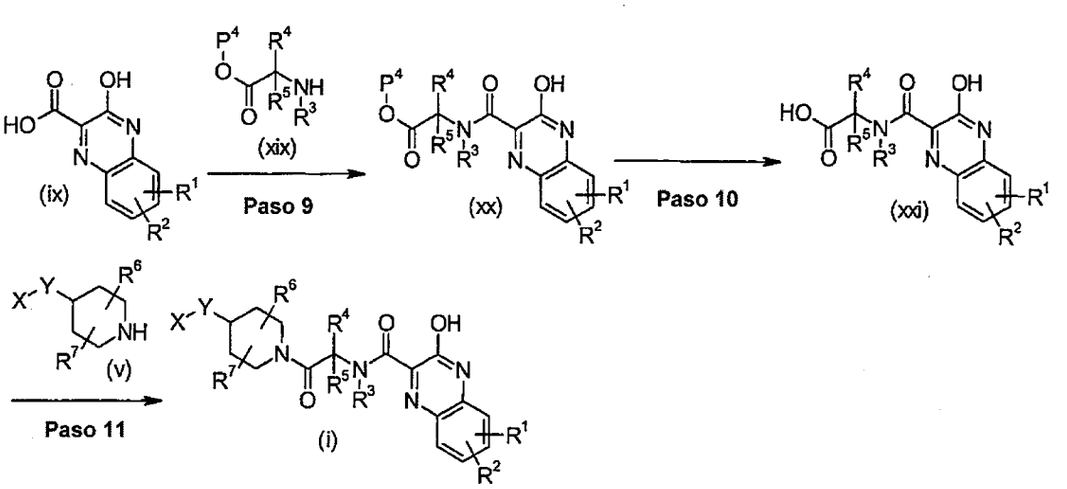
El compuesto representado por la fórmula (vii) se puede convertir hasta un compuesto de la presente invención representado por la fórmula (i), mediante un método que cumple con el esquema

empleado en el método de elaboración 1.

<Método de elaboración 3>

Este método de elaboración es un método para obtener un compuesto de la presente invención representado por la fórmula (i), mediante la síntesis de un ácido carboxílico representado por la fórmula general (xxi) a partir de un derivado de ácido carboxílico representado por la fórmula general (ix), y hacer reaccionar con un derivado de piperidina representado por la fórmula general (v), o una sal del mismo.

(Esquema 4)



En la fórmula anterior, R^1, R^2, R^3, R^4, R^5, R^6, R^7, X e Y son iguales a como se definen anteriormente. P^4 representa un grupo protector de un ácido carboxílico. Los ejemplos de los grupos protectores (P^4) incluyen un grupo metilo, un grupo etilo, un grupo terbutilo y un grupo bencilo.

Paso 9

Este paso es un paso para obtener un compuesto representado por la fórmula general (xx), mediante la reacción de un ácido carboxílico representado por la fórmula general (ix) con un aminoácido representado por la fórmula general (xix).

Esta reacción se puede lograr mediante un método que cumple con la condiciones de reacción empleadas en el Paso 3.

Paso 10

Este paso es un paso para obtener un derivado de ácido carboxílico representado por la fórmula general (xxi) mediante la remoción de un grupo protector (P^4) de un compuesto representado por la fórmula (xx) anteriormente mencionada, en un solvente.

Las condiciones de esta reacción para remover el grupo protector varían dependiendo de las propiedades químicas del grupo protector utilizado, y en el caso, por ejemplo, de un grupo metilo o un grupo etilo, el grupo protector se puede remover mediante hidrólisis utilizando una base adecuada, tal como un hidróxido de metal alcalino, tal como hidróxido de litio, hidróxido de sodio o hidróxido de potasio.

En el caso de un grupo terbutilo, el grupo protector se puede remover mediante el tratamiento con ácido trifluoro-acético o ácido clorhídrico.

En adición, en el caso de un grupo aril-metilo, tal como un grupo bencilo, el grupo protector se puede remover mediante hidrólisis utilizando un catalizador de paladio-carbón.

Los ejemplos de los solventes utilizados en esta reacción incluyen los solventes que son inertes en la reacción, incluyendo los solventes basados en halógeno, tales como cloruro de metileno, cloroformo, dicloro-etano o tetracloruro de carbono, los solventes basados en éter, tales como tetrahidrofurano, 1,2-dimetoxi-etano o dioxano, los solventes basados en aromáticos, tales como benceno o tolueno, los solventes basados en alcohol, tales como metanol, etanol o isopropanol, y los solventes basados en amida, tales como N,N-dimetil-formamida o N-metil-pirrolidona.

La temperatura de reacción es desde el enfriamiento hasta el calentamiento a reflujo (la temperatura a la cual el solvente se calienta y se pone a reflujo varía dependiendo del solvente), y específicamente es de 0°C a 200°C, y de preferencia es de 0°C a 150°C.

Aunque el tiempo de reacción varía dependiendo de la temperatura de reacción, de los compuestos de la materia prima, de los reactivos de la reacción, del solvente utilizado en la reacción, y similares, normalmente es de 30 minutos a 48 horas, y de preferencia es de 1 a 8 horas.

Paso 11

Este paso es un paso para obtener un compuesto representado por la fórmula general (i) mediante una reacción de condensación entre un derivado de ácido carboxílico representado por la fórmula (xxi) anteriormente mencionada, y un derivado de piperidina representado por la fórmula (v) anteriormente mencionada, o una sal

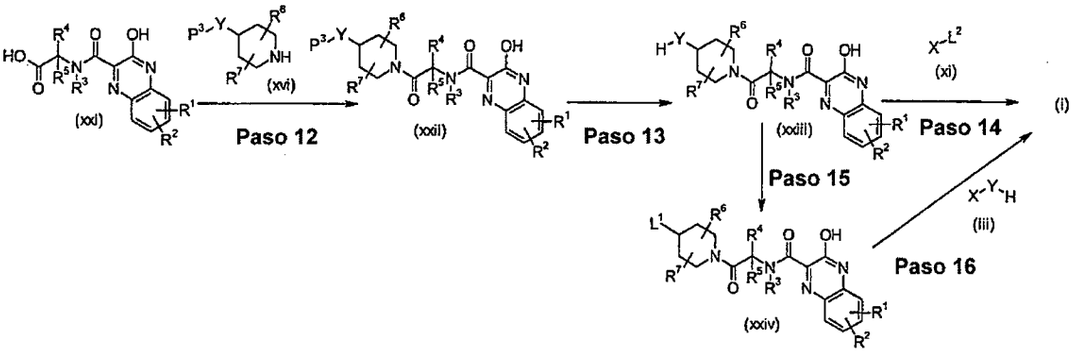
del mismo.

Esta reacción se puede lograr mediante un método que cumple con la condiciones de reacción empleadas en el Paso 3.

<Método de elaboración 4>

Este método de elaboración es un método para obtener un compuesto de la presente invención representado por la fórmula general (i) a partir de un compuesto representado por la fórmula general (xxi) pasando a través de un intermediario representado por la fórmula general (xxiv).

(Esquema 5)



En la fórmula anterior, R^1, R^2, R^3, R^4, R^5, R^6, R^7, L^1, L^2, P^3, X e Y son iguales a como se definen anteriormente.

Paso 12

Este paso es un paso para obtener un compuesto representado por la fórmula general (xxii) a partir de un derivado de ácido carboxílico representado por la fórmula (xxi) anteriormente mencionada, y un derivado de piperidina representado por la fórmula (xvi) anteriormente mencionada.

Esta reacción se puede lograr mediante un método que cumple con la condiciones de reacción empleadas en el Paso 3.

Paso 13

Este paso es un paso para obtener un compuesto representado por la fórmula general (xxiii), o una sal del mismo, mediante la remoción de un grupo protector (P^3) de un compuesto representado por la fórmula general (xxii) anteriormente mencionada.

Esta reacción se puede lograr mediante un método que cumple con la condiciones de reacción empleadas en el Paso 7.

Paso 14

Este paso es un paso para obtener un compuesto representado por la fórmula general (i), mediante la reacción de un compuesto representado por la fórmula (xi) anteriormente mencionada, con un compuesto representado por la fórmula (xxiii) anteriormente mencionada, o una sal del mismo.

Esta reacción se puede lograr mediante un método que cumple con la condiciones de reacción empleadas en el Paso 1.

Paso 15

Este paso es un paso para obtener un compuesto representado por la fórmula (xxiv) anteriormente mencionada, mediante la conversión de un grupo hidroxilo de un compuesto representado por la fórmula (xxiii) anteriormente mencionada, en donde Y representa un átomo de oxígeno, hasta un grupo saliente (grupo L^1).

Los ejemplos de los grupos salientes (L^1) utilizados incluyen un átomo de halógeno, tal como un grupo cloro o un grupo bromo, y un

grupo metan-sulfoniloxilo, un grupo p-toluen-sulfoniloxilo y un grupo trifluoro-metan-sulfoniloxilo, y de preferencia se utiliza un grupo metan-sulfoniloxilo.

En el caso en donde se selecciona un grupo metan-sulfoniloxilo para el grupo saliente, por ejemplo, esta reacción se puede llevar a cabo utilizando cloruro de metan-sulfonilo como un reactivo, y hacer reaccionar el reactivo de la reacción con un compuesto representado por la fórmula (xxiii) anteriormente mencionada, en un solvente, y en la presencia de una base.

Aunque los ejemplos de las bases incluyen las bases orgánicas, tales como piridina, trietil-amina, N,N-di-isopropil-etil-amina, 4-(dimetil-amino)-piridina, N-metil-morfolina, 2,6-lutidina o colidina, y los carbonatos, alcóxidos e hidróxidos de metales alcalinos o de metales alcalinotérreos, tales como carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, etóxido de sodio, butóxido de potasio, hidróxido de sodio o hidruro de potasio, de preferencia se utilizan trietil-amina y N,N-di-isopropil-etil-amina.

Los ejemplos de los solventes utilizados incluyen los solventes que son inertes en la reacción, incluyendo los solventes basados en halógeno, tales como cloruro de metileno, cloroformo, dicloro-etano o tetracloruro de carbono, los solventes basados en éter, tales como tetrahidrofurano, 1,2-dimetoxi-etano o dioxano, los solventes basados en aromáticos, tales como benceno o tolueno, y los solventes basados en amida, tales como N,N-dimetil-formamida o N-metil-pirrolidona.

La temperatura de reacción es desde el enfriamiento hasta el calentamiento a reflujo (la temperatura a la cual el solvente se calienta y se pone a reflujo varía dependiendo del solvente), y específicamente es de 0°C a 200°C, y de preferencia es de 0°C a 150°C.

Aunque el tiempo de reacción varía dependiendo de la temperatura de reacción, de los compuestos de la materia prima, de los reactivos de la reacción, del solvente utilizado en la reacción, y similares, normalmente es de 30 minutos a 48 horas, y de preferencia es de 1 a 8 horas.

Paso 16

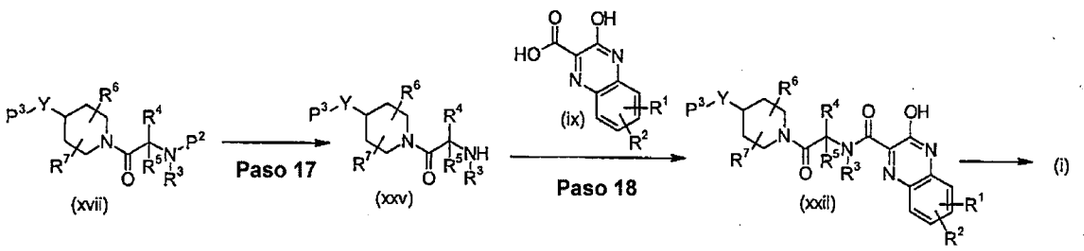
Este paso es un paso para obtener un compuesto de la presente invención representado por la fórmula general (i) a partir de un compuesto representado por la fórmula (xxiv) anteriormente mencionada, y un compuesto representado por la fórmula (iii) anteriormente mencionada.

Esta reacción se puede lograr mediante un método que cumple con la condiciones de reacción empleadas en el Paso 1.

<Método de elaboración 5>

Este método de elaboración es un método para obtener un compuesto de la presente invención representado por la fórmula general (i), mediante la síntesis de un compuesto representado por la fórmula general (xxii) a partir de un compuesto representado por la fórmula (xvii) anteriormente mencionada.

(Esquema 6)



En la fórmula anterior, R^1, R^2, R^3, R^4, R^5, R^6, R^7, P^2, P^3 e Y son iguales a como se definen anteriormente.

Aunque P^2 y P^3 son ambos un grupo amino, los grupos protectores en el caso en donde Y representa un grupo representado por la fórmula NRa, estos grupos protectores indican los grupos respectivos y separados, y se seleccionan respectivamente los grupos para los cuales P^3 es estable bajo las condiciones para remover P^2.

Paso 17

Este paso es un paso para obtener un compuesto representado por la fórmula (xxv) anteriormente mencionada, o una sal del mismo, mediante la remoción de un grupo protector (P^2) de un compuesto representado por la fórmula (xvii) anteriormente mencionada.

Esta reacción se puede lograr mediante un método que cumple con la condiciones de reacción empleadas en el Paso 2.

Paso 18

Este paso es un paso para obtener un compuesto representado por la fórmula (xxii) anteriormente mencionada, a partir de un derivado de amina representado por la fórmula (xxv) anteriormente

mencionada, o una sal del mismo, y un derivado de ácido carboxílico representado por la fórmula (ix) anteriormente mencionada.

Esta reacción se puede lograr mediante un método que cumple con la condiciones de reacción empleadas en el Paso 5.

El compuesto representado por la fórmula (xxii) anteriormente mencionada se puede convertir hasta un compuesto de la presente invención representado por la fórmula general (i), mediante un método que cumple con el esquema empleado en el método de elaboración 4.

En seguida de realizarse cada una de las reacciones anteriores, el compuesto deseado se pueden recuperar a partir de la mezcla de reacción de acuerdo con los métodos ordinarios.

Por ejemplo, después de neutralizar de una manera adecuada la mezcla de reacción, o después de remover la materia insoluble mediante filtración en el caso en donde está presente la materia insoluble, se agregan solventes mutuamente inmiscibles, tales como agua y acetato de etilo, seguido por el fraccionamiento de la capa orgánica, lavado con agua, y similares, y se separa la capa orgánica que contiene el compuesto deseado. El compuesto deseado se obtiene entonces mediante el secado con sulfato de magnesio anhidro y similares, y se destila el solvente.

El compuesto deseado resultante se puede separar y purificar, si es necesario, mediante la combinación adecuada de los métodos ordinarios, tales como recristalización, reprecipitación, o los métodos comúnmente empleados para separar y purificar compuestos

orgánicos, cuyos ejemplos incluyen cromatografía en columna de adsorción utilizando un vehículo, tal como gel de sílice, alúmina, o Florisil basado en magnesio-gel de sílice; un método utilizando un adsorbente sintético, tal como cromatografía en columna de división, utilizando un vehículo, tal como Sephadex LH-20 (Pharmacia), Amberlite XAD-11 (Rohm and Haas Chemical) o Diaion HP-20 (Mitsubishi Chemical), un método utilizando cromatografía de intercambio de iones o cromatografía en columna de fase hacia delante-de fase inversa, utilizando un gel de sílice o un gel de sílice alquilado (y de preferencia, cromatografía de líquidos de alto rendimiento), seguida por la elución con un eluyente adecuado.

Adicionalmente, cada uno de los compuestos (ii), (iii), (vi), (ix), (x), (xi), (xii), (xiii), (xiv), (xv), (xvi), y (xix) utilizados como materia prima de partida o como materiales auxiliares en los métodos de manufactura para la elaboración de los métodos 1 a 5, son cualquiera de ellos mismos compuestos conocidos, o son compuestos que se obtienen fácilmente a partir de los compuestos conocidos, mediante el tratamiento en cumplimiento con los métodos conocidos.

Debido a que los derivados de hidroxi-quinoxalin-carboxamida de la presente invención tienen una acción anticoagulante superior, son útiles como productos farmacéuticos, y en particular como agentes preventivos y/o terapéuticos para los trastornos de la coagulación sanguínea. Los ejemplos específicos incluyen los agentes preventivos y/o terapéuticos para los trastornos de la

coagulación sanguínea, tales como tromboembolismo, deficiencia congénita del factor anticoagulante, o anormalidad de plasminógeno, y los agentes preventivos para trombogénesis en seguida de cirugía de reemplazo de válvula artificial, o trombogénesis causada por fibrilación auricular no valvular, o fibrilación auricular que acompaña a cardiopatía valvular.

Los ejemplos de las formas de administración de un compuesto de la presente invención representado por la fórmula general (i), o una sal farmacológicamente aceptable del mismo, incluyen las formas de administración oral, tales como tabletas, cápsulas, gránulos, polvos o jarabes, y las formas de administración parenteral, tales como preparaciones para inyección o supositorios. Estas preparaciones se producen mediante los métodos comúnmente conocidos utilizando aditivos, tales como vehículos, lubricantes, aglutinantes, agentes desintegrantes, estabilizantes, correctivos o diluyentes.

En el caso de administrar una composición farmacéutica que tenga, como el agente primario de la misma, un compuesto de la presente invención representado por la fórmula general (i), o una sal farmacológicamente aceptable del mismo, la administración se puede llevar a cabo sistémicamente o localmente y oralmente o parenteralmente. Los ejemplos de las formas de fármaco utilizadas para su administración oral incluyen tabletas, píldoras, polvos, gránulos, cápsulas, soluciones, suspensiones, emulsiones, jarabes y elíxires. Los ejemplos de las formas de fármaco utilizadas para su

administración parenteral incluyen preparaciones para inyección, ungüentos, geles, cremas, cataplasmas, parches medicados, aerosoles, inhalantes, aspersiones, gotas para los ojos, gotas para la nariz, supositorios e inhalantes. Estas formas de fármacos se puede preparar de acuerdo con los métodos ordinarios utilizando aditivos seleccionados adecuadamente como sea necesario a partir de aditivos farmacéuticamente aceptables, tales como diluyentes, vehículos, aglutinantes, estabilizantes, antisépticos, colorantes, solubilizantes, agentes de suspensión, reguladores, o agentes humectantes.

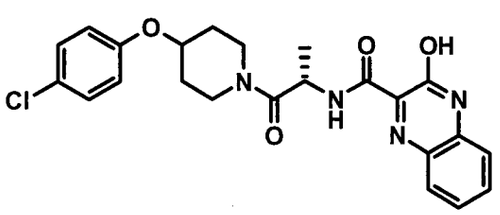
Aunque la cantidad utilizada varía dependiendo de los síntomas, del peso corporal, de la edad y del método de administración del sujeto que reciba la administración (animal de sangre caliente, tal como un ser humano), en el caso de la administración oral, por ejemplo, la cantidad empleada tiene un límite inferior de 0.001 miligramos/kilogramo de peso corporal (y de preferencia de 0.01 miligramos/kilogramo de peso corporal) por administración, y un límite superior de 500 miligramos/kilogramo de peso corporal (y de preferencia de 50 miligramos/kilogramo de peso corporal) por administración, aunque en el caso de la administración intravenosa, la cantidad empleada tiene un límite inferior de 0.005 miligramos/kilogramo de peso corporal (y de preferencia de 0.05 miligramos/kilogramo de peso corporal) por administración, y un límite superior de 50 miligramos/kilogramo de peso corporal (y de preferencia de 5 miligramos/kilogramo de peso corporal) por

administración, y la administración de preferencia se lleva a cabo de una a varias veces al día de una manera correspondiente a los síntomas.

[Ejemplos]

Lo siguiente proporciona una explicación más detallada de la presente invención a través de los ejemplos y de los ejemplos de prueba de los mismos, pero el alcance de la presente invención no está limitado a los mismos.

Ejemplo 1



N-{(1S)-2-[4-(4-cloro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 1-1

[(1S)-2-(4-hidroxi-piperidin-1-il)-1-metil-2-oxo-etil]-carbamato de terbutilo

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (2.30 gramos, 12.0 milimoles), y monohidrato de 1-hidroxi-benzotriazol (1.84 gramos, 12.0 milimoles) se agregaron a una solución en cloruro de metileno (50 mililitros) de 4-hidroxi-piperidina (1.00 gramos, 10.0 milimoles), y N-(terbutoxi-carbonil)-L-alanina (1.89 gramos, 10.0 milimoles), a 0°C, bajo una corriente de nitrógeno, seguido por otra adición de trietil-amina (1.21 mililitros,

12.0 mili-moles), y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se diluyó con cloruro de metileno, seguido por lavado en secuencia con una solución acuosa saturada de carbonato ácido de sodio, una solución acuosa saturada de cloruro de amonio, agua, y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., NH, 40+M), para proporcionar el [(1S)-2-(4-hidroxi-piperidin-1-il)-1-metil-2-oxo-etil]-carbamato de terbutilo (2.02 gramos, rendimiento del 74 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 5.57 (1H, d, J=7.5 Hz), 4.64 (1H, m), 4.15-3.66 (3H, m), 3.40-3.14 (2H, m), 1.99-1.84 (2H, m), 1.71-1.49 (2H, m), 1.44 (9H, s), 1.31 y 1.30 (3H, d, J=7.0 Hz).

MS (FAB, m/z): 273 $(M+H)^+$.

Ejemplo 1-2

{(1S)-2-[4-(4-cloro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-carbamato de terbutilo

Una solución al 40 por ciento en tolueno de azodicarboxilato de di-isopropilo (2.80 mililitros, 5.21 milimoles), se agregó a una solución en tolueno (18 mililitros) de [(1S)-2-(4-hidroxi-piperidin-1-il)-1-metil-2-oxo-etil]-carbamato de terbutilo (1.29 gramos, 4.74 milimoles), 4-cloro-fenol (670 miligramos, 5.21 milimoles), y trifenil-fosfina (1.37 gramos, 5.21 milimoles), a temperatura ambiente, bajo

una corriente de nitrógeno, y la agitación se llevó a cabo a 90°C durante la noche. La solución de la reacción se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., 40+M), para proporcionar el {(1S)-2-[4-(4-cloro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-carbamato de terbutilo (700 miligramos, rendimiento del 34 por ciento) como una sustancia amorfa color amarillo pálido.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.25 (2H, d, J=9.0 Hz), 6.85 (2H, d, J=9.0 Hz), 5.55 (1H, d, J=7.8 Hz), 4.65 (1H, m), 4.52 (1H, m), 3.88-3.36 (4H, m), 2.01-1.76 (4H, m), 1.44 (9H, s), 1.31 (3H, d, J=7.0 Hz).

MS (ESI, m/z): 383 $(M+H)^+$.

Ejemplo 1-3

N-{(1S)-2-[4-(4-cloro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida

Una solución en 1,4-dioxano de ácido clorhídrico 4N (5 mililitros), se agregó a una solución en 1,4-dioxano (5 mililitros) de {(1S)-2-[4-(4-cloro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-carbamato de terbutilo (701 miligramos, 1.83 milimoles), bajo una corriente de nitrógeno, y la mezcla se dejó reaccionar a temperatura ambiente durante la noche. La solución de la reacción se concentró para proporcionar el clorhidrato de (2S)-1-[4-(4-cloro-fenoxi)-piperidin-1-il]-1-oxopropan-2-amina (558 miligramos) como un sólido blanco.

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida

(115 miligramos, 0.600 milimoles), y el monohidrato de 1-hidroxi-benzotriazol (91.0 miligramos, 0.600 milimoles) se agregaron a una solución en cloruro de metileno (5.0 mililitros) del compuesto resultante (160 miligramos, 0.500 milimoles), y ácido 3-hidroxi-quinoxalin-2-carboxílico (98.0 miligramos, 0.500 milimoles), a temperatura ambiente, bajo una corriente de nitrógeno, seguido por otra adición de N-metil-morfolina (0.270 mililitros, 2.50 milimoles), y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se diluyó con cloruro de metileno, seguido por lavado en secuencia con una solución acuosa saturada de carbonato ácido de sodio, una solución acuosa saturada de cloruro de amonio, agua, y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. Después de que la capa orgánica se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., 25+M), el residuo resultante de la concentración se suspendió en un solvente mixto de cloruro de metileno-acetato de etilo, y la sustancia sólida se recolectó mediante filtración, para proporcionar el compuesto del título deseado (130 miligramos, rendimiento del 57 por ciento) como un sólido amarillo pálido.

^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.86 (1H, brs), 9.71 (1H, brs), 7.88 (1H, dd, J=7.4 Hz, 6.8Hz), 7.65 (1H, dd, J=7.8 Hz, 7.4 Hz), 7.40 (1H, d, J=6.8 Hz), 7.38 (1H, d, J=7.8 Hz), 7.34 (2H, d, J=7.4 Hz), 7.04 (2H, m), 5.03 (1H, m), 4.66 (1H, m), 4.06-3.16 (4H, m),

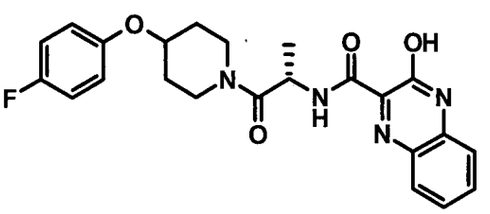
2.08-1.87 (2H, m), 1.73-1.45 (2H, m), 1.31 (3H, d, J=6.6 Hz).

IR (KBr) cm^{-1}: 2945, 1690, 1640, 1500, 1240.

MS (ESI, m/z): 455 $(M+H)^+$.

HRMS (ESI, m/z): 455.1478 (Calculado para $C_{23}H_{24}ClN_4O_4$: 455.1486).

Ejemplo 2



N-{(1S)-2-[4-(4-fluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 2-1

{(1S)-2-[4-(4-fluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-carbamato de terbutilo

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (460 miligramos, 2.40 milimoles), y el monohidrato de 1-hidroxi-benzotriazol (367 miligramos, 2.40 milimoles) se agregaron a una solución en cloruro de metileno (20 mililitros) de clorhidrato de 4-(4-fluoro-fenoxi)-piperidina (463 miligramos, 2.00 milimoles), y N-(terbutoxi-carbonil)-L-alanina (416 miligramos, 2.20 milimoles), a temperatura ambiente, bajo una corriente de nitrógeno, seguido por otra adición de N-metil-morfolina (1.10 mililitros, 10.0 milimoles), y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se vertió en una solución acuosa de ácido

clorhídrico 2N, seguido por extracción con cloruro de metileno, y lavado en secuencia con agua, una solución acuosa saturada de carbonato ácido de sodio, agua, y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., 25+M), para proporcionar el {(1S)-2-[4-(4-fluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-carbamato de terbutilo (683 miligramos, rendimiento del 93 por ciento) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 6.99 (2H, dd, J=8.6 Hz, 8.6 Hz), 6.87 (2H, m), 5.56(1H, d, J=6.6 Hz), 4.65 (1H, m), 4.48 (1H, m), 4.09-3.36 (4H, m), 2.00-1.74 (4H, m), 1.44 (9H, s), 1.31 (3H, d, J=7.0 Hz).

MS (FAB, m/z): 367 $(M+H)^+$.

Ejemplo 2-2

N-{(1S)-2-[4-(4-fluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida

Se agregó ácido clorhídrico concentrado (0.5 mililitros) a una solución en etanol (2.0 mililitros) de {(1S)-2-[4-(4-fluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-carbamato de terbutilo (111 miligramos, 0.300 milimoles), bajo una corriente de nitrógeno, y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se concentró para proporcionar el clorhidrato de (2S)-1-[4-(4-fluoro-fenoxi)-piperidin-1-il]-1-oxopropan-

2-amina (100 miligramos) como un sólido blanco.

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (69.6 miligramos, 0.360 milimoles), y el monohidrato de 1-hidroxi-benzotriazol (55.6 miligramos, 0.360 milimoles) se agregaron a una solución en cloruro de metileno (3.0 mililitros) del compuesto resultante (100 miligramos, 0.300 milimoles), y ácido 3-hidroxi-quinoxalin-2-carboxílico (57.5 miligramos, 0.300 milimoles), a temperatura ambiente, bajo una corriente de nitrógeno, seguido por otra adición de N-metil-morfolina (0.170 mililitros, 1.50 milimoles), y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se vertió en una solución acuosa de ácido clorhídrico 2N, seguido por extracción con acetato de etilo, y lavado en secuencia con agua, una solución acuosa saturada de carbonato ácido de sodio, agua, y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. Después de que la capa orgánica se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., 25+M), el residuo resultante de la concentración se suspendió en un solvente mixto de cloruro de metileno/dietil-éter, y la sustancia sólida se recolectó mediante filtración, para proporcionar el compuesto del título deseado (59.1 miligramos, rendimiento del 44 por ciento) como un sólido amarillo pálido.

^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.9 (1H, brs), 9.70 (1H, brs), 7.88 (1H, dd, J=7.8 Hz, 4.6 Hz), 7.65 (1H, dt, J=7.8 Hz, 1.0 Hz), 7.40

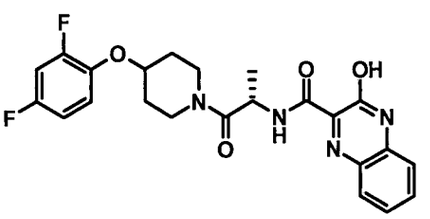
(1H, d, J=7.8 Hz), 7.38(1H, d, J=7.8 Hz), 7.13 (2H, m), 7.03 (2H, m), 5.02 (1H, m), 4.60 (1H, m), 4.02-3.19 (4H, m), 2.06-1.85 (2H, m), 1.72-1.44 (2H, m), 1.31 (3H, d, J=6.6 Hz).

IR (KBr) cm^{-1}: 2935, 1685, 1640, 1505, 1205.

MS (ESI, m/z): 439 $(M+H)^+$.

HRMS (ESI, m/z): 439.1791 (Calculado para $C_{23}H_{24}FN_4O_4$: 439.1782).

Ejemplo 3



N-{(1S)-2-[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 3-1

{(1S)-2-[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-carbamato de terbutilo

De una manera análoga al Ejemplo 1-2, se obtuvo el {(1S)-2-[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-carbamato de terbutilo (700 miligramos, rendimiento del 41 por ciento) a partir del [(1S)-2-(4-hidroxi-piperidin-1-il)-1-metil-2-oxo-etil]-carbamato de terbutilo (1.21 gramos, 4.44 milimoles), y 2,4-difluoro-fenol (640 miligramos, 4.89 milimoles) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.02-6.94 (1H, m), 6.92-6.84 (1H, m), 6.84-6.76 (1H, m), 5.55 (1H, d, J=7.4 Hz), 4.65 (1H, m), 4.42

(1H, m), 3.90-3.35 (4H, m), 2.00-1.77 (4H, m), 1.44 (9H, s), 1.32 y 1.31 (3H, d, J=7.0 Hz).

MS (ESI, m/z): 385 $(M+H)^+$.

Ejemplo 3-2

N-{(1S)-2-[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 1-3, se obtuvo el clorhidrato de (2S)-1-[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-1-oxopropan-2-amina (476 miligramos, rendimiento del 82 por ciento) a partir del {(1S)-2-[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-carbamato de terbutilo (700 miligramos, 1.82 milimoles). El compuesto resultante (160 miligramos, 0.500 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (98.0 miligramos, 0.500 milimoles), para proporcionar el compuesto del título deseado (164 miligramos, rendimiento del 67 por ciento) como un sólido amarillo pálido.

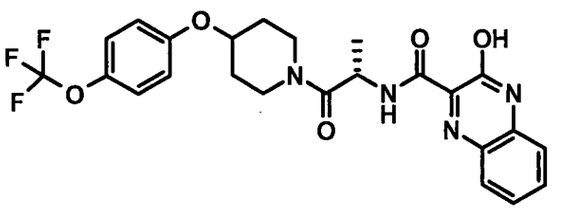
^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.86 (1H, brs), 9.77 (1H, brs), 7.87 (1H, d, J=7.4 Hz), 7.64 (1H, dd, J=7.8 Hz, 7.8 Hz), 7.37 (1H, dd, J=7.8 Hz, 7.4 Hz), 7.38 (1H, d, J=7.8 Hz), 7.35-7.27 (2H, m), 7.07-6.99 (1H, m), 5.02 (1H, m), 4.59 (1H, m), 4.11-3.65 (2H, m), 3.57-3.11 (2H, m), 2.10-1.85 (2H, m), 1.80-1.46 (2H, m), 1.32 y 1.31 (3H, d, J=6.6 Hz).

IR (KBr) cm^{-1}: 2950, 1685, 1640, 1630, 1500.

MS (ESI, m/z): 457 $(M+H)^+$.

HRMS (ESI, m/z): 457.1709 (Calculado para $C_{23}H_{23}F_2N_4O_4$: 457.1687).

Ejemplo 4



3-hidroxi-N-[(1S)-1-metil-2-oxo-2-{4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-etil]-quinoxalin-2-carboxamida

Ejemplo 4-1

[(1S)-1-metil-2-oxo-2-{4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-etil]-carbamato de terbutilo

De una manera análoga al Ejemplo 1-2, el [(1S)-1-metil-2-oxo-2-{4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-etil]-carbamato de terbutilo (824 miligramos, rendimiento del 39 por ciento) se obtuvo a partir del {(1S)-2-[(4-hidroxi-piperidin-1-il)-carbonil]-1-metil-2-oxo-etil}-carbamato de terbutilo (1.32 gramos, 4.85 milimoles), y 4-(trifluoro-metoxi)-fenol (950 miligramos, 5.33 milimoles) como un aceite amarillo pálido.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.16 (2H, d, J=9.0 Hz), 6.90 (2H, d, J=9.0 Hz), 5.55 (1H, d, J=7.6 Hz), 4.65 (1H, m), 4.55 (1H, m), 3.88-3.38 (4H, m), 2.28-1.44 (4H, m), 1.44 (9H, s), 1.31 y 1.27 (3H, d, J=6.6 Hz).

MS (ESI, m/z): 433 $(M+H)^+$.

Ejemplo 4-2

3-hidroxi-N-[(1S)-1-metil-2-oxo-2-{4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-etil]-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 1-3, el clorhidrato de (2S)-1-oxo-1-{4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-propan-2-amina se obtuvo a partir del [(1S)-1-metil-2-oxo-2-{4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-etil]-carbamato de terbutilo. El compuesto resultante (184 miligramos, 0.500 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (98.0 miligramos, 0.500 milimoles), para proporcionar el compuesto del título deseado (115 miligramos, 46 por ciento) como un sólido amarillo pálido.

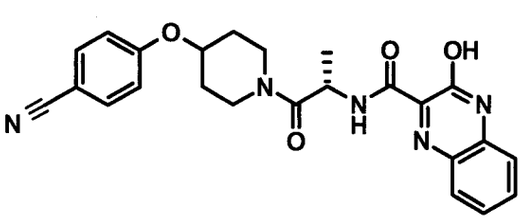
^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.85 (1H, brs), 9.71 (1H, brs), 7.88 (1H, dd, J=7.8 Hz, 7.4 Hz), 7.65 (1H, dd, J=7.8 Hz, 7.8 Hz), 7.40 (1H, d, J=7.4 Hz), 7.38 (1H, d, J=7.8 Hz), 7.30 (2H, d, J=9.0 Hz), 7.11 (2H, dd, J=9.0 Hz, 3.8 Hz), 5.03 (1H, m), 4.69 (1H, m), 4.04-3.72 (2H, m), 3.56-3.19 (2H, m), 2.08-1.86 (2H, m), 1.75-1.48 (2H, m), 1.32 (3H, d, J=6.6 Hz).

IR (KBr) cm^{-1}: 2945, 1685, 1640, 1620, 1505, 1240.

MS (ESI, m/z): 505 $(M+H)^+$.

HRMS (ESI, m/z): 505.1686 (Calculado para $C_{24}H_{24}F_3N_4O_5$: 505.1699).

Ejemplo 5



N-{(1S)-2-[4-(4-ciano-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 5-1

{(1S)-2-[4-(4-ciano-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-carbamato de terbutilo

De una manera análoga al Ejemplo 2-1, el {(1S)-2-[4-(4-ciano-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-carbamato de terbutilo (190 miligramos, rendimiento del 78 por ciento) se obtuvo a partir del clorhidrato de 4-[(piperidin-4-il)-oxi]-benzonitrilo (155 miligramos, 0.650 milimoles), y N-(terbutoxi-carbonil)-L-alanina (123 miligramos, 0.650 milimoles) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.60 (2H, d, J=9.0 Hz), 6.96 (2H, d, J=9.0 Hz), 5.52 (1H, d, J=7.8 Hz), 4.70-4.59 (2H, m), 4.90-4.30 (4H, m), 2.05-1.78 (4H, m), 1.44 (9H, s), 1.31 (3H, d, J=7.0 Hz).

MS (FAB, m/z): 374 $(M+H)^+$.

Ejemplo 5-2

N-{(1S)-2-[4-(4-ciano-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 1-3, el clorhidrato de 4-[(1-L-alanil-piperidin-4-il)-oxi]-benzonitrilo (133 miligramos, rendimiento del 84 por ciento) se obtuvo a partir del {(1S)-2-[4-(4-ciano-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-carbamato de terbutilo (190 miligramos, 0.510 milimoles). El compuesto resultante (108 miligramos, 0.350 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (68.6 miligramos, 0.350 milimoles), para proporcionar el compuesto del título deseado (107 miligramos, rendimiento del 68 por ciento) como un sólido amarillo pálido.

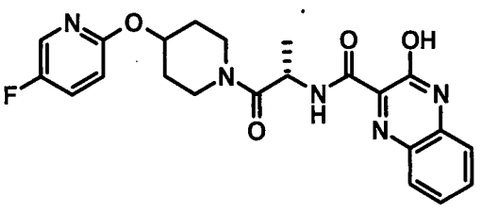
^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.87 (1H, brs), 9.70 (1H, brs), 7.88 (1H, dd, J=7.8 Hz, 7.4 Hz), 7.78 (2H, d, J=9.0 Hz), 7.65 (1H, dd, J=7.8 Hz, 7.8 Hz), 7.40 (1H, d, J=7.8 Hz), 7.38 (1H, d, J=7.4 Hz), 7.19 (2H, dd, J=9.0 Hz, 2.6 Hz), 5.03 (1H, m), 4.83 (1H, m), 4.07-3.73 (2H, m), 3.57-3.17 (2H, m), 2.12-1.89 (2H, m), 1.78-1.47 (2H, m), 1.31 (3H, d, J=7.0 Hz).

IR (KBr) cm^{-1}: 2945, 2220, 1685, 1640, 1605, 1505, 1255.

MS (ESI, m/z): 446 $(M+H)^+$.

HRMS (ESI, m/z): 446.1851 (Calculado para $C_{24}H_{24}N_5O_4$: 446.1828).

Ejemplo 6



N-[(1S)-2-{4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-1-metil-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 6-1

[(1S)-2-{4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-1-metil-2-oxo-etil]-carbamato de terbutilo

De una manera análoga al Ejemplo 2-1, se obtuvo el [(1S)-2-{4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-1-metil-2-oxo-etil]-carbamato de terbutilo (316 miligramos, rendimiento del 86 por ciento) a partir del diclorhidrato de 5-fluoro-2-[(piperidin-4-il)-oxi]-piridina (269 mili-

gramos, 1.00 milimoles), y N-(terbutoxi-carbonil)-L-alanina (189 miligramos, 1.00 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.98-7.94 (1H, m), 7.38-7.31 (1H, m), 6.70 (1H, dd, J=9.0 Hz, 3.4 Hz), 5.58 (1H, d, J=8.2 Hz), 5.23 (1H, m), 4.66 (1H, m), 4.01-3.34 (4H, m), 2.11-1.92 (2H, m), 1.89-1.72 (2H, m), 1.45 (9H, s), 1.32 (3H, d, J=7.0 Hz).

MS (FAB, m/z): 368 $(M+H)^+$.

Ejemplo 6-2

N-[(1S)-2-{4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-1-metil-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 1-3, el diclorhidrato de (2S)-1-{4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-1-oxopropan-2-amina (283 miligramos, rendimiento del 100 por ciento) se obtuvo a partir del [(1S)-2-{4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-1-metil-2-oxo-etil]-carbamato de terbutilo (306 miligramos, 0.831 milimoles). A partir del compuesto resultante (119 miligramos, 0.350 milimoles), a través de una condensación con ácido 3-hidroxi-quinoxalin-2-carboxílico (68.6 miligramos, 0.350 milimoles), se proporcionó el compuesto del título deseado (87.8 miligramos, rendimiento del 57 por ciento) como un sólido amarillo.

^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.88 (1H, brs), 9.75 (1H, brs), 8.16 (1H, d, J=3.0 Hz), 7.88 (1H, dd, J=7.6 Hz, 4.2 Hz), 7.74-7.62 (2H, m), 7.40 (1H, d, J=7.6 Hz), 7.38 (1H, d, J=7.6 Hz), 6.92-6.83 (1H, m), 5.18 (1H, m), 5.03 (1H, m), 4.10-3.73 (2H, m), 3.56-3.16 (2H, m), 2.14-1.91 (2H, m), 1.79-1.46 (2H, m), 1.32 y 1.31(3H,

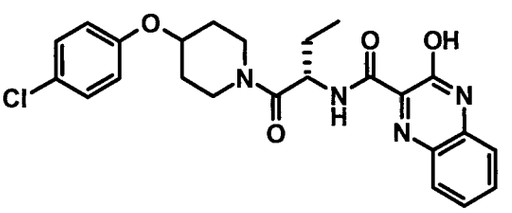
d, J=6.6 Hz).

IR (KBr) cm^{-1}: 2950, 1690, 1630, 1480, 1220.

MS (ESI, m/z): 440 $(M+H)^+$.

HRMS (ESI, m/z): 440.1736 (Calculado para $C_{23}H_{24}FN_5O_4$: 440.1734).

Ejemplo 7



N-[(1S)-1-{[4-(4-cloro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 7-1

{(1S)-1-[(4-hidroxi-piperidin-1-il)-carbonil]-propil}-carbamato de terbutilo

De una manera análoga al Ejemplo 1-1, el {(1S)-1-[(4-hidroxi-piperidin-1-il)-carbonil]-propil}-carbamato de terbutilo (5.95 gramos, rendimiento del 42 por ciento) se obtuvo a partir de 4-hidroxi-piperidina (5.06 gramos, 50.0 milimoles), y ácido (S)-2-(terbutoxi-carbonil-amino)-butírico (10.1 gramos, 50.0 milimoles) como una sustancia amorfa color amarillo pálido.

^{1}H-RMN ($CDCl_3$, 500 MHz) δ: 5.48 (1H, d, J=7.4Hz), 4.58 (1H, m), 4.32-3.70 (3H, m), 3.39-3.18 (2H, m), 2.00-1.82 (2H, m), 1.82-1.63 (2H, m), 1.63-1.48 (3H, m), 1.43 (9H, s), 1.01-0.88 (3H, m).

MS (FAB/z): 287 $(M+H)^+$.

Ejemplo 7-2

[(1S)-1-{[4-(4-cloro-fenoxi)-piperidin-1-il]-carbonil}-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 1-2, una mezcla (1.01 gramos) que contenía el [(1S)-1-{[4-(4-cloro-fenoxi)-piperidin-1-il]-carbonil}-propil]-carbamato de terbutilo, se obtuvo a partir del {(1S)-1-[(4-hidroxi-piperidin-1-il)-carbonil]-propil}-carbamato de terbutilo (1.00 gramos, 3.50 milimoles), y 4-cloro-fenol (490 miligramos, 3.85 milimoles). La mezcla se utilizó como estaba en la siguiente reacción sin mayor purificación.

MS (FAB, m/z): 397 $(M+H)^+$.

Ejemplo 7-3

N-[(1S)-1-{[4-(4-cloro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 1-3, el clorhidrato de (2S)-1-[4-(4-cloro-fenoxi)-piperidin-1-il]-1-oxobutan-2-amina (131 miligramos) se obtuvo a partir del [(1S)-1-{[4-(4-cloro-fenoxi)-piperidin-1-il]-carbonil}-propil]-carbamato de terbutilo (1.39 gramos, 3.50 milimoles). A partir del compuesto resultante (117 miligramos, 0.350 milimoles), a través de una condensación con ácido 3-hidroxi-quinoxalin-2-carboxílico (68.6 miligramos, 0.350 milimoles), se proporcionó el compuesto del título deseado (55.0 miligramos, rendimiento del 34 por ciento) como un sólido amarillo pálido.

^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.82 (1H, brs), 9.63 (1H, brs), 7.85 (1H, dd, J=7.4 Hz, 7.4 Hz), 7.63 (1H, dd, J=7.8 Hz, 7.4

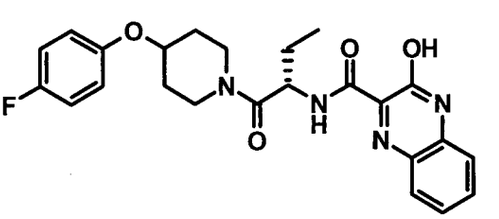
Hz), 7.37 (1H, d, J=7.4 Hz), 7.36 (1H, d, J=7.8 Hz), 7.33 (2H, d, J=9.0 Hz), 7.04 y 7.03 (2H, d, J=9.0 Hz), 4.98 (1H, m), 4.66 (1H, m), 4.02-3.78 (2H, m), 3.56-3.19 (2H, m), 2.07-1.45 (6H, m), 0.91 (3H, t, J=7.4 Hz).

IR (KBr) cm^{-1}: 2935, 1690, 1640, 1490, 1240.

MS (ESI, m/z): 469 $(M+H)^+$.

HRMS (ESI, m/z): 469.1650 (Calculado para $C_{24}H_{26}ClN_4O_4$: 469.1643).

Ejemplo 8



N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 8-1

N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 2-1, el N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-carbamato de terbutilo (703 miligramos, rendimiento del 92 por ciento) se obtuvo a partir del clorhidrato de 4-(4-fluoro-fenoxi)-piperidina (463 miligramos, 2.00 milimoles), y ácido (2S)-2-(terbutoxi-carbonil-amino)-butírico (407 miligramos, 2.00 milimoles) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 6.99 (2H, d, J=8.6 Hz), 6.87 (2H,

m), 5.44 (1H, d, J=8.6 Hz), 4.59 (1H, m), 4.47 (1H, m), 3.83-3.38 (4H, m), 1.70-1.63 (4H, m), 1.63-1.50 (2H, m), 1.44 (9H, s), 0.94 (3H, t, J=7.4 Hz).

MS (ESI, m/z): 381 $(M+H)^+$.

Ejemplo 8-2

N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 2-2, el clorhidrato de (2S)-1-[4-(4-fluoro-fenoxi)-piperidin-1-il]-1-oxobutan-2-amina (535 miligramos) se obtuvo a partir del [(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-carbamato de terbutilo (703 miligramos, 1.80 milimoles) como un sólido blanco. El compuesto resultante (317 miligramos, 1.00 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (190 miligramos, 1.00 milimoles), para proporcionar el compuesto del título deseado (358 miligramos, rendimiento del 79 por ciento) como un sólido amarillo pálido.

^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.86 (1H, brs), 9.56 (1H, m), 7.88 (1H, dd, J=7.8 Hz, 7.8 Hz), 7.65 (1H, dd, J=7.8 Hz, 7.8 Hz), 7.40 (1H, d, J=7.8 Hz), 7.38 (1H, d, J=7.8 Hz), 7.14 (2H, m), 7.03 (2H, m), 5.00 (1H, m), 4.60 (1H, m), 4.03-3.79 (2H, m), 3.57-3.20 (2H, m), 2.07-1.44 (6H, m), 0.92 (3H, t, J=7.4 Hz).

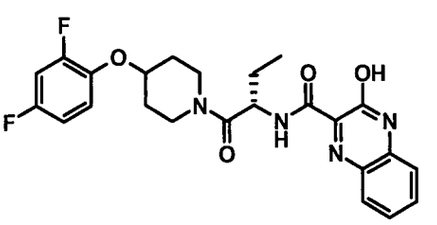
IR (KBr) cm^{-1}: 2965, 1690, 1630, 1505, 1205.

MS (ESI, m/z): 453 $(M+H)^+$.

HRMS (ESI, m/z): 453.1950 (Calculado para $C_{24}H_{26}FN_4O_4$: 453.1938)

Análisis calculado para $C_{24}H_{25}FN_4O_4$: C, 63.71; H, 5.57; N, 12.38; F, 4.20. Encontrado: C, 63.67; H, 5.46; N, 12.42; F, 4.09.

Ejemplo 9



N-[(1S)-1-{[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 1-2, una mezcla (1.88 gramos) que contenía el [(1S)-1-{[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-carbamato de terbutilo, se obtuvo a partir del {(1S)-2-[(4-hidroxi-piperidin-1-il)-carbonil]-propil}-carbamato de terbutilo (1.18 gramos, 4.13 milimoles), y 2,4-difluoro-fenol (590 miligramos, 4.54 milimoles). La mezcla se utilizó como estaba en la siguiente reacción sin mayor purificación.

De una manera análoga al Ejemplo 1-3, el clorhidrato de (2S)-1-[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-1-oxobutan-2-amina (629 miligramos) se obtuvo a partir de la mezcla resultante (1.65 gramos, 4.13 milimoles). El compuesto resultante (228 miligramos, 0.682 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (133 miligramos, 0.682 milimoles), para proporcionar el compuesto del título deseado (174 miligramos, rendimiento del 52 por ciento)

como un sólido amarillo pálido.

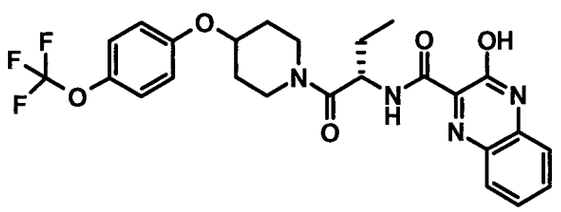
^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.84 (1H, brs), 9.54 (1H, brs), 7.90-7.83 (1H, m), 7.65 (1H, dd, J=8.6 Hz, 8.2 Hz), 7.40 (1H, d, J=7.4 Hz), 7.38 (1H, d, J=8.6 Hz), 7.35-7.27 (2H, m), 7.27-7.07 (1H, m), 4.99 (1H, m), 4.59 (1H, m), 4.02-3.78 (2H, m), 3.57-3.20 (2H, m), 2.09-1.49 (6H, m), 0.92 (3H, t, J=7.0 Hz).

IR (KBr) cm^{-1}: 2940, 1685, 1640, 1505, 1210.

MS (ESI, m/z): 471 $(M+H)^+$.

HRMS (ESI, m/z): 471.1848 (Calculado para $C_{24}H_{25}F_2N_4O_4$: 471.1844).

Ejemplo 10



3-hidroxi-N-[(1S)-1-({4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

Ejemplo 10-1

[(1S)-1-({4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 1-2, una mezcla (1.58 gramos) que contenía el [(1S)-1-({4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo, se obtuvo a partir del {(1S)-1-[(4-hidroxi-piperidin-1-il)-carbonil}-propil}-carbamato de terbutilo (1.13 gramos, 4.13 milimoles), y 4-(trifluoro-

metoxi)-fenol (590 miligramos, 4.54 milimoles). La mezcla se utilizó como estaba en la siguiente reacción sin mayor purificación.

MS (FAB, m/z): 447 $(M+H)^+$.

Ejemplo 10-2

3-hidroxi-N-[(1S)-1-({4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 1-3, el clorhidrato de (2S)-1-oxo-1-{4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-butan-2-amina (310 miligramos) se obtuvo a partir del [(1S)-1-({4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (1.84 gramos, 4.12 milimoles). El compuesto resultante (184 miligramos, 0.530 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (104 miligramos, 0.530 milimoles), para proporcionar el compuesto del título deseado (134 miligramos, rendimiento del 49 por ciento) como un sólido amarillo pálido.

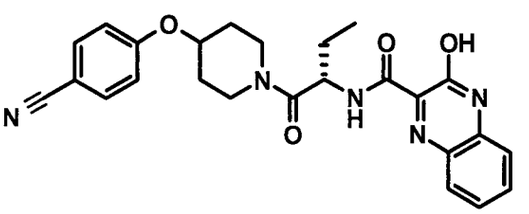
^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.84 (1H, brs), 9.56 (1H, m), 7.87 (1H, dd, J=7.8 Hz, 7.8 Hz), 7.65 (1H, dd, J=7.8 Hz, 7.8 Hz), 7.40 (1H, d, J=7.8 Hz), 7.38 (1H, d, J=7.8 Hz), 7.30 (2H, d, J=8.6 Hz), 7.11 (2H, dd, J=8.6 Hz, 5.0 Hz), 5.00 (1H, m), 4.69 (1H, m), 4.08-3.79 (2H, m), 3.58-3.20 (2H, m), 2.10-1.46 (6H, m), 0.92 (3H, t, J=7.4 Hz).

IR (KBr) cm^{-1}: 2945, 1685, 1640, 1505, 1240.

MS (ESI, m/z): 519 $(M+H)^+$.

HRMS (ESI, m/z): 519.1850 (Calculado para $C_{25}H_{26}F_3N_4O_5$: 519.1855).

Ejemplo 11



N-[(1S)-1-{[4-(4-ciano-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 11-1

[(1S)-1-{[4-(4-ciano-fenoxi)-piperidin-1-il]-carbonil}-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 2-1, el [(1S)-1-{[4-(4-ciano-fenoxi)-piperidin-1-il]-carbonil}-propil]-carbamato de terbutilo (226 miligramos, rendimiento del 90 por ciento) se obtuvo a partir del clorhidrato de 4-[(piperidin-4-il)-oxi]-benzonitrilo (155 miligramos, 0.650 milimoles), y ácido (2S)-2-(terbutoxi-carbonil-amino)-butírico (132 miligramos, 0.650 milimoles) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.60 (2H, d, J=9.0 Hz), 6.96 (2H, d, J=9.0 Hz), 5.41 (1H, d, J=8.6 Hz), 4.70-4.55 (2H, m), 3.90-3.41 (4H, m), 2.07-1.70 (4H, m), 1.44 (9H, s), 1.57 (2H, q, J=7.4 Hz), 0.94 (3H, t, J=7.4 Hz).

MS (FAB, m/z): 388 $(M+H)^+$.

Ejemplo 11-2

N-[(1S)-1-{[4-(4-ciano-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 1-3, el clorhidrato de 4-({1-

[(2S)-2-amino-butanoil]-piperidin-4-il}-oxi)-benzonitrilo (133 miligramos, rendimiento del 84 por ciento) se obtuvo a partir del [(1S)-1-{[4-(4-ciano-fenoxi)-piperidin-1-il]-carbonil}-propil]-carbamato de terbutilo (226 miligramos, 0.583 milimoles). El compuesto resultante (113 miligramos, 0.350 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (68.6 miligramos, 0.350 milimoles), para proporcionar el compuesto del título deseado (107 miligramos, rendimiento del 66 por ciento) como un sólido amarillo.

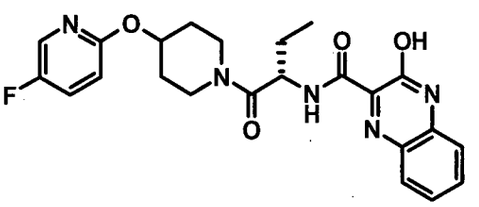
^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.85 (1H, brs), 9.56 (1H, m), 7.87 (1H, dd, J=8.2 Hz, 7.8 Hz), 7.78 (2H, d, J=9.0 Hz), 7.65 (1H, dd, J=7.8 Hz, 7.4 Hz), 7.40 (1H, d, J=7.4 Hz), 7.38 (1H, d, J=8.2 Hz), 7.19 (2H, dd, J=9.0 Hz, 4.2 Hz), 5.00 (1H, m), 4.83 (1H, m), 4.07-3.81 (2H, m), 3.61-3.16 (2H, m), 2.14-1.46 (6H, m), 0.92 (3H, t, J=7.4 Hz).

IR (KBr) cm^{-1}: 2965, 2220, 1685, 1630, 1505, 1250.

MS (ESI, m/z): 460 $(M+H)^+$.

HRMS (ESI, m/z): 460.1973 (Calculado para $C_{25}H_{26}N_5O_4$: 460.1984).

Ejemplo 12



N-[(1S)-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 12-1

[(1S)-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 2-1, el [(1S)-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (317 miligramos, rendimiento del 83 por ciento) se obtuvo a partir del diclorhidrato de 5-fluoro-2-[(piperidin-4-il)-oxi]-piridina (269 miligramos, 1.00 milimoles), y ácido (2S)-2-(terbutoxicarbonil-amino)-butírico (203 miligramos, 1.00 milimoles) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.96 (1H, dd, J=3.0 Hz, 3.0 Hz), 7.39-7.32 (1H, m), 6.70 (1H, dd, J=9.0 Hz, 3.4 Hz), 5.47 (1H, d, J=8.6 Hz), 5.23 (1H, m), 4.60 (1H, m), 3.99-3.38 (4H, m), 2.10-1.91 (2H, m), 1.88-1.70 (2H, m), 1.64-1.50 (2H, m), 1.44 (9H, s), 0.94 (3H, t, J=7.4 Hz).

MS (FAB, m/z): 382 $(M+H)^+$.

Ejemplo 12-2

N-[(1S)-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 1-3, el diclorhidrato de (2S)-1-{4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-1-oxobutan-2-amina (285 miligramos, rendimiento del 100 por ciento) se obtuvo a partir del [(1S)-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (307 miligramos, 0.805 milimoles). El compuesto resultante (124 miligramos, 0.350 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (68.6 mili-

gramos, 0.350 milimoles), para proporcionar el compuesto del título deseado (74.2 miligramos, rendimiento del 47 por ciento) como un sólido amarillo.

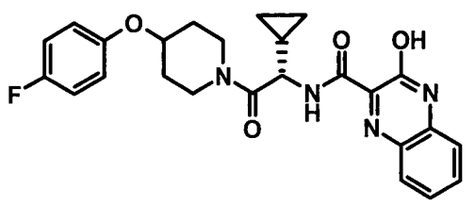
^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.85 (1H, brs), 9.58 (1H, d, J=7.0 Hz), 8.16 (1H, d, J=2.6 Hz), 7.88 (1H, dd, J=7.4 Hz, 5.4 Hz), 7.74-7.62 (2H, m), 7.40 (1H, d, J=7.4 Hz), 7.38 (1H, d, J=8.2 Hz), 6.93-6.84 (1H, m), 5.19 (1H, m), 5.00 (1H, m), 4.08-3.81 (2H, m), 3.58-3.16 (2H, m), 2.15-1.92 (2H, m), 1.88-1.48 (4H, m), 0.92 (3H, t, J=7.4 Hz).

IR (KBr) cm^{-1}: 2950, 1690, 1630, 1480, 1215.

MS (ESI, m/z): 454 $(M+H)^+$.

HRMS (ESI, m/z): 454.1890 (Calculado para $C_{23}H_{25}FN_5O_4$: 454.1891).

Ejemplo 13



N-{(1S)-1-ciclopropil-2-[4-(4-fluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 13-1

{(1S)-1-ciclopropil-2-[4-(4-fluoro-fenoxi)-piperidin-1-il)-2-oxo-etil}-carbamato de terbutilo

De una manera análoga al Ejemplo 2-1, el {(1S)-1-ciclopropil-2-[4-(4-fluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-carbamato de terbutilo

(3.06 gramos, rendimiento del 90 por ciento) se obtuvo a partir del clorhidrato de 4-(4-fluoro-fenoxi)-piperidina (2.00 gramos, 8.63 milimoles), y el ácido (2S)-2-(terbutoxi-carbonil-amino)-ciclopropil-acético (1.86 gramos, 8.63 milimoles) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 6.99 (2H, dd, J=8.6 Hz, 8.6 Hz), 6.87 (2H, dd, J=8.6Hz, 4.6 Hz), 5.46 (1H, d, J=7.8 Hz), 4.54-4.42 (2H, m), 3.84-3.44 (4H, m), 2.08-1.74 (4H, m), 1.44 (9H, s), 1.16-1.03 (1H, m), 0.58-0.31 (4H, m).

MS (ESI, m/z): 393 $(M+H)^+$.

Ejemplo 13-2

N-{(1S)-1-ciclopropil-2-[4-(4-fluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 2-2, el clorhidrato de (1S)-1-ciclopropil-2-[4-(4-fluoro-fenoxi)-piperidin-1-il]-2-oxo-etanamina (2.00 gramos, rendimiento del 88 por ciento) se obtuvo a partir del {(1S)-1-ciclopropil-2-[4-(4-fluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-carbamato de terbutilo (3.06 gramos, 7.80 milimoles) como un aceite incoloro. El compuesto resultante (2.00 gramos, 6.84 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (1.48 gramos, 7.80 milimoles) bajo una corriente de nitrógeno, para proporcionar el compuesto del título deseado (2.71 gramos, rendimiento del 85 por ciento) como un sólido amarillo pálido.

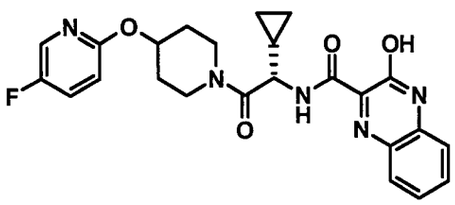
^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.88 (1H, s), 9.62 (1H, d, J=6.0 Hz), 7.87 (1H, dd, J=7.6 Hz, 2.0 Hz), 7.65 (1H, dt, J=7.6 Hz, 2.0 Hz), 7.40 (1H, dt, J=7.6 Hz, 2.0 Hz), 7.37 (1H, d, J=7.6 Hz), 7.12

(2H, m), 7.02 (2H, m), 4.76 (1H, q, J=8.4 Hz), 4.61 (1H, m), 4.12-3.80 (2H, m), 3.60-3.20 (2H, m), 2.08-1.88 (2H, m), 1.75-1.45 (2H, m), 1.23 (1H, dd, J=6.4 Hz), 0.53-0.38 (4H, m).

MS (ESI, m/z): 465 $(M+H)^+$.

Análisis calculado para $C_{25}H_{25}FN_4O_4$: C, 64.64; H, 5.42; N, 12.06. Encontrado: C, 64.27; H, 5.30; N, 12.01.

Ejemplo 14



N-[(1S)-1-ciclopropil-2-{4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 14-1

[(1S)-1-ciclopropil-2-{4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-2-oxo-etil]-carbamato de terbutilo

De una manera análoga al Ejemplo 2-1, el [(1S)-1-ciclopropil-2-{4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-2-oxo-etil]-carbamato de terbutilo (276 miligramos, rendimiento del 70 por ciento) se obtuvo a partir del diclorhidrato de 5-fluoro-2-[(piperidin-4-il)-oxi]-piridina (269 miligramos, 1.00 milimoles), y el ácido (2S)-2-(terbutoxi-carbonil-amino)-2-ciclopropil-acético (215 miligramos, 1.00 milimoles) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.97 (1H, d, J=2.6 Hz), 7.40-7.32 (1H, m), 6.71 (1H, dd, J=9.0 Hz, 3.4 Hz), 5.47 (1H, d, J=7.8 Hz), 5.24

(1H, m), 4.51 (1H, dd, J=7.4 Hz, 7.4 Hz), 3.99-3.73 (2H, m), 3.66-3.42 (2H, m), 2.12-1.94 (2H, m), 1.91-1.73 (2H, m), 1.44 (9H, s), 1.17-1.06 (1H, m), 0.58-0.34 (4H, m).

MS (FAB, m/z): 394 $(M+H)^+$.

Ejemplo 14-2

N-[(1S)-1-ciclopropil-2-{4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 1-3, el diclorhidrato de (1S)-1-ciclopropil-2-{4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-2-oxo-etanamina (248 miligramos, rendimiento del 100 por ciento) se obtuvo a partir del [(1S)-1-ciclopropil-2-{4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-2-oxo-etil]-carbamato de terbutilo (266 miligramos, 0.676 milimoles). El compuesto resultante (160 miligramos, 0.439 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (85.6 miligramos, 0.439 milimoles), para proporcionar el compuesto del título deseado (78.3 miligramos, rendimiento del 38 por ciento) como un sólido amarillo.

^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.87 (1H, brs), 9.67 (1H, brs), 8.16 (1H, d, J=2.6 Hz), 7.88 (1H, m), 7.76-7.62 (2H, m), 7.40 (1H, d, J=7.0 Hz), 7.39 (1H, d, J=8.6 Hz), 6.95-6.83 (1H, m), 5.19 (1H, m), 4.79 (1H, m), 4.10-3.82 (2H, m), 3.59-3.14 (2H, m), 2.17-1.45 (4H, m), 1.28-1.17 (1H, m), 0.53-0.36 (4H, m).

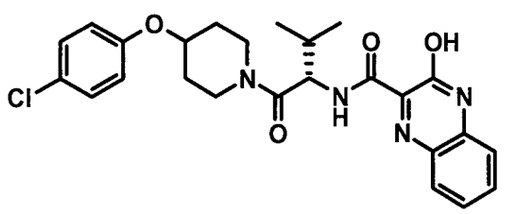
IR (KBr) cm^{-1}: 2960, 1690, 1630, 1530, 1480.

MS (ESI, m/z): 466$(M+H)^+$.

HRMS (ESI, m/z): 466.1882 (Calculado para $C_{24}H_{25}FN_5O_4$:

466.1891).

Ejemplo 15



N-[(1S)-1-{[4-(4-cloro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 15-1

N-[(1S)-1-{[4-(4-cloro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (844 miligramos, 4.40 milimoles), y el monohidrato de 1-hidroxi-benzotriazol (595 miligramos, 4.40 milimoles), se agregaron a una solución en cloruro de metileno (30 mililitros) de clorhidrato de 4-(4-cloro-fenoxi)-piperidina (910 miligramos, 3.67 milimoles), y N-(terbutoxi-carbonil)-L-valina (876 miligramos, 4.03 milimoles), a temperatura ambiente, bajo una corriente de nitrógeno, seguido por otra adición de N-metil-morfolina (0.888 mililitros, 8.07 milimoles), y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se vertió en una solución acuosa de ácido clorhídrico 2N, seguido por extracción con cloruro de metileno, y lavado en secuencia con agua, una solución acuosa saturada de carbonato ácido de sodio, agua, y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio

anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., 25+M), para proporcionar el [(1S)-1-{[4-(4-cloro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo (1.38 gramos, rendimiento del 92 por ciento) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.41-7.23 (2H, m), 7.07-6.83 (2H, m), 5.34 (1H, d, J=8.3 Hz), 4.53-4.48 (2H, m), 3.80-3.46 (4H, m), 2.00-1.78 (5H, m), 1.48-1.40 (9H, m), 0.97 (3H, d, J=6.8 Hz), 0.89 (3H, d, J=6.8 Hz).

MS (FAB, m/z): 411 $(M+H)^+$.

Ejemplo 15-2

N-[(1S)-1-{[4-(4-cloro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Se agregó ácido clorhídrico concentrado (6.0 mililitros) a una solución en etanol (12 mililitros) de [(1S)-1-{[4-(4-cloro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo (1.38 gramos, 3.36 milimoles), bajo una corriente de nitrógeno, y la mezcla se dejó reaccionar a temperatura ambiente durante la noche. La solución de la reacción se concentró para proporcionar el clorhidrato de (2S)-1-[4-(4-cloro-fenoxi)-piperidin-1-il]-3-metil-1-oxobutan-2-amina (1.17 gramos) como un sólido blanco.

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (149 miligramos, 0.777 milimoles), y el monohidrato de 1-hidroxi-benzotriazol (105 miligramos, 0.777 milimoles), se agregaron a una

solución en cloruro de metileno (5.0 mililitros) del compuesto resultante (180 miligramos, 0.518 milimoles), y ácido 3-hidroxi-quinoxalin-2-carboxílico (148 miligramos, 0.777 milimoles), a temperatura ambiente, bajo una corriente de nitrógeno, seguido por otra adición de trietil-amina (0.289 mililitros, 2.07 milimoles), y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se vertió en una solución acuosa de ácido clorhídrico 2N, seguido por extracción con acetato de etilo, y lavado en secuencia con agua, una solución acuosa saturada de carbonato ácido de sodio, agua, y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. Después de que la capa orgánica se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., 25+M), el residuo resultante de la concentración se suspendió en un solvente mixto de cloruro de metileno/dietil-éter, y la sustancia sólida se recolectó mediante filtración, para proporcionar el compuesto del título deseado (113 miligramos, rendimiento del 45 por ciento) como un sólido amarillo pálido.

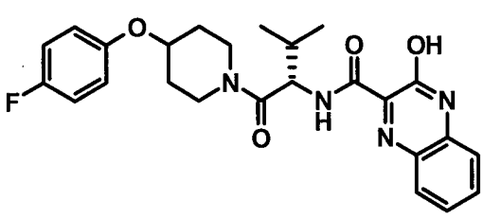
^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.86 (1H, s), 10.19 (1H, s), 7.97 (1H, t, J=7.0 Hz), 7.61 (1H, s), 7.53 (1H, s), 7.36 (1H, s), 7.26 (2H, t, J=7.0 Hz), 6.86 (2H, t, J=7.0 Hz), 5.09-5.07 (1H, m), 4.57-4.55 (1H, m), 4.01-3.68 (4H, m), 2.21-2.02 (5H, m), 1.14-1.11 (6H, m).

IR (KBr) cm^{-1}: 2960, 1690, 1640, 1490, 1240, 1150.

MS (FAB, m/z): 483 $(M+H)^+$.

HRMS (ESI, m/z): 483.1797 (Calculado para $C_{25}H_{28}ClN_4O_4$: 483.1799).

Ejemplo 16



N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 16-1

[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 2-1, el [(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo (745 miligramos, rendimiento del 86 por ciento) se obtuvo a partir del clorhidrato de 4-(4-fluoro-fenoxi)-piperidina (510 miligramos, 2.20 milimoles), y N-(terbutoxi-carbonil)-L-valina (478 miligramos, 2.20 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.01-6.95 (2H, m), 6.89-6.84 (2H, m), 5.34 (1H, d, J=8.8 Hz), 4.52-4.45 (2H, m), 3.82-3.45 (4H, m), 2.05-1.76 (5H, m), 1.44 (9H, s), 0.97 (3H, d, J=6.8 Hz), 0.89 (3H, d, J=6.8 Hz).

MS (ESI, m/z): 395 $(M+H)^+$.

Ejemplo 16-2

N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-

3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 2-2, el clorhidrato de (2S)-1-[4-(4-fluoro-fenoxi)-piperidin-1-il]-3-metil-1-oxobutan-2-amina (550 miligramos, 70 por ciento) se obtuvo a partir del [(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo (745 miligramos, 1.89 milimoles) como un aceite incoloro. El compuesto resultante (150 miligramos, 0.450 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (95.0 miligramos, 0.500 milimoles) bajo una corriente de nitrógeno, para proporcionar el compuesto del título deseado (101 miligramos, rendimiento del 48 por ciento) como un sólido amarillo pálido.

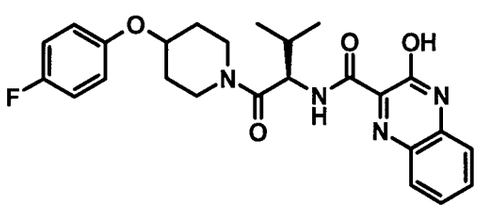
^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.51 (1H, brs), 10.14 (1H, brs), 8.05-7.96 (1H, m), 7.70-7.32 (3H, m), 7.04-6.84 (4H, m), 5.08 (1H, dd, J=7.6 Hz, 7.1 Hz), 4.53-4.46 (1H, m), 4.00-3.68 (4H, m), 2.38-2.09 (1H, m), 2.02-1.85 (4H, m), 1.17-1.07 (6H, m).

IR (ATR) cm^{-1}, 1685, 1630, 1500, 1450, 1275, 1245.

MS (ESI, m/z): 467 $(M+H)^+$.

Análisis calculado para $C_{25}H_{27}FN_4O_4$: C, 64.37; H, 5.83; F, 4.07; N, 12.01. Encontrado: C, 64.01; H, 5.81; F, 3.85; N, 11.69.

Ejemplo 17



N-[(1R)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-

3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 17-1

[(1R)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 2-1, el [(1R)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo (326 miligramos, rendimiento del 83 por ciento) se obtuvo a partir del clorhidrato de 4-(4-fluoro-fenoxi)-piperidina (232 miligramos, 1.00 milimoles), y N-(terbutoxi-carbonil)-D-valina (217 miligramos, 1.00 milimoles) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 500 MHz) δ: 8.72 (2H, dd, J=8.8 Hz, 8.0 Hz), 8.57 (2H, dd, J=8.8 Hz, 4.4 Hz), 5.34 (1H, d, J=8.8 Hz), 4.54-4.43 (2H, m), 3.82-3.40 (4H, m), 2.00-1.80 (5H, m), 1.44 (9H, s), 0.97 y 0.89 (6H, d, J=6.8 Hz).

MS (ESI, m/z): 395 $(M+H)^+$.

Ejemplo 17-2

N-[(1R)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 2-2, el clorhidrato de (2R)-1-[4-(4-fluoro-fenoxi)-piperidin-1-il]-3-metil-1-oxobutan-2-amina (113 miligramos, rendimiento del 46 por ciento) se obtuvo a partir del [(1R)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo (326 miligramos, 0.828 milimoles). El compuesto resultante (113 miligramos, 0.382 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (72.7 miligramos, 0.382

milimoles), para proporcionar el compuesto del título deseado (92.8 miligramos, rendimiento del 51 por ciento) como un sólido amarillo.

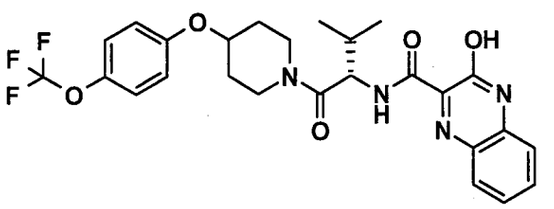
^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.67 (1H, brs), 10.17 (1H, brs), 8.05-7.96 (1H, m), 7.70-7.32 (3H, m), 7.04-6.84 (4H, m), 5.08 (1H, dd, J=7.6 Hz, 7.1 Hz), 4.53-4.46 (1H, m), 4.00-3.68 (4H, m), 2.38-2.09 (1H, m), 2.02-1.85 (4H, m), 1.17-1.07 (6H, m).

IR (KBr)cm^{-1}: 2960, 1690, 1630, 1505, 1210.

MS (ESI, m/z): 467 $(M+H)^+$.

HRMS (ESI, m/z): 467.2170 (Calculado para $C_{25}H_{28}FN_4O_4$: 467.2095).

Ejemplo 18



3-hidroxi-N-[(1S)-2-metil-1-({4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

Ejemplo 18-1

[(1S)-2-metil-1-({4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 1-2, el N-[(1S)-2-metil-1-{4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-carbonil}-propil]-carbamato de terbutilo (2.09 gramos, rendimiento del 76 por ciento) se obtuvo a partir del {(1S)-1-[(4-hidroxi-piperidin-1-il)-carbonil]-2-metil-propil}-carbamato de terbutilo (1.80 gramos, 6.00 milimoles), y 4-(trifluoro-

metoxi)-fenol (1.28 gramos, 7.20 milimoles) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.15 (2H, d, J=9.6 Hz), 6.90 (2H, dd, J=9.6 Hz, 2.4 Hz), 5.34 (1H, d, J=9.6 Hz), 4.51 (2H, m), 3.80-3.45 (4H, m), 2.00-1.80 (5H, m), 1.44 (9H, s), 0.97 (3H, d, J=6.4 Hz), 0.89 (3H, d, J=6.4 Hz).

MS (ESI, m/z): 461 $(M+H)^+$.

Ejemplo 18-2

3-hidroxi-N-[(1S)-2-metil-1-({4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 1-3, el clorhidrato de (2S)-3-metil-1-oxo-1-{4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-butan-2-amina se obtuvo a partir del [(1S)-2-metil-1-({4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (2.09 gramos, 4.54 milimoles) como un sólido blanco. El compuesto resultante (940 miligramos, 2.37 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (540 miligramos, 2.84 milimoles), para proporcionar el compuesto del título deseado (680 miligramos, rendimiento del 54 por ciento) como un sólido amarillo pálido.

^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.83 (1H, brs), 9.55 (1H, brs), 7.86 (1H, m), 7.61 (1H, m), 7.38 (2H, m), 7.28 (1H, m), 7.11 (3H, m), 4.90 (1H, dd, J=7.6 Hz, 7.1 Hz), 4.68 (1H, m), 3.99-3.80 (2H, m), 3.57-3.20 (2H, m), 2.05 (4H, m), 1.68 (1H, m), 0.94 (6H, d, J=6.4 Hz).

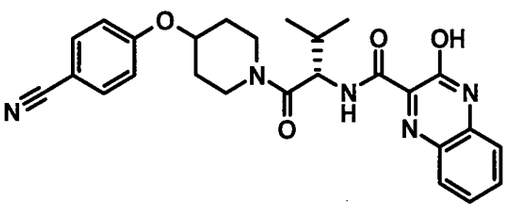
IR (KBr)cm^{-1}: 2960, 1690, 1640, 1505, 1240, 1160.

MS (ESI, m/z): 533 $(M+H)^+$.

HRMS (ESI, m/z): 533.1998 (Calculado para $C_{26}H_{28}F_3N_4O_5$: 533.2012).

Análisis calculado para $C_{26}H_{27}F_3N_4O_5$: C, 58.64; H, 5.11; N, 10.52. Encontrado: C, 58.28; H, 5.12; N, 10.51.

Ejemplo 19



N-[(1S)-1-{[4-(4-ciano-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 19-1

4-(4-ciano-fenoxi)-piperidin-1-carboxilato de terbutilo

De una manera análoga al Ejemplo 1-2, el 4-(4-ciano-fenoxi)-piperidin-1-carboxilato de terbutilo (2.30 gramos, rendimiento del 100 por ciento) se obtuvo a partir del 4-hidroxi-piperidin-1-carboxilato de terbutilo (1.50 gramos, 7.45 milimoles), y 4-ciano-fenol (980 miligramos, 8.20 milimoles) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.60 (2H, d, J=9.6 Hz), 6.95 (2H, d, J=9.6 Hz), 4.55 (1H, m), 3.70-3.60 (2H, m), 3.40-3.32 (2H, m), 2.00-1.90 (2H, m), 1.80-1.70 (2H, m), 1.44 (9H, s).

MS (ESI, m/z): 303 $(M+H)^+$.

Ejemplo 19-2

[(1S)-1-{[4-(4-ciano-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 2-2, el clorhidrato de 4-[(piperidin-4-il)-oxi]-benzonitrilo (1.43 gramos, rendimiento del 80 por ciento) se obtuvo a partir del 4-(4-ciano-fenoxi)-piperidin-1-carboxilato de terbutilo (2.25 gramos, 7.45 milimoles) como un aceite incoloro. El compuesto resultante (1.43 gramos, 5.97 milimoles) se condensó con N-(terbutoxi-carbonil)-L-valina (1.43 gramos, 6.56 milimoles), para proporcionar el [(1S)-1-{[4-(4-ciano-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo (2.28 gramos, rendimiento del 95 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.60 (2H, d, J=9.6 Hz), 6.95 (2H, d, J=9.6 Hz), 5.35 (1H, d, J=9.6 Hz), 4.65 (1H, m), 4.45 (1H, m), 3.90-3.50 (4H, m), 2.00-1.80 (5H, m), 1.44 (9H, s), 0.97 (3H, d, J=6.4 Hz), 0.89 (3H, d, J=6.4 Hz).

MS (ESI, m/z): 402 $(M+H)^+$.

Ejemplo 19-3

N-[(1S)-1-{[4-(4-ciano-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

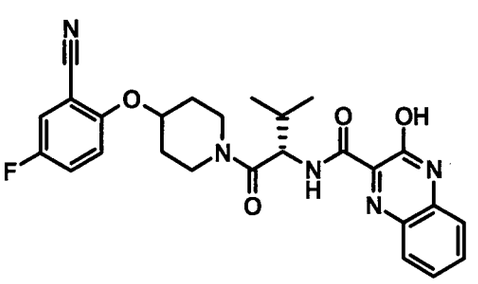
De una manera análoga al Ejemplo 1-3, el clorhidrato de 4-[(1-valil-piperidin-4-il)-oxi]-benzonitrilo (1.92 gramos, rendimiento del 100 por ciento) se obtuvo a partir del [(1S)-1-{[4-(4-ciano-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo (2.28 gramos, 5.68 milimoles) como un sólido blanco. El compuesto resultante (301 miligramos, 1.00 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (228 miligramos, 1.20 milimoles),

para proporcionar el compuesto del título deseado (255 miligramos, rendimiento del 54 por ciento) como un sólido amarillo pálido.

^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.82 (1H, brs), 9.48 (1H, brs), 7.86 (1H, t, J=7.2 Hz), 7.78 (2H, d, J=7.2 Hz), 7.64 (1H, t, J=5.6 Hz), 7.38 (2H, m), 7.18 (2H, m), 4.90 (1H, dd, J=12.4 Hz, 6.0 Hz), 4.84 (1H, m), 4.02-3.90 (2H, m), 3.57-3.20 (2H, m), 2.05 (4H, m), 1.55 (1H, m), 0.95 (6H, d, J=4.8 Hz).

LCMS (ESI, m/z): 474 $(M+H)^+$.

Ejemplo 20



N-[(1S)-1-{[4-(2-ciano-4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 20-1

2-ciano-4-fluoro-fenol

Se agregó piridina (3.00 mililitros, 37.5 milimoles) a una solución en etanol (20 mililitros) de 5-fluoro-salicil-aldehído (1.36 gramos, 9.71 milimoles) y clorhidrato de hidroxilamina (2.00 gramos, 29.1 milimoles), a 0°C, bajo una corriente de nitrógeno, y la agitación se llevó a cabo durante 2.5 horas a temperatura ambiente. La solución de la reacción se vertió en una solución acuosa de ácido clorhídrico 2N, seguido por extracción con acetato de etilo, y lavado

en secuencia con agua y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, para proporcionar la oxima de 5-fluoro-2-hidroxi-benzaldehído (1.47 gramos, rendimiento del 97 por ciento).

Se agregó ácido trifluoro-acético anhidro (3.93 mililitros, 28.4 milimoles) a una solución en cloruro de metileno (30 mililitros) del compuesto resultante (1.47 gramos, 9.48 milimoles), y trietil-amina (3.96 mililitros, 28.4 milimoles), a 0°C, bajo una corriente de nitrógeno, y la agitación se llevó a cabo durante 3 horas a temperatura ambiente. Además, se agregaron carbonato de potasio (1.96 gramos, 14.2 milimoles) y metanol (10 mililitros), y la agitación se llevó a cabo durante 10 minutos a temperatura ambiente. La solución de la reacción se concentró, seguido por vertido en agua, extracción con acetato de etilo, y lavado en secuencia con agua y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, para proporcionar el 2-ciano-4-fluoro-fenol (637 miligramos, rendimiento del 49 por ciento).

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.24-7.18 (2H, m), 6.97 (1H, m), 5.15 (1H, brs).

MS (ESI, m/z): 138 $(M+H)^+$.

Ejemplo 20-2

[(1S)-1-{[4-(2-ciano-4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 1-2, el [(1S)-1-{[4-(2-ciano-4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo (1.33 gramos, rendimiento del 68 por ciento) se obtuvo a partir del {(1S)-1-[(4-hidroxi-piperidin-1-il)-carbonil]-2-metil-propil}-carbamato de terbutilo (1.40 gramos, 4.65 milimoles), y 2-ciano-4-fluoro-fenol (637 miligramos, 4.65 milimoles) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.31-7.24 (2H, m), 6.96 (1H, dd, J=7.2 Hz, 3.2 Hz), 5.33 (1H, m), 4.68 (1H, m), 4.50 (1H, m), 4.02-3.50 (4H, m), 2.00-1.85 (5H, m), 1.44 (9H, s), 0.97 (3H, d, J=6.4 Hz), 0.89 (3H, d, J=6.4 Hz).

MS (ESI, m/z): 420 $(M+H)^+$.

Ejemplo 20-3

N-[(1S)-1-{[4-(2-ciano-4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 1-3, el clorhidrato de 5-fluoro-2-[(1-L-valil-piperidin-4-il)-oxi]-benzonitrilo se obtuvo a partir del [(1S)-1-{[4-(2-ciano-4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo (910 miligramos, 2.17 milimoles) como un sólido blanco.

El compuesto resultante se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (495 miligramos, 2.60 milimoles) bajo una corriente de nitrógeno, para proporcionar el compuesto del título deseado (987 miligramos, rendimiento del 93 por ciento) como un sólido amarillo pálido.

^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.82 (1H, brs), 9.52 (1H, d, J=8.8 Hz), 7.86 (1H, d, J=8.0 Hz), 7.77 (1H, dt, J=5.2 Hz, 2.8 Hz), 7.75-7.55 (2H, m), 7.44-7.40 (3H, m), 4.90 (2H, m), 4.02-3.40 (4H, m), 2.08-1.59 (5H, m), 0.95 (6H, d, J=6.4 Hz).

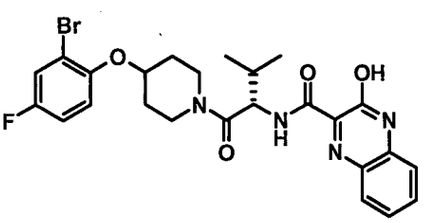
IR (KBr)cm^{-1}: 2965, 2230, 1690, 1640, 1495, 1275, 1210.

MS (ESI, m/z): 492 $(M+H)^+$.

HRMS (ESI, m/z): 514.1860 (Calculado para $C_{26}H_{26}FN_5NaO_4$: 514.1867).

Análisis calculado para $C_{26}H_{26}FN_5O_4$: C, 63.53; H, 5.33; N, 14.25. Encontrado:: C, 63.53; H, 5.59; N, 14.29.

Ejemplo 21



N-[(1S)-1-{[4-(2-bromo-4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 21-1

[(1S)-1-{[4-(2-bromo-4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 2-1, el [(1S)-1-{[4-(2-bromo-4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo (997 miligramos, rendimiento del 83 por ciento) se obtuvo a partir del clorhidrato de 4-(2-bromo-4-fluoro-fenoxi)-piperidina (786 miligramos, 2.53 milimoles), y N-(terbutoxi-carbonil)-L-valina (550

miligramos, 2.53 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.33-7.28 (1H, m), 7.01-6.95 (1H, m), 6.90-6.86 (1H, m), 5.35 (1H, d, J=9.0 Hz), 4.60-4.47 (2H, m), 4.01-3.50 (4H, m), 2.01-1.78 (5H, m), 1.44 (9H, s), 0.98 y 0.89 (6H, d, J=6.6 Hz).

MS (FAB, m/z): 473 $(M+H)^+$.

Ejemplo 21-2

N-[(1S)-1-{[4-(2-bromo-4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 2-2, el clorhidrato de (2S)-1-[4-(2-bromo-4-fluoro-fenoxi)-piperidin-1-il]-3-metil-1-oxobutan-2-amina (737 miligramos) se obtuvo a partir del [(1S)-1-{[4-(2-bromo-4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo (997 miligramos, 2.10 milimoles). El compuesto resultante (737 miligramos, 1.80 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (353 miligramos, 1.80 milimoles), para proporcionar el compuesto del título deseado (609 miligramos, rendimiento del 62 por ciento) como un sólido amarillo pálido.

^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.83 (1H, brs), 9.50 (1H, d, J=9.0 Hz), 7.90-7.84 (1H, m), 7.69-7.62 (1H, m), 7.60-7.53 (1H, m), 7.41-7.35 (2H, m), 7.33-7.20 (2H, m), 4.91 (1H, m), 4.74 (1H, m), 3.92-3.41 (4H, m), 3.92-3.41 (5H, m), 0.96 y 0.95 (6H, d, J=6.2 Hz).

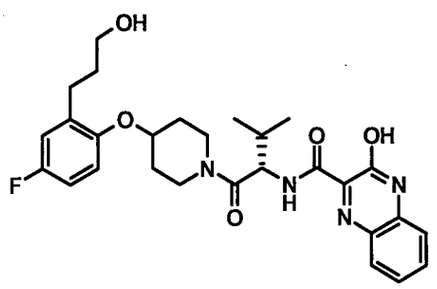
IR (KBr) cm^{-1}: 2960, 1690, 1630, 1530, 1485, 1190.

MS (ESI, m/z): 545 $(M+H)^+$;

HRMS (ESI, m/z): 545.1210 (Calculado para $C_{25}H_{27}BrFN_4O_4$:

545.1200).

Ejemplo 22



N-[(1S)-1-({4-[4-fluoro-2-(3-hidroxi-propil)-fenoxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 22-1

[(1S)-1-({4-[4-fluoro-2-(3-hidroxi-1-propinil)-fenoxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 1-2, el [(1S)-1-{[4-(2-bromo-4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo (1.58 gramos, rendimiento del 56 por ciento) se obtuvo a partir del {(1S)-1-[(4-hidroxi-piperidin-1-il)-carbonil]-2-metil-propil}-carbamato de terbutilo (1.80 gramos, 6.00 milimoles), y 2-bromo-4-fluoro-fenol (1.38 gramos, 7.20 milimoles) como un aceite incoloro.

El compuesto resultante (643 miligramos, 1.36 milimoles), y 2-propin-1-ol (107 miligramos, 1.90 milimoles) se disolvieron en un solvente mixto de N,N-dimetil-formamida (3.0 mililitros), y trietil-amina (3.0 mililitros), bajo una corriente de nitrógeno, y a temperatura ambiente se agregaron dicloruro de bis-(trifenil-fosfina)-paladio (98.0 miligramos, 0.140 milimoles), y yoduro de cobre (53.0 miligramos, 0.280 milimoles), seguido por agitación a 70°C durante 9

horas. La solución de la reacción se vertió en agua, seguido por extracción con acetato de etilo, y lavado en secuencia con agua y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, para proporcionar el [(1S)-1-({4-[4-fluoro-2-(3-hidroxi-1-propinil)-fenoxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (82.5 miligramos, rendimiento del 14 por ciento).

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.10 (1H, d, J=7.6 Hz), 6.99 (1H, m), 6.86 (1H, m), 5.33 (1H, m), 4.57 (1H, m), 4.50 y 4.35 (2H, d, J=4.8 Hz), 4.49 (1H, m), 3.90-3.50 (4H, m), 2.00-1.80 (5H, m), 1.44 (9H, s), 0.97 (3H, d, J=6.8 Hz), 0.89 (3H, d, J=6.8 Hz).

MS (ESI, m/z): 449 $(M+H)^+$.

Ejemplo 22-2

[(1S)-1-({4-[4-fluoro-2-(3-hidroxi-propil)-fenoxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo

El compuesto resultante (82.5 miligramos, 0.184 milimoles), y el catalizador de paladio al 10 por ciento sobre carbón (14.2 miligramos) se suspendieron en metanol (4.0 mililitros), bajo una corriente de hidrógeno, y la agitación se llevó a cabo a temperatura ambiente durante 4 horas. La solución de la reacción se filtró con Celite, y el licor madre se concentró, para proporcionar el [(1S)-1-({4-[4-fluoro-2-(3-hidroxi-propil)-fenoxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (77.1 miligramos, rendimiento del 93 por ciento).

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 6.90 (1H, dd, J=7.2 Hz, 3.2 Hz), 6.84 (1H, m), 6.78 (1H, dd, J=8.4 Hz, 4.8 Hz), 5.34 (1H, d, J=9.2 Hz), 4.50 (2H, m), 3.90-3.50 (4H, m), 3.63 (2H, t, J=5.2 Hz), 2.71 (2H, q, J=8.0 Hz), 2.00-1.80 (5H, m), 1.85 (2H, q, J=8.0 Hz), 1.44 (9H, s), 0.97 (3H, d, J=6.8 Hz), 0.89 (3H, d, J=6.8 Hz).

MS (ESI, m/z): 453 $(M+H)^+$.

Ejemplo 22-3

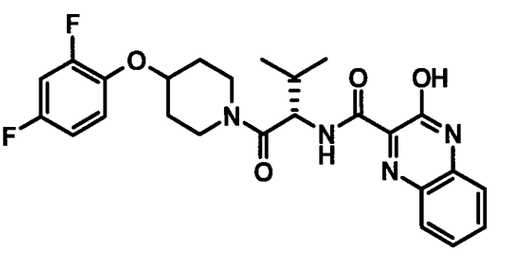
N-[(1S)-1-({4-[4-fluoro-2-(3-hidroxi-propil)-fenoxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 1-3, el 3-{5-fluoro-2-[(1-L-valil-piperidin-4-il)-oxi]-fenil}-propan-1-ol clorhidrato se obtuvo a partir del [(1S)-1-({4-[4-fluoro-2-(3-hidroxi-propil)-fenoxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (75.6 miligramos, 0.167 milimoles) como un sólido blanco. El compuesto resultante se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (38.0 miligramos, 0.200 milimoles), para proporcionar el compuesto del título deseado (44.6 miligramos, rendimiento del 51 por ciento) como un sólido amarillo pálido.

^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.82 (1H, brs), 9.56 (1H, brs), 7.85 (1H, t, J=8.0 Hz), 7.63 (1H, dt, J=8.0 Hz, 1.6 Hz), 7.37 (2H, m), 7.04-6.93 (3H, m), 4.90 (1H, t, J=7.6 Hz), 4.61 (1H, m), 3.90-3.40 (4H, m), 3.41 (2H, t, J=5.2 Hz), 2.67 (2H, q, J=8.0 Hz), 2.10 (1H, m), 2.00-1.55 (4H, m), 1.70 (2H, q, J=8.0 Hz), 0.97 (3H, d, J=6.4 Hz), 0.94 (3H, d, J=6.4 Hz).

LCMS (ESI, m/z): 525 $(M+H)^+$.

Ejemplo 23



N-[(1S)-1-{[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 23-1

4-(2,4-difluoro-fenoxi)-piperidin-1-carboxilato de terbutilo

Una solución al 40 por ciento en tolueno de azodicarboxilato de di-isopropilo (4.71 mililitros, 8.94 milimoles) se agregó a una solución en tolueno (30 mililitros) de 4-hidroxi-piperidin-1-carboxilato de terbutilo (1.50 gramos, 7.45 milimoles), 2,4-difluoro-fenol (1.07 gramos, 8.20 milimoles), y trifenil-fosfina (2.34 gramos, 8.94 milimoles), a temperatura ambiente, bajo una corriente de nitrógeno, y la agitación se llevó a cabo a 90°C durante la noche. La solución de la reacción se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., 40+M), para proporcionar el 4-(2,4-difluoro-fenoxi)-piperidin-1-carboxilato de terbutilo (2.28 gramos, rendimiento del 98 por ciento) como una sustancia oleosa color amarillo pálido.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 6.99-6.75 (3H, m), 4.35-4.30 (1H, m), 3.77-3.71 (2H, m), 3.32-3.28 (2H, m), 1.92-1.88 (2H, m), 1.79-

1.68 (2H, m), 1.53-1.38 (9H, m).

MS (FAB, m/z): 314 $(M+H)^+$.

Ejemplo 23-2

[(1S)-1-{[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo

Una solución en 1,4-dioxano de ácido clorhídrico 4N (30 mililitros) se agregó a una solución en 1,4-dioxano (30 mililitros) de 4-(2,4-difluoro-fenoxi)-piperidin-1-carboxilato de terbutilo (2.28 gramos, 7.28 milimoles), bajo una corriente de nitrógeno, y la mezcla se dejó reaccionar a temperatura ambiente durante la noche. La solución de la reacción se concentró, para proporcionar el clorhidrato de 4-(2,4-difluoro-fenoxi)-piperidina (1.63 gramos) como un sólido blanco.

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (1.50 gramos, 7.84 milimoles), y el monohidrato de 1-hidroxi-benzotriazol (1.06 gramos, 7.84 milimoles) se agregaron a una solución en cloruro de metileno (30 mililitros) del compuesto resultante (1.63 gramos, 6.53 milimoles), y N-(terbutoxi-carbonil)-L-valina (1.56 gramos, 7.18 milimoles), a temperatura ambiente, bajo una corriente de nitrógeno, seguido por otra adición de N-metil-morfolina (1.58 mililitros, 14.4 milimoles), y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se vertió en una solución acuosa de ácido clorhídrico 2N, seguido por extracción con cloruro de metileno, y lavado en secuencia con agua, una solución acuosa saturada de carbonato

ácido de sodio, agua, y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., 25+M), para proporcionar el [(1S)-1-{[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo (2.39 gramos, rendimiento del 89 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 500 MHz) δ: 7.00-6.99 (1H, m), 6.91-6.89 (1H, m), 6.83-6.81 (1H, m), 5.37-5.36 (1H, m), 4.52-4.45 (2H, m), 3.85-3.79 (2H, m), 3.64-3.45 (2H, m), 2.02-1.82 (5H, m), 1.51-1.48 (9H, m), 1.00 (3H, t, J=6.8 Hz), 0.92 (3H, t, J=6.8 Hz).

MS (FAB, m/z): 413 $(M+H)^+$.

Ejemplo 23-3

N-[(1S)-1-{[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Una solución en 1,4-dioxano de ácido clorhídrico 4N (30 mililitros) se agregó a una solución en 1,4-dioxano (30 mililitros) de [(1S)-1-{[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo (2.39 gramos, 5.79 milimoles), bajo una corriente de nitrógeno, y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se concentró, para proporcionar el clorhidrato de (2S)-1-[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-3-metil-1-oxobutan-2-amina (2.01 gramos) como un sólido blanco.

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (288 miligramos, 1.50 milimoles), y el monohidrato de 1-hidroxi-benzotriazol (203 miligramos, 1.50 milimoles) se agregaron a una solución en cloruro de metileno (5.0 mililitros) del compuesto resultante (350 miligramos, 1.00 milimoles), y ácido 3-hidroxi-quinoxalin-2-carboxílico (285 miligramos, 1.50 milimoles), a temperatura ambiente, bajo una corriente de nitrógeno, seguido por otra adición de trietil-amina (0.558 mililitros, 4.00 milimoles), y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se diluyó con cloruro de metileno, seguido por lavado en secuencia con una solución acuosa saturada de carbonato ácido de sodio, una solución acuosa saturada de cloruro de amonio, agua, y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. Después de que la capa orgánica se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., 25+M), el residuo resultante de la concentración se suspendió en un solvente mixto de cloruro de metileno-acetato de etilo, y la sustancia sólida se recolectó mediante filtración, para proporcionar el compuesto del título deseado (283 miligramos, rendimiento del 58 por ciento) como un sólido amarillo pálido.

^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.83 (1H, s), 9.47 (1H, t, J=4.1 Hz), 7.86 (1H, d, J=8.6 Hz), 7.64 (1H, t, J=8.6 Hz), 7.40-7.27 (4H, m), 7.02 (1H, t, J=8.8 Hz), 4.90 (1H, q, J=8.1 Hz), 4.60 (1H,

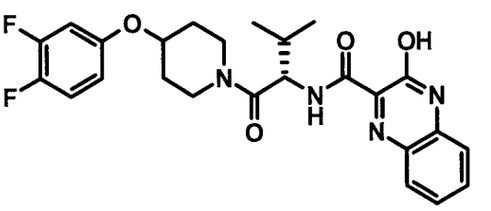
brs), 3.94-3.90 (2H, m), 3.57-3.22 (2H, m), 2.09-1.91 (3H, m), 1.73-1.52 (2H, m), 0.95 (6H, t, J=6.8 Hz).

IR (KBr) cm^{-1}: 2965, 1685, 1635, 1505, 1210.

MS (FAB, m/z): 485 $(M+H)^+$.

HRMS (ESI, m/z): 485.2007 (Calculado para $C_{25}H_{27}F_2N_4O_4$: 485.2000).

Ejemplo 24



N-[(1S)-1-{[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 24-1

4-(3,4-difluoro-fenoxi)-piperidin-1-carboxilato de terbutilo

De una manera análoga al Ejemplo 1-2, el 4-(3,4-difluoro-fenoxi)-piperidin-1-carboxilato de terbutilo (1.69 gramos, rendimiento del 89 por ciento) se obtuvo a partir del 4-hidroxi-piperidin-1-carboxilato de terbutilo (1.22 gramos, 6.07 milimoles), y 3,4-difluoro-fenol (790 miligramos, 6.07 milimoles) como una sustancia oleosa color amarillo pálido.

^{1}H-RMN ($CDCl_3$, 500 MHz) δ: 7.05 (1H, q, J=9.3 Hz), 6.77-6.67 (1H, m), 6.62-6.59 (1H, m), 4.38-4.34 (1H, m), 3.71-3.66 (2H, m), 3.36-3.31 (2H, m), 1.92-1.88 (2H, m), 1.74-1.71 (2H, m), 1.49-1.44 (9H, m).

MS (FAB, m/z): 314 $(M+H)^+$.

Ejemplo 24-2

[(1S)-1-{[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 23-2, el clorhidrato de 4-(3,4-difluoro-fenoxi)-piperidina (1.23 gramos) se obtuvo a partir del 4-(3,4-difluoro-fenoxi)-piperidin-1-carboxilato de terbutilo (1.69 gramos, 5.39 milimoles) como un sólido blanco.

El compuesto resultante (1.23 gramos, 4.93 milimoles) se condensó con N-(terbutoxi-carbonil)-L-valina (1.18 gramos, 5.42 milimoles) bajo una corriente de nitrógeno, para proporcionar el [(1S)-1-{[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo (2.03 gramos, rendimiento del 100 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.07 (1H, dd, J=18.0 Hz, 9.4 Hz), 6.75-6.72 (1H, m), 6.64-6.59 (1H, m), 5.34 (1H, d, J=9.0 Hz), 4.51-4.43 (2H, m), 3.80-3.57 (4H, m), 1.97-1.79 (5H, m), 1.43-1.41 (9H, m), 0.97 (3H, d, J=7.0 Hz), 0.88 (3H, d, J=7.0 Hz).

MS (FAB, m/z): 413 $(M+H)^+$.

Ejemplo 24-3

N-[(1S)-1-{[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 1-3, el clorhidrato de (2S)-1-[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-3-metil-1-oxobutan-2-amina (1.73 gramos) se obtuvo a partir del [(1S)-1-{[4-(3,4-difluoro-fenoxi)-

piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo (2.03 gramos, 4.92 milimoles) como un sólido blanco. El compuesto resultante (350 miligramos, 1.00 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (285 miligramos, 1.50 milimoles), para proporcionar el compuesto del título deseado (270 miligramos, rendimiento del 56 por ciento) como un sólido amarillo pálido.

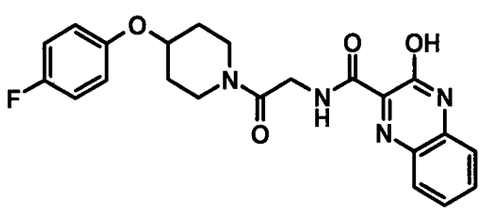
^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.83 (1H, s), 9.48 (1H, dd, J=8.8 Hz, 4.9 Hz), 7.87-7.85 (1H, m), 7.66-7.62 (1H, m), 7.38-7.33 (3H, m), 7.21-7.14 (1H, m), 6.84 (1H, s), 4.90 (1H, dd, J=13.9 Hz, 6.8 Hz), 4.65-4.64 (1H, m), 3.95-3.90 (2H, m), 3.56-3.22 (2H, m), 2.02-1.96 (3H, m), 1.69-1.49 (2H, m), 0.95-0.94 (6H, m).

IR (KBr) cm^{-1}: 2965, 1685, 1630, 1515, 1215, 1160.

MS (FAB, m/z): 485 $(M+H)^+$.

HRMS (ESI, m/z): 485.2022 (Calculado para $C_{25}H_{27}F_2N_4O_4$: 485.2000).

Ejemplo 25



N-{2-[4-(4-fluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 25-1

{2-[4-(4-fluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-carbamato de terbutilo

De una manera análoga al Ejemplo 2-1, el {2-[4-(4-fluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-carbamato de terbutilo (273 miligramos, rendimiento del 77 por ciento) se obtuvo a partir del clorhidrato de 4-(4-fluoro-fenoxi)-piperidina (231 miligramos, 1.00 milimoles), y N-(terbutoxi-carbonil)-glicina (175 miligramos, 1.00 milimoles) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 6.99 (2H, dd, J=9.0 Hz, 8.2 Hz), 6.87 (2H, dd, J=9.0 Hz, 4.2 Hz), 5.54 (1H, brs), 4.48 (1H, m), 3.99 (1H, d, J=4.6 Hz), 3.98 (1H, d, J=4.6 Hz), 3.73 (2H, t, J=5.8 Hz), 3.65-3.57 (1H, m), 3.38-3.30 (1H, m), 1.96-1.75 (4H, m), 1.96 (9H, s).

MS (ESI, m/z): 353 $(M+H)^+$.

Ejemplo 25-2

N-[2-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 2-2, el clorhidrato de 2-[4-(4-fluoro-fenoxi)-piperidin-1-il]-2-oxo-etanamina (190 miligramos, rendimiento del 85 por ciento) se obtuvo a partir del {2-[4-(4-fluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-carbamato de terbutilo (273 miligramos, 0.773 milimoles). A partir del compuesto resultante (144 miligramos, 0.500 milimoles), a través de una condensación con ácido 3-hidroxi-quinoxalin-2-carboxílico (95.1 miligramos, 0.500 milimoles), se proporcionó una mezcla que contenía el compuesto del título deseado. La re-purificación mediante cromatografía de capa delgada de preparación proporcionó el compuesto del título deseado (28.5 miligramos, rendimiento del 13 por ciento) como un

sólido amarillo.

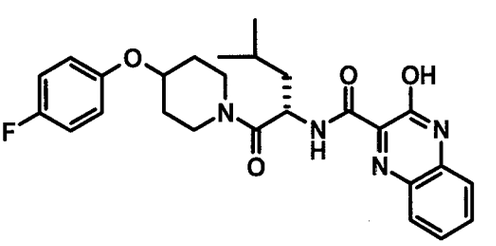
^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.85 (1H, brs), 9.79 (1H, brs), 7.88 (1H, d, J=8.2 Hz), 7.68-7.55 (1H, m), 7.41-7.30 (2H, m), 7.17-7.08 (2H, m), 7.07-6.98 (2H, m), 4.59 (1H, m), 4.28 (2H, d, J=4.6 Hz), 4.00-3.20 (4H, m), 2.04-1.85 (2H, m), 1.71-1.48 (2H, m).

IR (KBr) cm^{-1}: 2950, 1695, 1650, 1620, 1505, 1210.

MS (ESI, m/z): 425 $(M+H)^+$.

HRMS (ESI, m/z): 425.1626 (Calculado para $C_{22}H_{22}FN_4O_4$: 425.1625).

Ejemplo 26



N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-3-metil-butil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 26-1

[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-3-metil-butil]-carbamato de bencilo

De una manera análoga al Ejemplo 2-1, el [(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-3-metil-butil]-carbamato de bencilo (755 miligramos, rendimiento del 85 por ciento) se obtuvo a partir del clorhidrato de 4-(4-fluoro-fenoxi)-piperidina (463 miligramos, 2.00 milimoles), y N-(benciloxi-carbonil)-L-leucina (531 miligramos, 2.00

milimoles) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.38-7.30 (5H, m), 6.99 (2H, dd, J=9.0 Hz, 8.6 Hz), 6.87 (2H, dd, J=9.0 Hz, 4.2 Hz), 5.57 (1H, d, J=8.2 Hz), 5.10 (2H, s), 4.75 (1H, m), 4.47 (1H, m), 3.83-3.39 (4H, m), 2.00-1.64 (5H, m), 1.61-1.47 (1H, m), 1.44-1.34 (1H, m), 1.00 y 0.93 (6H, d, J=6.6 Hz).

Ejemplo 26-2

N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-3-metil-butil]-3-hidroxi-quinoxalin-2-carboxamida

Un catalizador de paladio al 5 por ciento sobre carbón (75.0 miligramos) se agregó a una solución en etanol (22.5 mililitros) de [(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-3-metil-butil]-carbamato de bencilo (755 miligramos, 1.70 milimoles), bajo una corriente de hidrógeno, y la agitación se llevó a cabo a temperatura ambiente durante 2 horas. Después de que el catalizador se filtró con Celite y se lavó con cloruro de metileno, el licor madre se concentró, para proporcionar la (2S)-1-[4-(4-fluoro-fenoxi)-piperidin-1-il]-4-metil-1-oxopentan-2-amina (521 miligramos) como un aceite incoloro.

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (230 miligramos, 1.20 milimoles), y el monohidrato de 1-hidroxi-benzotriazol (184 miligramos, 1.20 milimoles) se agregaron a una solución en cloruro de metileno (10 mililitros) del compuesto resultante (308 miligramos, 1.00 milimoles), y ácido 3-hidroxi-quinoxalin-2-carboxílico (190 miligramos, 1.00 milimoles), a

temperatura ambiente, bajo una corriente de nitrógeno, seguido por otra adición de N-metil-morfolina (0.550 mililitros, 5.00 milimoles), y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se diluyó con cloruro de metileno, seguido por lavado en secuencia con una solución acuosa saturada de carbonato ácido de sodio, una solución acuosa saturada de cloruro de amonio, agua, y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. Después de que la capa orgánica se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., 25+M), el residuo resultante de la concentración se suspendió en un solvente mixto de cloruro de metileno-acetato de etilo, y la sustancia sólida se recolectó mediante filtración, para proporcionar el compuesto del título deseado (126 miligramos, rendimiento del 26 por ciento) como un sólido amarillo pálido.

^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.83 (1H, brs), 9.52 (1H, d, J=7.8 Hz), 7.86 (1H, dd, J=7.4 Hz, 7.0 Hz), 7.65 (1H, dd, J=7.8 Hz, 7.4 Hz), 7.40 (1H, d, J=7.0 Hz), 7.38 (1H, d, J=7.4 Hz), 7.17-7.09 (2H, m), 7.07-6.99 (2H, m), 5.08 (1H, m), 4.60 (1H, m), 4.02-3.18 (4H, m), 2.11-1.84 (2H, m), 1.76-1.44 (5H, m), 0.96 y 0.92 (6H, d, J=6.6 Hz).

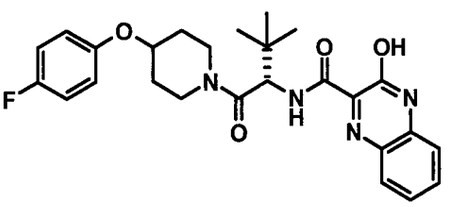
IR (KBr) cm^{-1}: 2955, 1685, 1640, 1505, 1205.

MS (ESI, m/z): 481 $(M+H)^+$.

HRMS (ESI, m/z): 481.2268 (Calculado para $C_{26}H_{30}FN_4O_4$:

481.2251).

Ejemplo 27



N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2,2-dimetil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 27-1

[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2,2-dimetil-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 2-1, el [(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2,2-dimetil-propil]-carbamato de terbutilo (619 miligramos, rendimiento del 76 por ciento) se obtuvo a partir del clorhidrato de 4-(4-fluoro-fenoxi)-piperidina (463 miligramos, 2.00 milimoles), y ácido (2S)-N-(terbutoxi-carbonil)-2-amino-3,3-dimetil-butírico (462 miligramos, 2.00 milimoles) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.02-6.95 (2H, m), 6.95-6.89 (2H, m), 5.36 (1H, d, J=9.8 Hz), 4.56 (1H, d, J=9.8 Hz), 4.51-4.40 (1H, m), 3.93-3.47 (4H, m), 2.00-1.74 (4H, m), 1.43 (9H, s), 0.99 (9H, s).

MS (ESI, m/z): 409 $(M+H)^+$.

Ejemplo 27-2

N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2,2-dimetil-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 2-2, el clorhidrato de (2S)-1-[4-(4-fluoro-fenoxi)-piperidin-1-il]-3,3-dimetil-1-oxobutan-2-amina (522 miligramos, rendimiento del 100 por ciento) se obtuvo a partir del [(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2,2-dimetil-propil]-carbamato de terbutilo (619 miligramos, 1.52 milimoles). A partir del compuesto resultante, a través de una condensación con ácido 3-hidroxi-quinoxalin-2-carboxílico (190 miligramos, 1.00 milimoles), se proporcionó el compuesto del título deseado (160 miligramos, rendimiento del 33 por ciento) como un sólido amarillo pálido.

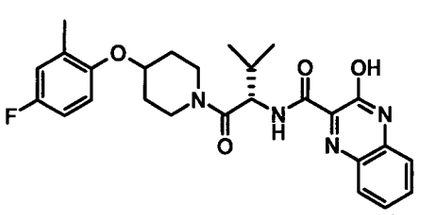
^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.86 (1H, brs), 9.71 y 9.68 (1H, d, J=9.0 Hz), 7.89 (1H, d, J=8.2 Hz), 7.66 (1H, dd, J=8.2 Hz, 7.8 Hz), 7.44-7.37 (2H, m), 7.16-7.09 (2H, m), 7.07-6.99 (2H, m), 5.07 y 5.05 (1H, d, J=9.0 Hz), 4.61 (1H, m), 4.11-3.14 (4H, m), 2.07-1.84 (2H, m), 1.74-1.41 (2H, m), 1.03 (9H, s).

IR (KBr) cm^{-1}: 2950, 1690, 1630, 1505, 1205.

MS (ESI, m/z): 481 $(M+H)^+$.

HRMS (ESI, m/z): 481.2280 (Calculado para $C_{26}H_{30}FN_4O_4$: 481.2251).

Ejemplo 28



N-[(1S)-1-{[4-(4-fluoro-2-metil-fenoxi)-piperidin-1-il]-carbonil}-2-metil-

propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 28-1

[(1S)-1-{[4-(4-fluoro-2-metil-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 1-2, el [(1S)-1-{[4-(4-fluoro-2-metil-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo (480 miligramos, rendimiento del 60 por ciento) se obtuvo a partir del {(1S)-1-[(4-hidroxi-piperidin-1-il)-carbonil]-2-metil-propil}-carbamato de terbutilo (601 miligramos, 2.00 milimoles), y 4-fluoro-cresol (277 miligramos, 2.20 milimoles) como un aceite incoloro.

^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 6.91-6.86 (1H, m), 6.85-6.78 (1H, m), 6.78-6.73 (1H, m), 5.36 (1H, d, J=9.4 Hz), 4.53-4.44 (2H, m), 3.88-3.45 (4H, m), 2.24 y 2.22 (3H, s), 2.02-1.74 (5H, m), 1.44 (9H, s), 0.98 y 0.90 (6H, d, J=7.0 Hz).

MS (FAB, m/z): 409 $(M+H)^+$.

Ejemplo 28-2

N-[(1S)-1-{[4-(4-fluoro-2-metil-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 1-3, el clorhidrato de (2S)-1-[4-(4-fluoro-2-metil-fenoxi)-piperidin-1-il]-3-metil-1-oxobutan-2-amina (388 miligramos, rendimiento del 96 por ciento) se obtuvo a partir del [(1S)-1-{[4-(4-fluoro-2-metil-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo (480 miligramos, 1.18 milimoles). El compuesto resultante (194 miligramos, 0.564 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (110 mili-

gramos, 0.564 milimoles), para proporcionar el compuesto del título deseado (89.5 miligramos, rendimiento del 33 por ciento) como un sólido amarillo pálido.

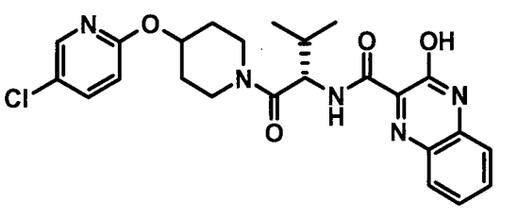
^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.82 (1H, brs), 9.52 (1H, brs), 7.90-7.82 (1H, m), 7.69-7.61 (1H, m), 7.43-7.36 (2H, m), 7.08-7.01 (2H, m), 7.00-6.92 (1H, m), 4.96 (1H, m), 4.60 (1H, m), 3.94-3.35 (4H, m), 2.19 y 2.16 (3H, s), 2.10-1.84 (3H, m), 1.76-1.64 (1H, m), 1.62-1.52 (1H, m), 0.98-0.92 (6H, m).

IR (KBr) cm^{-1}: 2965, 1690, 1630, 1495, 1205.

MS (ESI, m/z): 481 $(M+H)^+$.

HRMS (ESI, m/z): 481.2255 (Calculado para $C_{26}H_{30}FN_4O_4$: 481.2251).

Ejemplo 29



N-[(1S)-1-({4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 29-1

4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo

El 4-(metan-sulfoniloxi)-piperidin-1-carboxilato de terbutilo (3.02 gramos, 10.8 milimoles), y carbonato de potasio (2.35 gramos, 17.0 milimoles) se agregaron a una solución en N,N-dimetil-formamida (77 mililitros) de 5-cloro-2-hidroxi-piridina (1.00 gramos,

7.72 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a 75°C durante la noche. Después de que la solución de la reacción se enfrió a temperatura ambiente, se agregó agua a los residuos resultantes de la concentración, seguido por extracción con cloruro de metileno. La capa orgánica resultante se secó sobre sulfato de sodio anhidro, y el residuo resultante de la concentración se purificó mediante cromatografía en columna de gel de sílice, para proporcionar el 4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo (1.57 gramos, rendimiento del 65 por ciento) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.06 (1H, d, J=2.7 Hz), 7.51 (1H, dd, J=8.8 Hz, 2.7 Hz), 6.67 (1H, d, J=8.8 Hz), 5.18-5.13 (1H, m), 3.79-3.73 (2H, m), 3.31-3.24 (2H, m), 1.99-1.93 (2H, m), 1.74-1.66 (2H, m), 1.47 (9H, s).

Ejemplo 29-2

[(1S)-1-({4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo

Se agregó ácido clorhídrico concentrado (5.0 mililitros) a una solución en etanol (10 mililitros) de 4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo (1.57 gramos, 5.02 milimoles), a 0°C, y la agitación se llevó a cabo a temperatura ambiente durante 2 días. La solución de la reacción se concentró, para proporcionar el diclorhidrato de 5-cloro-2-[(piperidin-4-il)-oxi]-piridina (1.61 gramos).

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (1.44 gramos, 7.53 milimoles) se agregó a una solución en cloruro de

metileno (50 mililitros) del compuesto resultante (1.61 gramos), N-(terbutoxi-carbonil)-L-valina (1.09 gramos, 5.02 milimoles), monohidrato de 1-hidroxi-benzotriazol (814 miligramos, 6.02 milimoles), y N-metil-morfolina (3.31 mililitros, 30.1 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a temperatura ambiente durante la noche. Se agregó agua a la solución de la reacción, seguida por extracción con cloruro de metileno y el lavado subsiguiente en secuencia con una solución acuosa saturada de carbonato ácido de sodio, agua, y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, para proporcionar el [(1S)-1-({4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (1.94 gramos, rendimiento del 94 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.08-8.06 (1H, m), 7.53 (1H, dd, J=8.8 Hz, 2.8 Hz), 6.68 (1H, dd, J=8.8 Hz, 1.2 Hz), 5.35 (1H, d, J=8.8 Hz), 5.28-5.21 (1H, m), 4.50 (1H, dd, J=8.8 Hz, 5.7 Hz), 3.98-3.43 (4H, m), 2.09-1.73 (5H, m), 1.44 (9H, s), 0.97 (3H, d, J=6.6 Hz), 0.89 (3H, d, J=6.6 Hz).

Ejemplo 29-3

Diclorhidrato de (2S)-1-{4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina

Se agregó ácido clorhídrico concentrado (5.0 mililitros) a una solución en etanol (10 mililitros) de [(1S)-1-({4-[(5-cloro-piridin-2-il)-

oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (1.94 gramos, 4.71 milimoles), a 0°C, y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se concentró, para proporcionar el diclorhidrato de (2S)-1-{4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina (1.93 gramos, rendimiento del 100 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.43 (2H, brs), 8.13-8.12 (1H, m), 7.69 (1H, brs), 6.92 (1H, brs), 5.36 (1H, brs), 4.51 (1H, brs), 3.88-3.46 (4H, m), 2.28-1.86 (5H, m), 1.20-1.11 (6H, m).

MS (ESI, m/z): 312 $(M+H)^+$.

Ejemplo 29-4

N-[(1S)-1-({4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (150 miligramos, 0.780 milimoles) se agregó a una solución en cloruro de metileno (5.2 mililitros) de diclorhidrato de (2S)-1-{4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina (200 miligramos, 0.520 milimoles), ácido 3-hidroxi-quinoxalin-2-carboxílico (102 miligramos, 0.520 milimoles), monohidrato de 1-hidroxi-benzotriazol (84.3 miligramos, 0.620 milimoles), y N-metil-morfolina (0.343 mililitros, 3.12 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a temperatura ambiente durante 3 días. Se agregó agua a la solución de la reacción, seguida por extracción con cloruro de metileno y el lavado subsiguiente en secuencia con una

solución acuosa saturada de carbonato ácido de sodio, agua, y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. Después de que la capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, el residuo resultante de la concentración se suspendió en un solvente mixto de etanol/dietil-éter, y la sustancia sólida se recolectó mediante filtración, para proporcionar el compuesto del título deseado (190 miligramos, rendimiento del 76 por ciento) como un sólido amarillo.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 12.44 (1H, brs), 10.15 (1H, brs), 8.08 (1H, dd, J=6.3 Hz, 2.7 Hz), 8.02-8.00 (1H, m), 7.61-7.37 (4H, m), 6.70 (1H, t, J=9.2 Hz), 5.32-5.27 (1H, m), 5.09 (1H, t, J=7.4 Hz), 4.06-3.59 (4H, m), 2.34-1.82 (5H, m), 1.14-1.10 (6H, m).

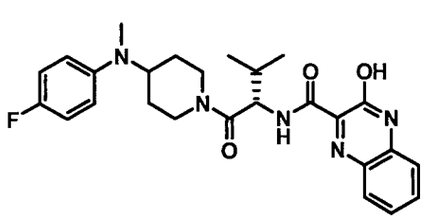
IR (KBr) cm^{-1}: 2965, 1690, 1630, 1525, 1465.

MS (ESI, m/z): 484 $(M+H)^+$.

HRMS (ESI, m/z): 484.1765 (Calculado para $C_{24}H_{27}ClN_5O_4$: 484.1752).

Análisis calculado para $C_{24}H_{26}ClN_5O_4$: C, 59.56; H, 5.42; N, 14.47; Cl, 7.33. Encontrado: C, 59.48; H, 5.50; N, 14.49; Cl, 7.16.

Ejemplo 30



N-[(1S)-1-({4-[(4-fluoro-fenil)-(metil)-amino]-piperidin-1-il}-carbonil)-

2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 30-1

4-[(4-fluoro-fenil)-amino]-piperidin-1-carboxilato de terbutilo

Se agregó ciano-borohidruro de sodio (661 miligramos, 10.0 milimoles) a una solución en cloruro de metileno (30 mililitros) de 4-oxo-piperidin-1-carboxilato de terbutilo (2.66 gramos, 13.1 milimoles), 4-fluoro-anilina (1.46 gramos, 13.1 milimoles), y ácido acético (0.750 mililitros, 13.1 milimoles), a 0°C, y la agitación se llevó a cabo a temperatura ambiente durante 15 horas. A la solución de la reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio, seguido por extracción con acetato de etilo, y el extracto se lavó en secuencia con agua y una solución salina, y se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se lavó con di-isopropil-éter, seguido por secado, para proporcionar el 4-[(4-fluoro-fenil)-amino]-piperidin-1-carboxilato de terbutilo (3.09 gramos, rendimiento del 80 por ciento) como un sólido blanco.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 6.91-6.84 (2H, m), 6.56-6.51 (2H, m), 4.12-3.97 (2H, m), 3.36-3.32 (2H, m),2.95-2.87 (1H, m), 2.06-1.98 (2H, m), 1.47 (9H, s), 1.36-1.24 (2H, m).

Ejemplo 30-2

Diclorhidrato de N-(4-fluoro-fenil)-N-metil-piperidin-4-amina

Se agregó ciano-borohidruro de sodio (641 miligramos, 10.2 milimoles) a una solución en ácido acético (14 mililitros) de 4-[(4-fluoro-fenil)-amino]-piperidin-1-carboxilato de terbutilo (1.50 gramos,

5.10 milimoles), y formaldehído (2.07 mililitros, 25.5 milimoles), a 0°C, y la agitación se llevó a cabo a temperatura ambiente durante 31 horas. La solución de la reacción se concentró bajo presión reducida, y se agregó una solución acuosa saturada de carbonato ácido de sodio al residuo, seguido por extracción con acetato de etilo. El extracto se lavó en secuencia con agua y una solución salina, y se secó sobre sulfato de sodio anhidro. Después de que la capa orgánica se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Yamazen Corporation, W-Prep 2XY), el residuo resultante de la concentración se disolvió en etanol (24 mililitros), y entonces se agregó ácido clorhídrico concentrado (10 mililitros), bajo enfriamiento con hielo, seguido por agitación a temperatura ambiente durante 12 horas. La solución de la reacción se concentró bajo presión reducida, para proporcionar el diclorhidrato de N-(4-fluoro-fenil)-N-metil-piperidin-4-amina (1.28 gramos, rendimiento del 89 por ciento) como una sustancia amorfa.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.84-7.79 (2H, m), 7.43-7.37 (2H, m), 4.14-4.05 (1H, m), 3.61-3.49 (2H, m), 3.33 (3H, s), 3.17-3.04 (2H, m), 2.38-1.94 (4H, m).

Ejemplo 30-3

diclorhidrato de 1-[(2S)-2-amino-3-metil-butanoil]-N-(4-fluoro-fenil)-N-metil-piperidin-4-amina

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (364 miligramos, 1.90 milimoles) se agregó a una solución en cloruro

de metileno (30 mililitros) de diclorhidrato de N-(4-fluoro-fenil)-N-metil-piperidin-4-amina (445 miligramos, 1.58 milimoles), N-(terbutoxi-carbonil)-L-valina (343 miligramos, 1.48 milimoles), monohidrato de 1-hidroxi-benzotriazol (257 miligramos, 1.90 milimoles), y N-metil-morfolina (0.556 mililitros, 5.06 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a temperatura ambiente durante 4 horas. La solución de la reacción se concentró bajo presión reducida, y se agregó agua al residuo, seguido por extracción con acetato de etilo. El extracto se lavó en secuencia con agua, una solución acuosa saturada de carbonato ácido de sodio, y una solución salina saturada, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Yamazen Corporation, W-Prep 2XY), y el residuo resultante se disolvió en etanol (10 mililitros). A esto se le agregó ácido clorhídrico concentrado (5.0 mililitros) bajo enfriamiento con hielo, y la agitación se llevó a cabo a temperatura ambiente durante 12 horas. La solución de la reacción se concentró bajo presión reducida, para proporcionar el compuesto del título deseado (528 miligramos, rendimiento del 88 por ciento) como una sustancia amorfa.

^{1}H-RMN (CD_3OD, 400 MHz) δ: 7.84-7.72 (2H, m), 7.42-7.30 (2H, m), 4.74-4.63 (1H, m), 4.42-4.29 (1H, m), 4.16-3.08 (2H, m), 3.28 (3H, s), 3.27-3.18 (1H, m), 2.80-2.69 (1H, m), 2.26-1.60 (5H, m), 1.12-0.98 (6H, m).

Ejemplo 30-4

N-[(1S)-1-({4-[(4-fluoro-fenil)-(metil)-amino]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (113 miligramos, 0.590 milimoles) se agregó a una solución en cloruro de metileno (5.0 mililitros) de diclorhidrato de 1-[(2S)-2-amino-3-metil-butanoil]-N-(4-fluoro-fenil)-N-metil-piperidin-4-amina (150 miligramos, 0.390 milimoles), ácido 3-hidroxi-quinoxalin-2-carboxílico (77.3 miligramos, 0.390 milimoles), monohidrato de 1-hidroxi-benzotriazol (64.0 miligramos, 0.470 milimoles), y N-metil-morfolina (0.217 mililitros, 1.97 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a temperatura ambiente durante la noche. Se agregó agua a la solución de la reacción, seguida por extracción con cloruro de metileno y el lavado subsiguiente en secuencia con una solución acuosa saturada de carbonato ácido de sodio, agua, y una solución salina, y la capa orgánica resultante se secó sobre sulfato de sodio anhidro. Después de que la capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, el residuo resultante de la concentración se suspendió en un solvente mixto de etanol/dietil-éter, y la sustancia sólida se recolectó mediante filtración, para proporcionar el compuesto del título deseado (135 miligramos, rendimiento del 71 por ciento) como un sólido amarillo.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 12.20 (1H, brs), 10.16 (1H, brs), 8.06-8.02 (1H, m), 7.64-7.40 (3H, m), 6.99-6.93 (2H, m), 6.80 (2H,

dq, J=16.0 Hz, 3.6 Hz), 5.14-5.06 (1H, m), 4.84 (1H, s), 4.35 (1H, s), 3.67 (1H, s), 3.29-3.18 (1H, m), 2.75-2.69 (4H, m), 2.27 (1H, m), 1.96-1.62 (4H, m), 1.10 (6H, dd, J=13.2 Hz, 5.2 Hz).

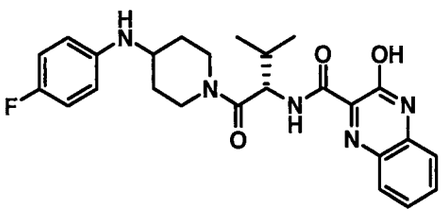
IR (KBr) cm^{-1}: 2960, 1685, 1640, 1510.

MS (ESI, m/z): 480 $(M+H)^+$.

HRMS (ESI, m/z): 480.2414 (Calculado para $C_{26}H_{31}FN_5O_3$: 480.2411).

Análisis calculado para $C_{26}H_{30}FN_5O_3$: C, 65.12; H, 6.31; N, 14.60; F, 3.96. Encontrado: C, 64.97; H, 6.32; N, 14.34; F, 3.94.

Ejemplo 31



N-[(1S)-1-({4-[(4-fluoro-fenil)-amino]-piperidin-1-il}-carbonil]-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Se agregó ácido clorhídrico concentrado (5.0 mililitros) a una solución en etanol (10 mililitros) de 4-[(4-fluoro-fenil)-amino]-piperidin-1-carboxilato de terbutilo (1.00 gramos, 3.40 milimoles), bajo enfriamiento con hielo, y la agitación se llevó a cabo a temperatura ambiente durante 12 horas. La solución de la reacción se concentró bajo presión reducida, y el residuo resultante se lavó con dietil-éter y n-hexano, para proporcionar el diclorhidrato de 1-[(2S)-2-amino-3-metil-butanoil]-N-(4-fluoro-fenil)-piperidin-4-amina (768 miligramos, rendimiento del 84 por ciento) como un aceite color

naranja.

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (118 miligramos, 0.610 milimoles) se agregó a una solución en cloruro de metileno (5.0 mililitros) de diclorhidrato de 1-[(2S)-2-amino-3-metil-butanoil]-N-(4-fluoro-fenil)-piperidin-4-amina (150 miligramos, 0.410 milimoles), ácido 3-hidroxi-quinoxalin-2-carboxílico (80.3 miligramos, 0.410 milimoles), monohidrato de 1-hidroxi-benzotriazol (66.4 miligramos, 0.490 milimoles), y N-metil-morfolina (0.225 mililitros, 2.05 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a temperatura ambiente durante la noche. Se agregó agua a la solución de la reacción, seguida por extracción con cloruro de metileno y el lavado subsiguiente en secuencia con una solución acuosa saturada de carbonato ácido de sodio, agua, y una solución salina, y la capa orgánica resultante se secó sobre sulfato de sodio anhidro. Después de que la capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, el residuo resultante de la concentración se suspendió en un solvente mixto de etanol/dietil-éter, y la sustancia sólida se recolectó mediante filtración, para proporcionar el compuesto del título deseado (121 miligramos, rendimiento del 64 por ciento) como un sólido amarillo.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 12.19 (1H, brs), 10.11 (1H, brs), 8.00 (1H, m), 7.62 (1H, m), 7.44-7.26 (2H, m), 6.90 (2H, q, J=7.2 Hz), 6.59-6.54 (2H, m), 5.08-5.05 (1H, m), 4.67-4.51 (1H, m), 4.24 (1H, brs), 3.51-3.30 (3H, m), 3.07-2.90 (1H, m), 2.32-2.12 (3H, m),

1.48-1.35 (2H, m), 1.13-1.09 (6H, m).

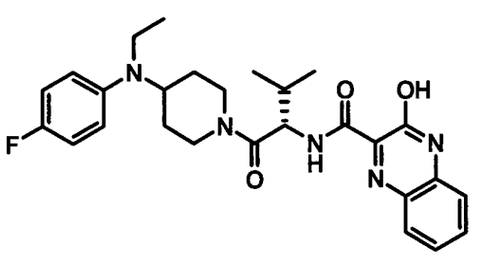
IR (KBr) cm^{-1}: 2960, 1685, 1630, 1510, 1215.

MS (FAB, m/z): 466 $(M+H)^+$.

HRMS (FAB, m/z): 466.2242 (Calculado para $C_{25}H_{29}FN_5O_3$: 466.2255).

Análisis calculado para $C_{25}H_{28}FN_5O_3$: C, 64.50; H, 6.06; N, 15.04; F, 4.08. Encontrado: C, 64.18; H, 5.77; N, 14.93; F, 4.02.

Ejemplo 32



N-[(1S)-1-({4-[(Etil)-(4-fluoro-fenil)-amino]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 32-1

4-[(etil)-(4-fluoro-fenil)-amino]-piperidin-1-carboxilato de terbutilo

Se agregó ciano-borohidruro de sodio (661 miligramos, 10.0 milimoles) a una solución en acetonitrilo (5.0 mililitros) de 4-[(4-fluoro-fenil)-amino]-piperidin-1-carboxilato de terbutilo (1.47 gramos, 5.00 milimoles), acetaldehído (0.559 mililitros, 5.00 milimoles), y ácido acético (0.0570 mililitros, 1.00 milimoles), a 0°C, y la agitación se llevó a cabo a temperatura ambiente durante 3 horas. Se agregó ácido acético adicional (2.0 mililitros), y la agitación se llevó a cabo durante 30 minutos. A la solución de la reacción se le agregó una

solución acuosa saturada de carbonato ácido de sodio, seguido por extracción con acetato de etilo y el lavado subsiguiente en secuencia con agua y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, para proporcionar el 4-[(etil)-(4-fluoro-fenil)-amino]-piperidin-1-carboxilato de terbutilo (1.27 gramos, rendimiento del 79 por ciento) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 6.94 (2H, t, J=8.8 Hz), 6.74 (2H, dd, J=8.8 Hz, 4.5 Hz), 4.20 (2H, brs), 3.48 (1H, tt, J=11.6 Hz, 3.6 Hz), 3.18 (2H, q, J=7.0 Hz), 2.78-2.72 (2H, m), 1.78 (2H, d, J=12.1 Hz), 1.62-1.46 (2H, m), 1.46 (9H, s), 1.08 (3H, t, J=7.0 Hz).

MS (ESI, m/z): 323 $(M+H)^+$.

Ejemplo 32-2

[(1S)-1-({4-[(etil)-(4-fluoro-fenil)-amino]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 29-2, el [(1S)-1-({4-[(etil)-(4-fluoro-fenil)-amino]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (1.36 gramos, rendimiento del 82 por ciento) se obtuvo a partir del 4-[(etil)-(4-fluoro-fenil)-amino]-piperidin-1-carboxilato de terbutilo (1.27 gramos, 3.94 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 6.97-6.92 (2H, m), 6.80-6.73 (2H, m), 5.34 (1H, d, J=6.6 Hz), 4.68 (1H, t, J=13.2 Hz), 4.50-4.47 (1H, m), 4.08-4.00 (1H, m), 3.59-3.51 (1H, m), 3.17-3.07 (3H, m), 2.68-

2.61 (1H, m), 1.93-1.84 (3H, m), 1.68-1.43 (11H, m), 1.08-1.05 (3H, m), 0.97 (3H, dd, J=12.4 Hz, 5.2 Hz), 0.89 (3H, dd, J=8.4 Hz, 5.2 Hz).

Ejemplo 32-3

Diclorhidrato de 1-[(2S)-2-amino-3-metil-butanoil]-N-etil-N-(4-fluoro-fenil)-piperidin-4-amina

De una manera análoga al Ejemplo 29-3, el diclorhidrato de 1-[(2S)-2-amino-3-metil-butanoil]-N-etil-N-(4-fluoro-fenil)-piperidin-4-amina (1.37 gramos, rendimiento del 100 por ciento) se obtuvo a partir del [(1S)-1-({4-[etil-(4-fluoro-fenil)-amino]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (1.36 gramos, 3.23 milimoles), como una sustancia amorfa incolora.

^{1}H-RMN (CD_3OD, 400 MHz) δ: 7.78-7.72 (2H, m), 7.44-7.39 (2H, m), 4.69-3.13 (8H, m), 2.74-1.73 (5H, m), 1.12-1.06 (6H, m), 0.99 (3H, t, J=7.6 Hz).

MS (ESI, m/z): 322 $(M+H)^+$.

Ejemplo 32-4

N-[(1S)-1-({4-[etil-(4-fluoro-fenil)-amino]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 29-4, el compuesto del título deseado (179 miligramos, rendimiento del 72 por ciento) se obtuvo a partir del diclorhidrato de 1-[(2S)-2-amino-3-metil-butanoil]-N-etil-N-(4-fluoro-fenil)-piperidin-4-amina (200 miligramos, 0.510 milimoles) como un sólido amarillo.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 12.33 (1H, brs), 10.14 (1H, brs),

8.04 (1H, t, J=9.2 Hz), 7.65-7.26 (3H, m), 6.99-6.91 (2H, m), 6.84-6.74 (2H, m), 5.14-5.06 (1H, m), 4.82-4.74 (1H, m), 4.32 (1H, brs), 3.64-3.55 (1H, m), 3.24-3.12 (3H, m), 2.78-2.71 (1H, m), 2.28 (1H, brs), 2.03-1.55 (4H, m), 1.11-1.03 (9H, m).

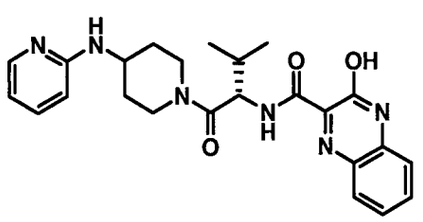
IR (KBr) cm^{-1}: 2965, 1690, 1635, 1510, 1450.

MS (ESI, m/z): 494 $(M+H)^+$, 516 $(M+Na)^+$.

HRMS (ESI, m/z): 516.2399 (Calculado para $C_{27}H_{32}FN_5NaO_3$: 516.2387).

Análisis calculado para $C_{27}H_{32}FN_5O_3$: C, 65.70; H, 6.53; N, 14.19; F, 3.85. Encontrado: C, 65.34; H, 6.48; N, 14.02; F, 3.79.

Ejemplo 33



N-[(1S)-2-metil-1-{[4-(piridin-2-il-amino)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 33-1

[(1S)-2-metil-1-({4-[(piridin-2-il-amino)-piperidin-1-il]-carbonil}-propil]-carbamato de terbutilo

Se agregó triacetoxi-borohidruro de sodio (1.41 gramos, 6.31 milimoles) a una solución en cloruro de metileno (53 mililitros) de 2-amino-piridina (500 miligramos, 5.26 milimoles), 4-oxo-piperidin-1-carboxilato de terbutilo (1.06 gramos, 5.26 milimoles), y ácido

acético (0.301 mililitros, 5.26 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a temperatura ambiente durante la noche. A la solución de la reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio, seguido por extracción con cloruro de metileno. El extracto se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, para proporcionar el 4-[(piridin-2-il-amino)-piperidin-1-carboxilato de terbutilo (335 miligramos).

Se agregó ácido clorhídrico concentrado (3.5 mililitros) a una solución en etanol (7.0 mililitros) del compuesto resultante (335 miligramos), a 0°C, y la agitación se llevó a cabo a temperatura ambiente durante 7 horas. La solución de la reacción se concentró, para proporcionar el triclorhidrato de N-(piperidin-4-il)-2-amino-piridina.

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (347 miligramos, 1.81 milimoles) se agregó a una solución en cloruro de metileno (12 mililitros) del compuesto resultante, N-(terbutoxi-carbonil)-L-valina (262 miligramos, 1.21 milimoles), monohidrato de 1-hidroxi-benzotriazol (196 miligramos, 1.45 milimoles), y N-metil-morfolina (0.797 mililitros, 7.25 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a temperatura ambiente durante la noche. Se agregó agua a la solución de la reacción, seguida por extracción con cloruro de metileno y el lavado subsiguiente en secuencia con una solución acuosa saturada de carbonato ácido de sodio, agua, y una solución salina, y entonces la capa orgánica

resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, para proporcionar el [(1S)-2-metil-1-{[4-(piridin-2-il-amino)-piperidin-1-il]-carbonil)-propil]-carbamato de terbutilo (316 miligramos, rendimiento del 16 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.09 (1H, d, J=5.1 Hz), 7.43-7.38 (1H, m), 6.60-6.56 (1H, m), 6.37 (1H, d, J=7.8 Hz), 5.36-5.34 (1H, m), 4.54-4.45 (2H, m), 4.32-4.18 (1H, m), 3.99-3.91 (2H, m), 3.32-3.21 (1H, m), 2.98-2.86 (1H, m), 2.23-2.08 (2H, m), 1.96-1.89 (1H, m), 1.44 (9H, s), 1.42-1.24 (2H, m), 0.99-0.87 (6H, m).

MS (ESI, m/z): 377 $(M+H)^+$.

Ejemplo 33-2

N-[(1S)-2-metil-1-{[4-(piridin-2-il-amino)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida

Se agregó ácido clorhídrico concentrado (3.0 mililitros) a una solución en etanol (5.0 mililitros) de [(1S)-2-metil-1-({4-[(piridin-2-il)-amino]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (316 miligramos, 0.840 milimoles), a 0°C, y la agitación se llevó a cabo a temperatura ambiente durante la noche. La capa orgánica se concentró, para proporcionar el triclorhidrato de N-{1-[(2S)-2-amino-3-metil-butanoil]-piperidin-4-il}-piridin-2-amina como una sustancia amorfa incolora.

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (241 miligramos, 1.26 milimoles) se agregó a una solución en cloruro

de metileno (10 mililitros) del compuesto resultante, ácido 3-hidroxi-quinoxalin-2-carboxílico (165 miligramos, 0.840 milimoles), monohidrato de 1-hidroxi-benzotriazol (136 miligramos, 1.01 milimoles), y N-metil-morfolina (0.646 mililitros, 5.88 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a temperatura ambiente durante la noche. Se agregó agua a la solución de la reacción, seguida por extracción con cloruro de metileno y el lavado subsiguiente en secuencia con una solución acuosa saturada de carbonato ácido de sodio, agua, y una solución salina, y la capa orgánica resultante se secó sobre sulfato de sodio anhidro. Después de que la capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, el residuo resultante de la concentración se suspendió en un solvente mixto de etanol/dietil-éter, y la sustancia sólida se recolectó mediante filtración, para proporcionar el compuesto del título deseado (248 miligramos, rendimiento del 66 por ciento) como un sólido amarillo.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 10.11-9.94 (2H, m), 8.12-8.10 (1H, m), 8.01 (1H, d, J=8.0 Hz), 7.64-7.37 (4H, m), 6.60 (1H, q, J=6.2 Hz), 6.43-6.39 (1H, m), 5.12-4.52 (3H, m), 4.23-4.17 (1H, m), 4.00-3.94 (1H, m), 3.49-3.32 (1H, m), 3.12-3.00 (1H, m), 2.36-2.17 (3H, m), 1.68-1.44 (2H, m), 1.12-1.08 (6H, m).

IR (KBr) cm^{-1}: 2960, 1685, 1635, 1605, 1520.

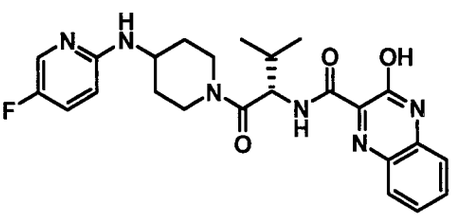
MS (ESI, m/z): 449 $(M+H)^+$.

HRMS (ESI, m/z): 449.2299 (Calculado para $C_{24}H_{29}N_6O_3$:

449.2301).

Análisis calculado para $C_{24}H_{28}N_6O_3 \cdot 0.5H_2O$: C, 63.00; H, 6.39; N, 18.37. Encontrado: C, 63.17; H, 6.48; N, 18.44.

Ejemplo 34



N-[(1S)-1-({4-[(5-fluoro-piridin-2-il)-amino]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 34-1

4-[(5-fluoro-piridin-2-il)-amino]-piperidin-1-carboxilato de terbutilo

Se agregó triacetoxi-borohidruro de sodio (4.78 gramos, 21.4 milimoles) a una solución en cloruro de metileno (90 mililitros) de 2-amino-5-fluoro-piridina (2.00 gramos, 17.8 milimoles), 4-oxo-piperidin-1-carboxilato de terbutilo (3.59 gramos, 17.8 milimoles), y ácido acético (1.02 mililitros, 17.8 milimoles), a 0°C, y la agitación se llevó a cabo a temperatura ambiente durante 4 días. A la solución de la reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio, seguido por extracción con cloruro de metileno. La capa orgánica se concentró, para proporcionar el 4-[(5-fluoro-piridin-2-il)-amino]-piperidin-1-carboxilato de terbutilo (2.53 gramos, rendimiento del 48 por ciento) como un sólido blanco.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.94 (1H, d, J=2.4 Hz), 7.18 (1H,

td, J=6.8 Hz, 2.4 Hz), 6.32 (1H, dd, J=6.8 Hz, 2.8 Hz), 4.22 (1H, d, J=6.3 Hz), 4.05 (2H, brs), 3.77-3.72 (1H, m), 2.96-2.92 (2H, m), 2.04-2.01 (2H, m), 1.46 (9H, s), 1.38-1.31 (2H, m).

MS (ESI, m/z): 196 $(M-Boc+H)^+$.

Ejemplo 34-2

[(1S)-1-({4-[(5-fluoro-piridin-2-il)-amino]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 29-2, el [(1S)-1-({4-[(5-fluoro-piridin-2-il)-amino]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (1.29 gramos, rendimiento del 97 por ciento) se obtuvo a partir del 4-[(5-fluoro-piridin-2-il)-amino]-piperidin-1-carboxilato de terbutilo (1.00 gramos, 3.39 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.95-7.94 (1H, m), 7.21-7.16 (1H, m), 6.34-6.32 (1H, m), 5.36-5.34 (1H, m), 4.54-4.46 (2H, m), 4.22 (1H, dd, J=12.8 Hz, 6.2 Hz), 3.99-3.87 (2H, m), 3.30-3.20 (1H, m), 2.96-2.84 (1H, m), 2.21-2.07 (2H, m), 1.96-1.90 (1H, m), 1.44 (9H, s), 1.43-1.31 (2H, m), 0.98-0.87 (6H, m).

MS (ESI, m/z): 295 $(M-Boc+H)^+$.

Ejemplo 34-3

Triclorhidrato de N-{1-[(2S)-2-amino-3-metil-butanoil]-piperidin-4-il}-5-fluoro-piridin-2-amina

De una manera análoga al Ejemplo 29-3, el triclorhidrato de N-{1-[(2S)-2-amino-3-metil-butanoil]-piperidin-4-il}-5-fluoro-piridin-2-amina (1.25 gramos, rendimiento del 95 por ciento) se obtuvo a partir

del [(1S)-1-({4-[(5-fluoro-piridin-2-il)-amino]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (1.29 gramos, 3.27 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN (CD_3OD, 400 MHz) δ: 7.96-7.93 (2H, m), 7.17-7.13 (1H, m), 4.60-4.35 (2H, m), 4.08-3.90 (2H, m), 3.44-3.25 (1H, m), 3.12-2.94 (1H, m), 2.24-2.09 (3H, m), 1.71-1.48 (2H, m), 1.12 (3H, dd, J=10.2 Hz, 6.8 Hz), 1.03 (3H, dd, J=12.0 Hz, 6.8 Hz).

MS (ESI, m/z): 295 $(M+H)^+$.

Ejemplo 34-4

N-[(1S)-1-({4-[(5-fluoro-piridin-2-il)-amino]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 29-4, el compuesto del título deseado (173 miligramos, rendimiento del 75 por ciento) se obtuvo a partir del triclorhidrato de N-{1-[(2S)-2-amino-3-metil-butanoil]-piperidin-4-il}-5-fluoro-piridin-2-amina (200 miligramos, 0.510 milimoles) como un sólido amarillo.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 12.59 (1H, brs), 10.10 (1H, brs), 8.01-7.95 (2H, m), 7.63-7.39 (3H, m), 7.24-7.17 (1H, m), 6.36 (1H, td, J=7.6 Hz, 2.8 Hz), 5.08 (1H, t, J=5.6 Hz), 4.68-4.35 (2H, m), 4.23 (1H, d, J=10.6 Hz), 4.01-3.90 (1H, m), 3.47-3.32 (1H, m), 3.08-2.93 (1H, m), 2.36-2.14 (3H, m), 1.52-1.39 (2H, m), 1.12-1.09 (6H, m).

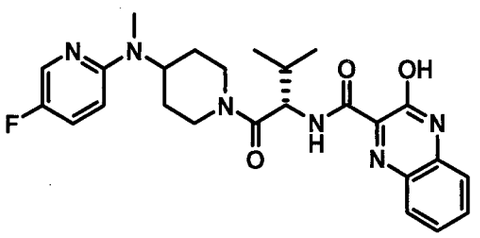
IR (KBr) cm^{-1}: 2965, 1685, 1635, 1525, 1495.

MS (ESI, m/z): 467 $(M+H)^+$, 489 $(M+Na)^+$.

HRMS (ESI, m/z): 489.2013 (Calculado para $C_{24}H_{27}FN_6NaO_3$: 489.2026).

Análisis calculado para $C_{24}H_{27}FN_6O_3 \cdot 0.25H_2O$: C, 61.20; H, 5.88; N, 17.84; F, 4.03. Encontrado: C, 61.24; H, 5.68; N, 17.86; F, 4.04.

Ejemplo 35



N-[(1S)-1-({4-[(5-fluoro-piridin-2-il)-(metil)-amino]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 35-1

4-[N-(5-fluoro-piridin-2-il)-(metil)-amino]-piperidin-1-carboxilato de terbutilo

Se agregó ciano-borohidruro de sodio (685 miligramos, 10.4 milimoles) a una solución en acetonitrilo (52 mililitros) de 4-[(5-fluoro-piridin-2-il)-amino]-piperidin-1-carboxilato de terbutilo (1.53 gramos, 5.18 milimoles), formaldehído (1.93 mililitros, 25.9 milimoles), y ácido acético (0.297 mililitros, 5.18 milimoles), a 0°C, y la agitación se llevó a cabo a temperatura ambiente durante 4 horas. Se agregó ácido acético adicional (1.0 mililitros), y la agitación se llevó a cabo durante la noche. Se agregó etanol (26 mililitros) a la solución de la reacción, y la agitación se llevó a cabo durante la noche. A la solución de la reacción se le agregó una solución acuosa

saturada de carbonato ácido de sodio, y la capa orgánica se concentró, seguido por extracción con cloruro de metileno. La capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, para proporcionar el 4-[N-(5-fluoropiridin-2-il)-(metil)-amino]-piperidin-1-carboxilato de terbutilo (332 miligramos, rendimiento del 22 por ciento) como un sólido blanco.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.01 (1H, d, J=2.4 Hz), 7.25-7.21 (1H, m), 6.43 (1H, dd, J=7.2 Hz, 2.4 Hz), 4.65-4.59 (1H, m), 4.24 (2H, brs), 2.86-2.81 (2H, m), 2.81 (3H, s), 1.66-1.60 (4H, m), 1.48 (9H, s).

MS (ESI, m/z): 210 $(M-Boc+H)^+$.

Ejemplo 35-2

[(1S)-1-({4-[(5-fluoro-piridin-2-il)-(metil)-amino]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 29-2, el [(1S)-1-({4-[(5-fluoro-piridin-2-il)-(metil)-amino]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (368 miligramos, rendimiento del 84 por ciento) se obtuvo a partir del 4-[(5-fluoro-piridin-2-il)-(metil)-amino]-piperidin-1-carboxilato de terbutilo (332 miligramos, 1.07 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.01 (1H, dd, J=4.4 Hz, 2.4 Hz), 7.26-7.22 (1H, m), 6.45-6.41 (1H, m), 5.37 (1H, d, J=7.4 Hz), 4.85-4.74 (2H, m), 4.53-4.50 (1H, m), 4.08-4.05 (1H, m), 3.25-3.17 (1H,

m), 2.79 (3H, d, J=9.0 Hz), 2.70 (1H, t, J=10.4 Hz), 1.98-1.90 (1H, m), 1.84-1.58 (4H, m), 1.45-1.44 (9H, m), 1.02-0.88 (6H, m).

MS (ESI, m/z): 309 $(M-Boc+H)^+$.

Ejemplo 35-3

Triclorhidrato de N-{1-[(2S)-2-amino-3-metil-butanoil]-piperidin-4-il}-5-fluoro-N-metil-piridin-2-amina

De una manera análoga al Ejemplo 29-3, el triclorhidrato de N-{1-[(2S)-2-amino-3-metil-butanoil]-piperidin-4-il}-5-fluoro-N-metil-piridin-2-amina (370 miligramos, rendimiento del 98 por ciento) se obtuvo a partir del [(1S)-1-({4-[(5-fluoro-piridin-2-il)-(metil)-amino]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (368 miligramos, 0.900 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN (CD_3OD, 400 MHz) δ: 8.08-8.03 (2H, m), 7.56-7.53 (1H, m), 4.71 (1H, d, J=14.0 Hz), 4.42-4.35 (2H, m), 4.14-4.08 (1H, m), 3.43-3.34 (1H, m), 3.11 (3H, s), 2.95-2.87 (1H, m), 2.27-2.15 (1H, m), 2.06-1.79 (4H, m), 1.17-1.02 (6H, m).

MS (ESI, m/z): 309 $(M+H)^+$.

Ejemplo 35-4

N-[(1S)-1-({4-[(5-fluoro-piridin-2-il)-(metil)-amino]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 29-4, el compuesto del título deseado (171 miligramos, rendimiento del 82 por ciento) se obtuvo a partir del triclorhidrato de N-{1-[(2S)-2-amino-3-metil-butanoil]-piperidin-4-il}-5-fluoro-N-metil-piridin-2-amina (181 miligramos, 0.430 milimoles), como un sólido amarillo.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 12.59 (1H, brs), 10.21 (1H, brs), 8.05-8.01 (2H, m), 7.61-7.45 (3H, m), 7.28-7.23 (1H, m), 6.48-6.42 (1H, m), 5.17-5.09 (1H, m), 4.89-4.80 (2H, m), 4.44-4.33 (1H, m), 3.37-3.28 (1H, m), 2.86-2.78 (4H, m), 2.39-2.29 (1H, m), 1.92-1.63 (4H, m), 1.12 (6H, dd, J=16.2 Hz, 5.3 Hz).

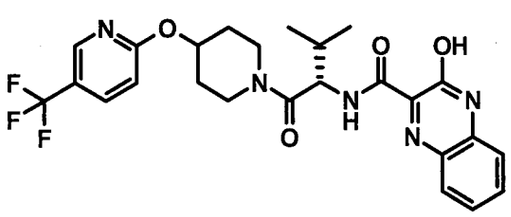
IR (KBr) cm^{-1}: 3460, 2960, 1685, 1640, 1490.

MS (ESI, m/z): 481 $(M+H)^+$.

HRMS (ESI, m/z): 503.2200 (Calculado para $C_{25}H_{29}FN_6NaO_3$: 503.2183).

Análisis calculado para $C_{25}H_{29}FN_6O_3$: C, 62.49; H, 6.08; N, 17.49; F, 3.95. Encontrado: C, 62.10; H, 6.25; N, 17.19; F, 4.00.

Ejemplo 36



3-hidroxi-N-{(1S)-2-metil-1-[(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida

Ejemplo 36-1

4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-carboxilato de terbutilo

De una manera análoga al Ejemplo 29-1, el 4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-carboxilato de terbutilo (1.26 gramos, rendimiento del 61 por ciento) se obtuvo a partir de 5-trifluoro-metil-2-piridinol (1.00 gramos, 5.95 milimoles) como un

sólido blanco.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.41 (1H, m), 7.76 (1H, dd, J=8.6 Hz, 2.4 Hz), 6.79 (1H, d, J=8.6 Hz), 5.32-5.26 (1H, m), 3.81-3.75 (2H, m), 3.33-3.26 (2H, m), 2.02-1.96 (2H, m), 1.78-1.69 (2H, m), 1.48 (9H, s).

Ejemplo 36-2

{(1S)-2-metil-1-[(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-carbamato de terbutilo

De una manera análoga al Ejemplo 29-2, el {(1S)-2-metil-1-[(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-carbamato de terbutilo (1.57 gramos, rendimiento del 97 por ciento) se obtuvo a partir del 4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-carboxilato de terbutilo (1.26 gramos, 3.64 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.41 (1H, s), 7.78 (1H, dd, J=9.0 Hz, 2.4 Hz), 6.80 (1H, d, J=8.6 Hz), 5.39-5.30 (2H, m), 4.51 (1H, dd, J=9.0 Hz, 5.6 Hz), 4.01-3.44 (4H, m), 2.12-1.74 (5H, m), 1.44 (9H, s), 0.98 (3H, d, J=6.8 Hz), 0.90 (3H, d, J=6.8 Hz).

MS (ESI, m/z): 446 $(M+H)^+$.

Ejemplo 36-3

diclorhidrato de (2S)-3-metil-1-oxo-1-(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-butan-2-amina

De una manera análoga al Ejemplo 29-3, el diclorhidrato de (2S)-3-metil-1-oxo-1-(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-butan-2-amina (1.51 gramos, rendimiento del 100 por ciento) se

obtuvo a partir del {(1S)-2-metil-1-[(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-carbamato de terbutilo (1.57 gramos, 3.52 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.44 (5 horas, brs), 7.90 (1H, brs), 7.00 (1H, brs), 5.46 (1H, brs), 4.54 (1H, brs), 4.13-3.48 (4H, m), 2.31-1.89 (5H, m), 1.28-1.14 (6H, m).

MS (ESI, m/z): 346 $(M+H)^+$.

Ejemplo 36-4

3-hidroxi-N-{(1S)-2-metil-1-[(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 29-4, el compuesto del título deseado (214 miligramos, rendimiento del 87 por ciento) se obtuvo a partir del diclorhidrato de (2S)-3-metil-1-oxo-1-(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-butan-2-amina (200 miligramos, 0.480 milimoles) como un sólido amarillo.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 12.12 (1H, brs), 10.12 (1H, brs), 8.44-8.42 (1H, m), 8.04-8.01 (1H, m), 7.81-7.37 (4H, m), 6.82 (1H, t, J=9.2 Hz), 5.45-5.39 (1H, m), 5.11-5.08 (1H, m), 4.08-3.57 (4H, m), 2.34-1.89 (5H, m), 1.11 (6H, d, J=7.0 Hz).

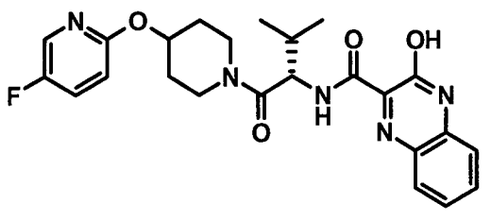
IR (KBr) cm^{-1}: 2965, 1690, 1630, 1615, 1525, 1325.

MS (ESI, m/z): 518 $(M+H)^+$.

HRMS (ESI, m/z): 518.1993 (Calculado para $C_{25}H_{27}F_3N_5O_4$: 518.2015).

Análisis calculado para $C_{25}H_{26}F_3N_5O_4$: C, 58.02; H, 5.06; N, 13.53; F, 11.01. Encontrado: C, 57.80; H, 5.00; N, 13.51; F, 11.01.

Ejemplo 37



N-[(1S)-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 37-1

4-{(5-fluoro-piridin-2-il)-oxi}-piperidin-1-carboxilato de terbutilo

De una manera análoga al Ejemplo 29-1, el 4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo (1.46 gramos, rendimiento del 48 por ciento) se obtuvo a partir de la 5-fluoro-2-hidroxi-piridina (1.00 gramos, 8.84 milimoles) como un sólido blanco.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.95 (1H, d, J=3.2 Hz), 7.35-7.30 (1H, m), 6.68 (1H, dd, J=9.2 Hz, 3.6 Hz), 5.16-5.10 (1H, m), 3.80-3.74 (2H, m), 3.30-3.24 (2H, m), 1.99-1.94 (2H, m), 1.74-1.66 (2H, m), 1.47 (9H, s).

MS (ESI, m/z): 241 $(M\text{-}tBu+H)^+$.

Ejemplo 37-2

[(1S)-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 29-2, el [(1S)-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (1.92 gramos, rendimiento del 99 por ciento) se obtuvo a partir del 4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-

carboxilato de terbutilo (1.46 gramos, 4.93 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.97-7.95 (1H, m), 7.34 (1H, ddd, J=9.0 Hz, 7.4 Hz, 3.1 Hz), 6.69 (1H, ddd, J=9.0 Hz, 3.1 Hz, 2.0 Hz), 5.36 (1H, d, J=9.0 Hz), 5.24-5.19 (1H, m), 4.51 (1H, dd, J=8.6 Hz, 5.6 Hz), 3.98-3.42 (4H, m), 2.09-1.71 (5H, m), 1.44 (9H, s), 0.98 (3H, d, J=6.6 Hz), 0.89 (3H, d, J=6.6 Hz).

MS (ESI, m/z): 396 $(M+H)^+$.

Ejemplo 37-3

Diclorhidrato de (2S)-1-{4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina

De una manera análoga al Ejemplo 29-3, el diclorhidrato de (2S)-1-{4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina (1.93 gramos, rendimiento del 100 por ciento) se obtuvo a partir del [(1S)-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (1.92 gramos, 4.85 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.42 (4H, brs), 7.99 (1H, brs), 7.46 (1H, brs), 7.24 (1H, brs), 5.33 (1H, brs), 4.48 (1H, brs), 4.09-3.41 (4H, m), 2.26-1.83 (5H, m), 1.18-1.10 (6H, m).

MS (ESI, m/z): 296 $(M+H)^+$.

Ejemplo 37-4

N-[(1S)-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 29-4, el compuesto del

título deseado (200 miligramos, rendimiento del 79 por ciento) se obtuvo a partir del diclorhidrato de (2S)-1-{4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina (200 miligramos, 0.540 milimoles) como un sólido amarillo.

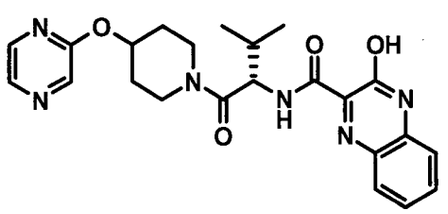
^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 12.32 (1H, brs), 10.13 (1H, brs), 8.02-7.96 (2H, m), 7.62-7.32 (4H, m), 6.71 (1H, td, J=9.2 Hz, 3.6 Hz), 5.29-5.24 (1H, m), 5.11-5.08 (1H, m), 4.04-3.59 (4H, m), 2.33-1.85 (5H, m), 1.11 (6H, d, J=6.6 Hz).

IR (KBr) cm^{-1}: 2965, 1685, 1640, 1530, 1480.

MS (ESI, m/z): 468 $(M+H)^+$.

HRMS (ESI, m/z): 468.2042 (Calculado para $C_{24}H_{27}FN_5O_4$: 468.2047).

Ejemplo 38



3-hidroxi-N-[(1S)-2-metil-1-({4-[(pirazin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

Ejemplo 38-1

4-[pirazin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo

El 4-hidroxi-piperidin-1-carboxilato de terbutilo (3.73 gramos, 18.0 milimoles) se agregó a una suspensión en N,N-dimetil-formamida (10 mililitros) de hidruro de sodio al 60 por ciento (533 miligramos, 14.0 milimoles), a 0°C, y la agitación se llevó a cabo a

temperatura ambiente durante 30 minutos. Además de agregó cloro-pirazina (1.15 gramos, 10.0 milimoles) a temperatura ambiente, y la agitación se llevó a cabo durante 1.5 horas. Se agregó agua a la solución de la reacción, seguida por extracción con acetato de etilo y el lavado subsiguiente en secuencia con agua y una solución salina, y la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, para proporcionar el 4-[(pirazin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo (2.79 gramos, rendimiento del 100 por ciento) como un sólido blanco.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.20 (1H, s), 8.10 (1H, d, J=2.8 Hz), 8.05 (1H, dd, J=2.8 Hz, 1.2 Hz), 5.24-5.18 (1H, m), 3.82-3.76 (2H, m), 3.33-3.27 (2H, m), 2.02-1.97 (2H, m), 1.79-1.70 (2H, m), 1.48 (9H, s).

MS (ESI, m/z): 224 $(M\text{-}tBu+H)^+$.

Ejemplo 38-2

Diclorhidrato de 2-[(piperidin-4-il)-oxi]-pirazina

Se agregó ácido clorhídrico concentrado (10 mililitros) a una solución en etanol (20 mililitros) de 4-[(pirazin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo (2.79 gramos, 10.0 milimoles), a 0°C, y la agitación se llevó a cabo a temperatura ambiente durante la noche. La capa orgánica se concentró, para proporcionar el diclorhidrato de 2-[(piperidin-4-il)-oxi]-pirazina (2.50 gramos, rendimiento del 99 por ciento) como un sólido blanco.

^{1}H-RMN (CD_3OD, 400 MHz) δ: 8.27-8.17 (3H, m), 5.39 (1H, brs), 3.48-3.23 (4H, m), 2.24 (2H, s), 2.12 (2H, s).

MS (ESI, m/z): 180 $(M+H)^+$.

Ejemplo 38-3

[(1S)-2-metil-1-({4-[(pirazin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (1.44 gramos, 7.50 milimoles) se agregó a una solución en cloruro de metileno (50 mililitros) de diclorhidrato de 2-[(piperidin-4-il)-oxi]-pirazina (1.26 gramos, 5.00 milimoles), N-(terbutoxi-carbonil)-L-valina (1.09 gramos, 5.00 milimoles), monohidrato de 1-hidroxi-benzotriazol (811 miligramos, 6.00 milimoles), y N-metil-morfolina (3.30 mililitros, 30.0 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a temperatura ambiente durante la noche. Se agregó agua a la solución de la reacción, seguida por extracción con cloruro de metileno y el lavado subsiguiente en secuencia con una solución acuosa saturada de carbonato ácido de sodio, agua, y una solución salina, y la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, para proporcionar el [(1S)-2-metil-1-({4-[(pirazin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (1.82 gramos, rendimiento del 96 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.22 (1H, d, J=1.2 Hz), 8.13 (1H, d, J=2.8 Hz), 8.07-8.05 (1H, m), 5.36-5.26 (2H, m), 4.53-4.49 (1H,

m), 3.98-3.49 (4H, m), 2.11-1.77 (5H, m), 1.44 (9H, s), 0.98 (3H, d, J=7.0 Hz), 0.90 (3H, d, J=6.6 Hz).

MS (ESI, m/z): 379 $(M+H)^+$.

Ejemplo 38-4

Diclorhidrato de (2S)-3-metil-1-oxo-1-{4-[(pirazin-2-il)-oxi]-piperidin-1-il}-butan-2-amina

De una manera análoga al Ejemplo 29-3, el diclorhidrato de (2S)-3-metil-1-oxo-1-{4-[(pirazin-2-il)-oxi]-piperidin-1-il}-butan-2-amina (1.85 gramos, rendimiento del 100 por ciento) se obtuvo a partir del [(1S)-2-metil-1-({4-[(pirazin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (1.82 gramos, 4.81 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 8.30 (1H, d, J=3.9 Hz), 8.22-8.17 (6H, m), 5.32-5.22 (1H, m), 4.31-4.28 (1H, m), 4.11-3.75 (2H, m), 3.56-3.20 (2H, m), 2.11-1.97 (3H, m), 1.78-1.57 (2H, m), 1.00-0.92 (6H, m).

MS (ESI, m/z): 279 $(M+H)^+$.

Ejemplo 38-5

3-hidroxi-N-[(1S)-2-metil-1-({4-[(pirazin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 29-4, el compuesto del título deseado (232 miligramos, rendimiento del 91 por ciento) se obtuvo a partir del diclorhidrato de (2S)-3-metil-1-oxo-1-{4-[(pirazin-2-il)-oxi]-piperidin-1-il}-butan-2-amina (200 miligramos, 0.570 milimoles) como un sólido amarillo.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 12.37 (1H, brs), 10.16 (1H, brs), 8.25-8.21 (1H, m), 8.15-8.13 (1H, m), 8.09-8.00 (2H, m), 7.63-7.26 (3H, m), 5.38-5.30 (1H, m), 5.12-5.07 (1H, m), 4.09-3.58 (4H, m), 2.36-1.85 (5H, m), 1.11 (6H, d, J=6.6 Hz).

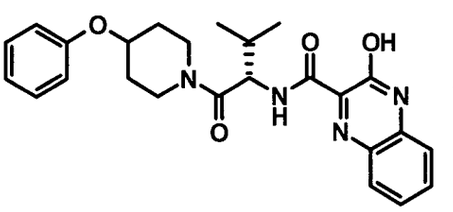
IR (KBr) cm^{-1}: 2960, 1685, 1640, 1525, 1410.

MS (ESI, m/z): 451 $(M+H)^+$, 473 $(M+Na)^+$.

HRMS (ESI, m/z): 473.1929 (Calculado para $C_{23}H_{26}N_6NaO_4$: 473.1913).

Análisis calculado para $C_{23}H_{26}N_6O_4$: C, 61.32; H, 5.82; N, 18.66. Encontrado: C, 61.23; H, 5.83; N, 18.60.

Ejemplo 39



3-hidroxi-N-{(1S)-2-metil-1-[(4-fenoxi-piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida

Ejemplo 39-1

Clorhidrato de (2S)-3-metil-1-oxo-1-(4-fenoxi-piperidin-1-il)-butan-2-amina

Una solución al 40 por ciento en tolueno de azodicarboxilato de di-isopropilo (2.10 mililitros, 3.99 milimoles) se agregó a una solución en tolueno (15 mililitros) de {(1S)-1-[(4-hidroxi-piperidin-1-il)-carbonil]-2-metil-propil}-carbamato de terbutilo (1.00 gramos, 3.33 milimoles), fenol (344 miligramos, 3.33 milimoles), y trifenil-fosfina

(1.05 gramos, 3.99 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se concentró, y el residuo resultante se diluyó con acetato de etilo, seguido por lavado en secuencia con una solución acuosa de hidróxido de sodio 1N, agua, y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, para proporcionar el N-{(1S)-2-metil-1-[(4-fenoxi-piperidin-1-il)-carbonil]-propil}-carbamato de terbutilo (1.04 gramos) como un aceite incoloro. Se agregó ácido clorhídrico concentrado (2.8 mililitros) a una solución en etanol (5.6 mililitros) del compuesto resultante (1.04 gramos), a 0°C, y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se concentró, para proporcionar el clorhidrato de (2S)-3-metil-1-oxo-1-(4-fenoxi-piperidin-1-il)-butan-2-amina (880 miligramos, rendimiento del 84 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN (CD_3OD, 400 MHz) δ: 7.30-7.25 (2H, m), 6.98-6.92 (3H, m), 4.71-4.62 (1H, m), 4.34 (1H, d, J=5.1 Hz), 4.02-3.46 (4H, m), 2.24-1.70 (5H, m), 1.11 (3H, d, J=7.0 Hz), 1.02 (3H, d, J=7.0 Hz).

MS (ESI, m/z): 277 $(M+H)^+$.

Ejemplo 39-2

3-hidroxi-N-{(1S)-2-metil-1-[(4-fenoxi-piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 29-4, el compuesto del

título deseado (174 miligramos, rendimiento del 61 por ciento) se obtuvo a partir del clorhidrato de (2S)-3-metil-1-oxo-1-(4-fenoxi-piperidin-1-il)-butan-2-amina (200 miligramos, 0.640 milimoles) como un sólido amarillo.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 12.69 (1H, brs), 10.16 (1H, brs), 8.00-7.97 (1H, m), 7.61-7.26 (5H, m), 7.00-6.92 (3H, m), 5.11-5.06 (1H, m), 4.65-4.59 (1H, m), 4.00-3.71 (4H, m), 2.35-1.88 (5H, m), 1.14-1.10 (6H, m).

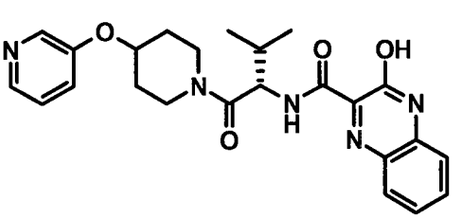
IR (KBr) cm^{-1}: 2960, 1685, 1640, 1530, 1455.

MS (ESI, m/z): 448 $(M+H)^+$.

HRMS (ESI, m/z): 471.2004 (Calculado para $C_{25}H_{28}N_4NaO_4$: 471.2008).

Análisis calculado para $C_{25}H_{28}N_4O_4 \cdot 0.25H_2O$: C, 66.28; H, 6.34; N, 12.37. Encontrado: C, 66.34; H, 6.32; N, 12.32.

Ejemplo 40



3-hidroxi-N-[(1S)-2-metil-1-({4-[(piridin-3-il)-oxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

Ejemplo 40-1

[(1S)-2-metil-1-({4-[(piridin-3-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo

Una solución al 40 por ciento en tolueno de azodicarboxilato de

di-isopropilo (2.10 mililitros, 3.99 milimoles) se agregó a una solución en tolueno (15 mililitros) de 4-hidroxi-piperidin-1-carboxilato de terbutilo (1.00 gramos, 3.33 milimoles), 3-hidroxi-piridina (348 miligramos, 3.66 milimoles), y trifenil-fosfina (1.05 gramos, 3.99 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a temperatura ambiente durante 4 días. La solución de la reacción se concentró, y el residuo resultante se diluyó con acetato de etilo, seguido por lavado en secuencia con una solución acuosa de hidróxido de sodio 1N, agua, y solución salina. La capa orgánica resultante se extrajo con ácido clorhídrico 1N, y se agregó una solución acuosa de hidróxido de sodio 1N a la capa acuosa para hacerla alcalina. La capa acuosa se extrajo con acetato de etilo, y la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, para proporcionar el [(1S)-2-metil-1-({4-[(piridin-3-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (767 miligramos, rendimiento del 61 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) : 8.33 (1H, brs), 8.24 (1H, brs), 7.26-7.22 (2H, m), 5.34-5.30 (1H, m), 4.61 (1H, brs), 4.49 (1H, brs), 3.83-3.47 (4H, m), 2.05-1.82 (5H, m), 1.44 (9H, s), 0.97 (3H, d, J=6.6 Hz), 0.90 (3H, d, J=6.3 Hz).

MS (ESI, m/z): 378 $(M+H)^+$.

Ejemplo 40-2

Diclorhidrato de (2S)-3-metil-1-oxo-1-{4-[(piridin-3-il)-oxi]-piperidin-1-il}-butan-2-amina

Se agregó ácido clorhídrico concentrado (2.0 mililitros) a una solución en etanol (4.0 mililitros) de [(1S)-2-metil-1-({4-[(piridin-3-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (767 miligramos, 2.03 milimoles), a 0°C, y la agitación se llevó a cabo a temperatura ambiente durante la noche. La capa orgánica se concentró, para proporcionar el diclorhidrato de (2S)-3-metil-1-oxo-1-{4-[(piridin-3-il)-oxi]-piperidin-1-il}-butan-2-amina (786 miligramos, rendimiento del 100 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN (CD_3OD, 400 MHz) δ: 8.71-8.70 (1H, m), 8.48 (1H, d, J=5.6 Hz), 8.35-8.33 (1H, m), 8.05 (1H, dd, J=8.8 Hz, 5.6 Hz), 5.06-4.95 (1H, m), 4.39 (1H, d, J=5.2 Hz), 4.14-3.45 (4H, m), 2.25-1.77 (5H, m), 1.12 (3H, d, J=6.6 Hz), 1.03 (3H, d, J=6.6 Hz).

MS (ESI, m/z): 278 $(M+H)^+$.

Ejemplo 40-3

3-hidroxi-N-[(1S)-2-metil-1-({4-[(piridin-3-il)-oxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 29-4, el compuesto del título deseado (148 miligramos, rendimiento del 58 por ciento) se obtuvo a partir del diclorhidrato de (2S)-3-metil-1-oxo-1-{4-[(piridin-3-il)-oxi]-piperidin-1-il}-butan-2-amina (200 miligramos, 0.570 milimoles) como un sólido amarillo.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.37-8.34 (1H, m), 8.26-8.25 (1H, m), 8.04-8.01 (1H, m), 7.65-7.24 (5H, m), 5.10-5.06 (1H, m), 4.67 (1H, brs), 4.03-3.68 (4H, m), 2.33-1.88 (5H, m), 1.13-1.10 (6H, m).

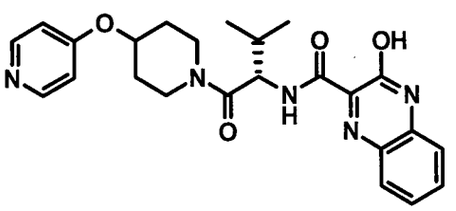
IR (KBr) cm^{-1}: 2965, 1685, 1630, 1525, 1475.

MS (ESI, m/z): 472 $(M+Na)^+$.

HRMS (ESI, m/z): 472.1971 (Calculado para $C_{24}H_{27}N_5NaO_4$: 472.1961).

Análisis calculado para $C_{24}H_{27}N_5O_4 \cdot 0.25H_2O$: C, 63.49; H, 6.11; N, 15.43. Encontrado:: C, 63.41; H, 5.90; N, 15.39.

Ejemplo 41



3-hidroxi-N-[(1S)-2-metil-1-({4-[(piridin-4-il)-oxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

Ejemplo 41-1

[(1S)-2-metil-1-({4-[(piridin-4-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 2-1, el [(1S)-2-metil-1-({4-[(piridin-4-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (940 miligramos, rendimiento del 100 por ciento) se obtuvo a partir del diclorhidrato de 4-[(piperidin-4-il)-oxi]-piridina (580 miligramos, 2.30 milimoles), y N-(terbutoxi-carbonil)-L-valina (500 miligramos, 2.30 milimoles) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$ 400 MHz) δ: 8.44 (2H, dd, J=6.3 Hz, 1.5 Hz), 6.81 (2H, dd, J=6.3 Hz, 1.5 Hz), 5.33 (1H, d, J=9.5 Hz), 4.72-4.40 (1H, m), 4.49 (1H, dd, J=8.3 Hz, 6.1 Hz), 3.88-3.50 (4H, m), 2.15-1.80 (5H, m), 1.44 (9H, s), 0.97 (3H, d, J=6.8 Hz), 0.90 (3H, d, J=6.8

Hz).

IR (ATR) cm^{-1}: 2965, 1700, 1635, 1590, 1500, 1440, 1365, 1280.

MS (ESI, m/z): 378 $(M+H)^+$.

Ejemplo 41-2

3-hidroxi-N-[(1S)-2-metil-1-({4-[(piridin-4-il)-oxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 2-2, el diclorhidrato de (2S)-3-metil-1-oxo-1-{4-[(piridin-4-il)-oxi]-piperidin-1-il}-butan-2-amina se obtuvo a partir de la N-(terbutoxi-carbonil)-L-valina (500 miligramos, 2.30 milimoles), y a partir del [(1S)-2-metil-1-({4-[(piridin-4-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (940 miligramos, 2.49 milimoles) como una sustancia amorfa. El compuesto resultante (150 miligramos, 0.430 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (81.0 miligramos, 0.430 milimoles), para proporcionar el compuesto del título deseado (104 miligramos, rendimiento del 63 por ciento) como un sólido blanco.

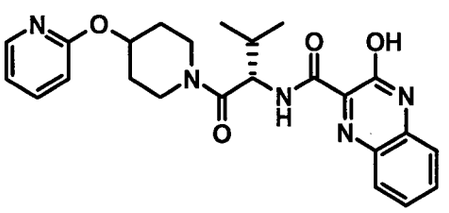
^{1}H-RMN ($CDCl_3$ 400 MHz) δ: 10.16 (1H, s), 8.47 (2H, dt, J=4.6 Hz, 1.2 Hz), 7.98 (1H, dd, J=7.3 Hz, 6.4 Hz), 7.59 (1H, dd, J=7.5 Hz, 7.1 Hz), 7.53 (1H, d, J=8.3 Hz), 7.36 (1H, t, J=7.5 Hz), 6.84 (2H, t, J=6.4 Hz), 5.08 (1H, t, J=7.3 Hz), 4.78-4.68 (1H, m), 4.08-3.99 (1H, m), 3.97-3.63 (3H, m), 2.40-1.86 (5H, m), 1.13 (3H, d, J=6.8 Hz), 1.10 (3H, d, J=6.8 Hz).

IR (ATR) cm^{-1}: 1685, 1630, 1590, 1525, 1495, 1470, 1450, 1275.

MS (ESI, m/z): 450 $(M+H)^+$.

Análisis calculado para $C_{24}H_{27}N_5O_3 \cdot 0.25H_2O$: C, 63.49; H, 6.11; N, 15.43. Encontrado: C, 63.10; H, 6.13; N, 15.34.

Ejemplo 42



3-hidroxi-N-[(1S)-2-metil-1-({4-[(piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

Ejemplo 42-1

[(1S)-2-metil-1-({4-[(piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 2-1, el [(1S)-2-metil-1-({4-[(piridin-2-il)-oxi]-piperidin-1-il]-carbonil}-propil)-carbamato de terbutilo (948 miligramos, rendimiento del 100 por ciento) se obtuvo a partir del diclorhidrato de 2-[(piperidin-4-il)-oxi]-piridina (580 miligramos, 2.30 milimoles), y N-(terbutoxi-carbonil)-L-valina (500 miligramos, 2.30 milimoles) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$ 400 MHz) δ: 8.14-8.11 (1H, m), 7.57 (1H, dt, J=7.1 Hz, 2.0 Hz), 6.86 (1H, dd, J=6.8 Hz, 6.1 Hz), 6.72 (1H, d, J=8.3 Hz), 5.37 (1H, d, J=9.1 Hz), 5.34-5.28 (1H, m), 4.51 (1H, dd, J=8.5 Hz, 5.9 Hz), 3.98-3.73 (2H, m), 3.62-3.42 (2H, m), 2.10-1.73 (5H, m), 1.44 (9H, s), 0.98 (3H, d, J=6.6 Hz), 0.89 (3H, d, J=6.6 Hz).

IR (ATR) cm^{-1}: 2965, 1700, 1635, 1595, 1470, 1430, 1365,

1305.

MS (ESI, m/z): 378 $(M+H)^+$.

Ejemplo 42-2

3-hidroxi-N-[(1S)-2-metil-1-({4-[(piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 2-2, el diclorhidrato de (2S)-3-metil-1-oxo-1-{4-[(piridin-4-il)-oxi]-piperidin-1-il}-butan-2-amina (734 miligramos, rendimiento del 91 por ciento) se obtuvo a partir del [(1S)-2-metil-1-({4-[(piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (948 miligramos, 2.21 milimoles) como una sustancia amorfa. El compuesto resultante (150 miligramos, 0.430 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (81.0 miligramos, 0.430 milimoles), para proporcionar el compuesto del título deseado (71.0 miligramos, rendimiento del 43 por ciento) como un sólido blanco.

^{1}H-RMN ($CDCl_3$ 400 MHz) δ: 12.77 y 10.14 (1H, brs), 8.14 (1H, t, J=4.9 Hz), 7.98 (1H, d, J=8.1 Hz), 7.66-7.50 (3H, m), 7.37 (1H, brs), 6.86 (1H, dd, J=11.7 Hz, 4.9 Hz), 6.73 (1H, t, J=8.8 Hz), 5.40-5.32 (1H, m), 5.09 (1H, t, J=7.1 Hz), 4.10-3.91 (2H, m), 3.82-3.62 (2H, m), 2.39-2.17 (1H, m), 2.12-1.98 (2H, m), 1.95-1.83 (2H, m), 1.11 (6H, d, J=6.6 Hz).

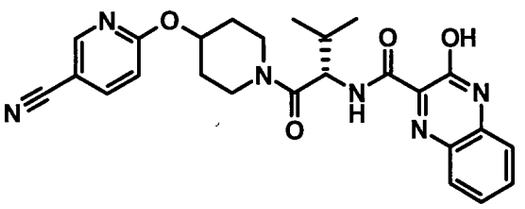
IR (ATR) cm^{-1}: 1685, 1630, 1525, 1470, 1430, 1270, 1250, 1215.

MS (ESI, m/z): 450 $(M+H)^+$.

Análisis calculado para $C_{24}H_{27}N_5O_3 \cdot 0.75H_2O$: C, 62.26; H, 6.20,

N, 15.13. Encontrado: C, 61.95; H, 5.86; N, 15.15.

Ejemplo 43



N-[(1S)-1-({4-[(5-ciano-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 43-1

4-[(5-ciano-piridin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo

El 4-hidroxi-piperidin-1-carboxilato de terbutilo (2.49 gramos, 12.0 milimoles) se agregó a una suspensión en N,N-dimetil-formamida (10 mililitros) de hidruro de sodio al 60 por ciento (419 miligramos, 11.0 milimoles), a 0°C, y la agitación se llevó a cabo a temperatura ambiente durante 30 minutos. Además, a 0°C, se agregó 6-cloro-piridin-3-carbonitrilo (1.43 gramos, 10.0 milimoles), y la agitación se llevó a cabo durante 1.25 horas. Se agregó agua a la solución de la reacción, seguida por extracción con acetato de etilo y el lavado subsiguiente en secuencia con agua y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, para proporcionar el 4-[(5-ciano-piridin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo (2.71 gramos, rendimiento del 89 por ciento) como un sólido blanco.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.45 (1H, dd, J=2.4 Hz, 0.8 Hz), 7.78 (1H, dd, J=8.6 Hz, 2.4 Hz), 6.79 (1H, dd, J=8.6 Hz, 0.8 Hz), 5.32-5.26 (1H, m), 3.81-3.75 (2H, m), 3.32-3.25 (2H, m), 2.01-1.96 (2H, m), 1.77-1.69 (2H, m), 1.47 (9H, s).

MS (ESI, m/z): 304 $(M+H)^+$, 204 $(M-Boc+H)^+$.

Ejemplo 43-2

[(1S)-1-({4-[(5-ciano-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo

Se agregó ácido clorhídrico concentrado (8.9 mililitros) a una solución en etanol (17.8 mililitros) de 4-[(5-ciano-piridin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo (2.71 gramos, 8.93 milimoles), a 0°C, y la agitación se llevó a cabo a temperatura ambiente durante la noche. La capa orgánica se concentró, para proporcionar el diclorhidrato de 6-(piperidin-4-il)-oxi-piridin-3-carbonitrilo (2.34 gramos) como un sólido blanco.

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (2.57 gramos, 13.4 milimoles) se agregó a una solución en cloruro de metileno (90 mililitros) del compuesto resultante (2.34 gramos), N-(terbutoxi-carbonil)-L-valina (1.94 gramos, 8.93 milimoles), monohidrato de 1-hidroxi-benzotriazol (1.45 gramos, 10.7 milimoles), y N-metil-morfolina (4.91 mililitros, 44.7 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a temperatura ambiente durante 3 días. Se agregó agua a la solución de la reacción, seguida por extracción con acetato de etilo y el lavado subsiguiente en secuencia con una solución acuosa saturada de carbonato ácido de

sodio, agua, y una solución salina, y la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, para proporcionar el [(1S)-1-({4-[(5-ciano-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (3.50 gramos, rendimiento del 97 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.46-8.45 (1H, m), 7.79 (1H, dd, J=8.6 Hz. 2.3 Hz), 6.80 (1H, d, J=8.6 Hz), 5.42-5.30 (2H, m), 4.52-4.48 (1H, m), 4.03-3.43 (4H, m), 2.11-1.76 (5H, m), 1.44 (9H, s), 0.97 (3H, d, J=6.6 Hz), 0.90 (3H, d, J=7.0 Hz).

MS (ESI, m/z): 302 $(M-Boc+H)^+$.

Ejemplo 43-3

Diclorhidrato de 6-[(1-L-valil-piperidin-4-il)-oxi]-nicotinonitrilo

De una manera análoga al Ejemplo 29-3, el diclorhidrato de 6-[(1-L-valil-piperidin-4-il)-oxi]-nicotinonitrilo (3.28 gramos, rendimiento del 100 por ciento) se obtuvo a partir del [(1S)-1-({4-(5-ciano-piridin-2-il)-oxi}-piperidin-1-il)-carbonil]-2-metil-propil]-carbamato de terbutilo (3.50 gramos, 8.70 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN (CD_3OD, 400 MHz) δ: 8.54 (1H, d, J=2.4 Hz), 8.00-7.97 (1H, m), 6.94 (1H, dd, J=12.0 Hz, 8.4 Hz), 5.48-5.39 (1H, m), 4.37 (1H, d, J=3.9 Hz), 4.12-3.41 (4H, m), 2.24-1.74 (5H, m), 1.11 (3H, d, J=6.6 Hz), 1.03 (3H, d, J=6.6 Hz).

MS (ESI, m/z): 303 $(M+H)^+$.

413

Ejemplo 43-4

N-[(1S)-1-({4-[(5-ciano-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 29-4, el compuesto del título deseado (182 miligramos, rendimiento del 72 por ciento) se obtuvo a partir del diclorhidrato de 6-[(1-L-valil-piperidin-4-il)-oxi]-nicotinonitrilo (200 miligramos, 0.530 milimoles) como un sólido amarillo.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 12.00 (1H, brs), 10.11 (1H, brs), 8.47 (1H, dd, J=6.0 Hz, 2.4 Hz), 8.04-8.02 (1H, m), 7.82-7.78 (1H, m), 7.63 (1H, brs), 7.44-7.22 (2H, m), 6.82 (1H, t, J=9.6 Hz), 5.45-5.39 (1H, m), 5.08 (1H, t, J=7.6 Hz), 4.11-3.53 (4H, m), 2.35-1.85 (5H, m), 1.10 (5 horas, d, J=6.6 Hz).

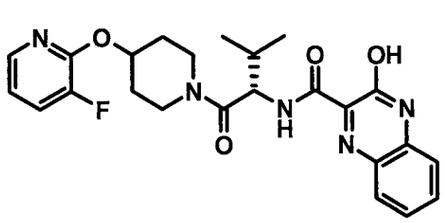
IR (KBr) cm^{-1}: 2965, 2225, 1685, 1630, 1480.

MS (ESI, m/z): 475 $(M+H)^+$, 497 $(M+Na)^+$.

HRMS (ESI, m/z): 497.1920 (Calculado para $C_{25}H_{26}N_6NaO_4$: 497.1913).

Análisis calculado para $C_{25}H_{26}N_6O_4 \cdot 1/4H_2O$: C, 62.68; H, 5.58; N, 17.54. Encontrado: C, 62.76; H, 5.47; N, 17.48.

Ejemplo 44



N-[(1S)-1-({4-[(3-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-

metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 44-1

4-[(3-fluoro-piridin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo

El 4-(metan-sulfoniloxi)-piperidin-1-carboxilato de terbutilo (2.96 gramos, 10.6 milimoles), y carbonato de potasio (2.69 gramos, 19.5 milimoles), se agregaron a una solución en N,N-dimetil-formamida (45 mililitros) de 3-fluoro-2-hidroxi-piridina (1.00 gramos, 8.84 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a 75°C durante la noche. La solución de la reacción se enfrió a temperatura ambiente, y se agregó agua a los residuos resultantes de la concentración, seguido por extracción con cloruro de metileno. Después de que la capa orgánica resultante se secó sobre sulfato de sodio anhidro, el residuo resultante de la concentración se purificó mediante cromatografía en columna de gel de sílice, para proporcionar el 4-[(3-fluoro-piridin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo (1.63 gramos, rendimiento del 62 por ciento) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.88 (1H, d, J=3.9 Hz), 7.33-7.29 (1H, m), 6.84-6.81 (1H, m), 5.32-5.27 (1H, m), 3.81-3.77 (2H, m), 3.33-3.28 (2H, m), 2.02-1.98 (2H, m), 1.82-1.75 (2H, m), 1.47 (9H, s).

MS (ESI, m/z): 241 $(M\text{-}tBu+H)^+$.

Ejemplo 44-2

[(1S)-1-({4-[(3-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo

Se agregó ácido clorhídrico concentrado (2.7 mililitros) a una

solución en etanol (5.4 mililitros) de 4-[(3-fluoro-piridin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo (800 miligramos, 2.70 milimoles), a 0°C, y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se concentró, para proporcionar el diclorhidrato de 3-fluoro-2-[(piperidin-4-il)-oxi]-piridina (633 miligramos) como un sólido blanco.

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (776 miligramos, 4.05 milimoles) se agregó a una solución en cloruro de metileno (27 mililitros) del compuesto resultante (633 miligramos), N-(terbutoxi-carbonil)-L-valina (586 miligramos, 2.70 milimoles), monohidrato de 1-hidroxi-benzotriazol (438 miligramos, 3.24 milimoles), y N-metil-morfolina (1.48 mililitros, 13.5 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a temperatura ambiente durante la noche. Se agregó agua a la solución de la reacción, seguida por extracción con acetato de etilo y el lavado subsiguiente en secuencia con una solución acuosa saturada de carbonato ácido de sodio, agua, y una solución salina, y la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, para proporcionar el [(1S)-1-({4-[(3-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (1.00 gramos, rendimiento del 94 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.90-7.88 (1H, m), 7.35-7.31 (1H, m), 6.87-6.84 (1H, m), 5.42-5.34 (2H, m), 4.53-4.50 (1H, m), 3.98-

3.46 (4H, m), 2.11-1.80 (5H, m), 1.44 (9H, s), 0.98 (3H, d, J=5.5 Hz), 0.90 (3H, dd, J=5.5 Hz, 2.0 Hz).

MS (ESI, m/z): 295 $(M-Boc+H)^+$.

Ejemplo 44-3

Diclorhidrato de (2S)-1-{4-[(3-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina

De una manera análoga al Ejemplo 29-3, el diclorhidrato de (2S)-1-{4-[(3-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina (975 miligramos, rendimiento del 100 por ciento) se obtuvo a partir del [(1S)-1-({4-[(3-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (1.00 gramos, 2.53 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN (CD_3OD, 400 MHz) δ: 7.92 (1H, d, J=4.8 Hz), 7.53-7.48 (1H, m), 6.99-6.95 (1H, m), 5.45-5.39 (1H, m), 4.37 (1H, d, J=5.2 Hz), 4.08-3.45 (4H, m), 2.24-2.01 (3H, m), 1.95-1.77 (2H, m), 1.12 (3H, d, J=6.6 Hz), 1.03 (3H, d, J=7.0 Hz).

MS (ESI, m/z): 296 $(M+H)^+$.

Ejemplo 44-4

N-[(1S)-1-({4-[(3-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 29-4, el compuesto del título deseado (189 miligramos, rendimiento del 74 por ciento) se obtuvo a partir del diclorhidrato de (2S)-1-{4-[(3-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina (200 miligramos, 0.540 milimoles) como un sólido amarillo.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 12.20 (1H, brs), 10.13 (1H, brs), 8.02 (1H, brs), 7.92-7.89 (1H, m), 7.62-7.26 (4H, m), 6.89-6.84 (1H, m), 5.44 (1H, brs), 5.13-5.09 (1H, m), 4.07-3.65 (4H, m), 2.37-1.90 (5H, m), 1.11 (6H, d, J=6.3 Hz).

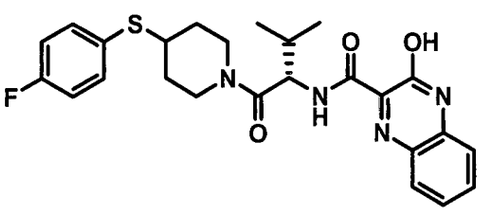
IR (KBr) cm^{-1}: 2965, 1685, 1635, 1530, 1460.

MS (ESI, m/z): 490 $(M+Na)^+$.

HRMS (ESI, m/z): 490.1852 (Calculado para $C_{25}H_{26}FN_5NaO_4$: 490.1867).

Análisis calculado para $C_{25}H_{26}FN_5O_4$: C, 61.66; H, 5.61; N, 14.98; F, 4.06. Encontrado: C, 61.54; H, 5.51; N, 14.95; F, 4.03.

Ejemplo 45



N-[(1S)-1-({4-[(4-fluoro-fenil)-tio]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 45-1

[(1S)-1-({4-[(4-fluoro-fenil)-tio]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (947 miligramos, 4.94 milimoles) se agregó a una solución en cloruro de metileno (41 mililitros) de clorhidrato de 4-[(4-fluoro-fenil)-sulfanil]-piperidina (1.02 gramos, 4.12 milimoles), N-(terbutoxi-carbonil)-L-valina (894 miligramos, 4.12 milimoles), monohidrato de

1-hidroxi-benzotriazol (612 miligramos, 4.53 milimoles), y N-metil-morfolina (1.36 mililitros, 12.4 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a temperatura ambiente durante la noche. Se agregó agua a la solución de la reacción, seguida por extracción con acetato de etilo y el lavado subsiguiente en secuencia con una solución acuosa saturada de carbonato ácido de sodio, agua, y una solución salina, y la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, para proporcionar el [(1S)-1-({4-[(4-fluoro-fenil)-tio]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (1.64 gramos, rendimiento del 97 por ciento) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.43 (2H, dd, J=8.6 Hz, 5.6 Hz), 7.02 (2H, td, J=8.6 Hz, 2.4 Hz), 5.31 (1H, t, J=7.8 Hz), 4.46-4.27 (2H, m), 3.96-3.85 (1H, m), 3.25-3.12 (2H, m), 3.03-2.87 (1H, m), 2.03-1.84 (3H, m), 1.57-1.46 (2H, m), 1.43 (9H, d, J=6.0 Hz), 0.94 (3H, dd, J=8.4 Hz, 6.8 Hz), 0.86 (3H, dd, J=6.8 Hz, 4.4 Hz).

MS (ESI, m/z): 312 $(M\text{-}Boc+H)^+$.

Ejemplo 45-2

N-[(1S)-1-({4-[(4-fluoro-fenil)-tio]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 2-2, se obtuvo el compuesto del título deseado (213 miligramos, rendimiento del 73 por ciento) a partir del [(1S)-1-({4-[(4-fluoro-fenil)-tio]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (248 miligramos,

0.600 milimoles) como un sólido amarillo.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 12.78-12.45 (1H, m), 10.13 (1H, brs), 8.04-7.98 (1H, m), 7.62-6.98 (7H, m), 5.08-5.01 (1H, m), 4.48-4.16 (2H, m), 3.43-3.00 (3H, m), 2.29-1.55 (5H, m), 1.12-1.05 (6H, m).

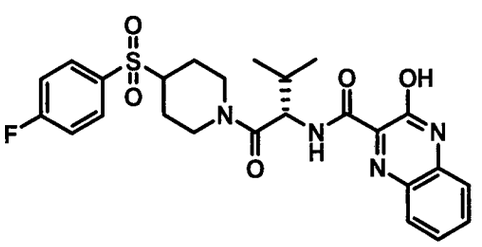
IR (KBr) cm^{-1}: 2965, 1685, 1635, 1525, 1490.

MS (ESI, m/z): 505 $(M+Na)^+$.

HRMS (ESI, m/z): 505.1675 (Calculado para $C_{25}H_{27}FN_4NaO_3S$: 505.1686).

Análisis calculado para $C_{25}H_{27}FN_4O_3S$: C, 62.22; H, 5.64; N, 11.61; F, 3.94; S, 6.64. Encontrado: C, 62.03; H, 5.36; N, 11.59; F, 4.24; S, 6.82.

Ejemplo 46



N-[(1S)-1-({4-[(4-fluoro-fenil)-sulfonil]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 46-1

[(1S)-1-({4-[(4-fluoro-fenil)-sulfonil]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo

se agregó ácido m-cloro-perbenzoico (504 miligramos, 1.90 milimoles) a una solución en cloruro de metileno (6.3 mililitros) de

[(1S)-1-({4-[(4-fluoro-fenil)-tio]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (260 miligramos, 0.630 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a temperatura ambiente durante 30 minutos. Se agregó ácido m-cloro-perbenzoico adicional (504 miligramos, 1.90 milimoles) a temperatura ambiente, y la agitación se llevó a cabo a temperatura ambiente durante 30 minutos. La solución de la reacción se diluyó con cloruro de metileno, seguido por lavado en secuencia con una solución acuosa de hidróxido de sodio 1N y solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, para proporcionar el [(1S)-1-({4-[(4-fluoro-fenil)-sulfonil]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (282 miligramos, rendimiento del 100 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.92-7.86 (2H, m), 7.30-7.24 (2H, m), 5.26-5.19 (1H, m), 4.79-4.66 (1H, m), 4.43-4.35 (1H, m), 4.17-4.08 (1H, m), 3.16-2.98 (2H, m), 2.65-2.51 (1H, m), 2.10-1.57 (5H, m), 1.41 (9H, s), 0.94-0.85 (6H, m).

MS (ESI, m/z): 343 $(M\text{-}Boc+H)^+$.

Ejemplo 46-2

N-[(1S)-1-({4-[(4-fluoro-fenil)-sulfonil]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 2-2, el compuesto del título deseado (221 miligramos, rendimiento del 68 por ciento) se obtuvo a

partir del [(1S)-1-({4-[(4-fluoro-fenil)-sulfonil]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (280 miligramos, 0.630 milimoles) como un sólido amarillo.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 12.36 (1H, brs), 10.12 (1H, brs), 8.08-7.21 (8H, m), 5.07-4.74 (2H, m), 4.42 (1H, brs), 3.29-3.10 (2H, m), 2.77-2.63 (1H, m), 2.31-2.05 (3H, m), 1.86-1.57 (2H, m), 1.10-1.03 (6H, m).

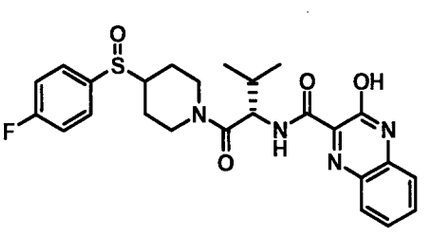
IR (KBr) cm^{-1}: 3470, 2965, 1690, 1645, 1530.

MS (ESI, m/z): 537 $(M+Na)^+$.

HRMS (ESI, m/z): 537.1587 (Calculado para $C_{25}H_{27}FN_4NaO_5S$: 537.1584).

Análisis calculado para $C_{25}H_{27}FN_4O_5S$: C, 58.35; H, 5.29; N, 10.89; F, 3.69; S, 6.23. Encontrado:: C, 58.09; H, 5.26; N, 10.82; F, 3.72; S, 6.28.

Ejemplo 47



N-[(1S)-1-({4-[(4-fluoro-fenil)-sulfinil]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 47-1

[(1S)-1-({4-[(4-fluoro-fenil)-sulfinil]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo

Se agregó ácido m-cloro-perbenzoico (268 miligramos, 1.01

milimoles) a una solución en cloruro de metileno (10 mililitros) de [(1S)-1-({4-[(4-fluoro-fenil)-tio]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (415 miligramos, 1.01 milimoles), a 0°C, y la agitación se llevó a cabo a 0°C durante 1 hora. Se agregó una solución acuosa de hidróxido de sodio 1N a la solución de la reacción, seguido por extracción con cloruro de metileno. Después de que el extracto se lavó con solución salina, la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, para proporcionar el [(1S)-1-({4-[(4-fluoro-fenil)-sulfinil]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (379 miligramos, rendimiento del 88 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.62-7.58 (2H, m), 7.26-7.22 (2H, m), 5.30-5.24 (1H, m), 4.75-4.62 (1H, m), 4.44-4.38 (1H, m), 4.15-4.04 (1H, m), 3.15-3.00 (1H, m), 2.82-2.56 (2H, m), 1.93-1.54 (5H, m), 1.44-1.41 (9H, m), 0.96-0.84 (6H, m).

MS (ESI, m/z): 328 $(M\text{-}Boc+H)^+$.

Ejemplo 47-2

N-[(1S)-1-({4-[(4-fluoro-fenil)-sulfinil]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 2-2, el compuesto del título deseado (203 miligramos, rendimiento del 46 por ciento) se obtuvo a partir del [(1S)-1-({4-[(4-fluoro-fenil)-sulfinil]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (377 miligramos, 0.880 mili-

moles) como un sólido amarillo.

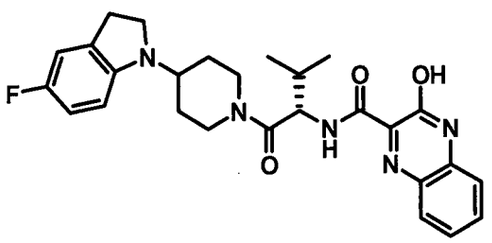
^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 9.95 (1H, brs), 8.05-8.00 (1H, m), 7.64-7.20 (7H, m), 5.06-4.98 (1H, m), 4.85-4.69 (1H, m), 4.40-4.35 (1H, m), 3.72 (1H, t, J=3.6 Hz), 3.32-3.12 (1H, m), 2.81-2.67 (2H, m), 2.42-1.55 (5H, m), 1.10-1.02 (6H, m).

IR (KBr) cm^{-1}: 2960, 1685, 1640, 1530, 1450.

MS (ESI, m/z): 521 $(M+Na)^+$.

HRMS (ESI, m/z): 521.1623 (Calculado para $C_{25}H_{27}FN_4NaO_4S$: 521.1635).

Ejemplo 48



N-[(1S)-1-{[4-(5-fluoro-2,3-dihidro-1H-indol-1-il)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 48-1

4-(5-fluoro-2,3-dihidro-1H-indol-1-il)-piperidin-1-carboxilato de terbutilo

Se agregó triacetoxi-borohidruro de sodio (1.79 gramos, 8.04 milimoles) a una solución en cloruro de metileno (33.5 mililitros) de 5-fluoro-2,3-dihidro-1H-indol (919 miligramos, 6.70 milimoles), 4-oxo-piperidin-1-carboxilato de terbutilo (1.35 gramos, 6.70 milimoles), y ácido acético (0.384 mililitros, 6.70 milimoles), a 0°C, y la agitación

se llevó a cabo a temperatura ambiente durante 3 horas. A la solución de la reacción se le agregó una solución acuosa saturada de carbonato ácido de sodio, seguido por extracción con cloruro de metileno. El extracto se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, para proporcionar el 4-(5-fluoro-2,3-dihidro-1H-indol-1-il)-piperidin-1-carboxilato de terbutilo (1.68 gramos, rendimiento del 78 por ciento).

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 6.80 (1H, dd, J=8.4 Hz, 2.8 Hz), 6.76-6.71 (1H, m), 6.29 (1H, dd, J=8.6 Hz, 4.3 Hz), 4.25 (2H, brs), 3.47-3.39 (1H, m), 3.33 (2H, t, J=8.2 Hz), 2.92 (2H, t, J=8.2 Hz), 2.80-2.73 (2H, m), 1.77 (2H, d, J=12.5 Hz), 1.55-1.48 (2H, m), 1.47 (9H, s).

MS (ESI, m/z): 220 $(M\text{-}tBu+H)^+$.

Ejemplo 48-2

N-[(1S)-1-{[4-(5-fluoro-2,3-dihidro-1H-indol-1-il)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 29-2, el N-[(1S)-1-{[4-(5-fluoro-2,3-dihidro-1H-indol-1-il)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo (2.05 gramos, rendimiento del 93 por ciento) se obtuvo a partir del 4-(5-fluoro-2,3-dihidro-1H-indol-1-il)-piperidin-1-carboxilato de terbutilo (1.68 gramos, 5.24 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 6.81 (1H, dd, J=8.4 Hz, 2.4 Hz), 6.78-6.71 (1H, m), 6.33-6.28 (1H, m), 5.34 (1H, d, J=8.4 Hz), 4.80-4.75 (1H, m), 4.52-4.48 (1H, m), 4.13-4.07 (1H, m), 3.58-3.50 (1H,

m), 3.31 (2H, dd, J=16.8 Hz, 8.4 Hz), 3.19-3.09 (1H, m), 2.94-2.90 (2H, m), 2.68-2.60 (1H, m), 1.96-1.82 (3H, m), 1.69-1.49 (2H, m), 1.44 (9H, s), 0.97 (3H, dd, J=9.2 Hz, 6.8 Hz), 0.89 (3H, dd, J=9.6 Hz, 6.8 Hz).

MS (ESI, m/z): 420 $(M+H)^+$.

Ejemplo 48-3

Diclorhidrato de (2S)-1-[4-(5-fluoro-2,3-dihidro-1H-indol-1-il)-piperidin-1-il]-3-metil-1-oxobutan-2-amina

De una manera análoga al Ejemplo 29-3, el diclorhidrato de (2S)-1-[4-(5-fluoro-2,3-dihidro-1H-indol-1-il)-piperidin-1-il]-3-metil-1-oxobutan-2-amina (1.96 gramos, rendimiento del 100 por ciento) se obtuvo a partir del [(1S)-1-{[4-(5-fluoro-2,3-dihidro-1H-indol-1-il)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo (2.05 gramos, 4.89 milimoles) como una sustancia amorfa color rojo pálido.

^{1}H-RMN (CD_3OD, 400 MHz) δ: 7.71-7.67 (1H, m), 7.31 (1H, d, J=8.2 Hz), 7.28-7.23 (1H, m), 4.70 (1H, d, J=13.6 Hz), 4.40-4.05 (5H, m), 3.36 (2H, t, J=7.2 Hz), 3.31-3.24 (1H, m), 2.81 (1H, t, J=12.8 Hz), 2.25-1.65 (5H, m), 1.14-1.00 (6H, m).

MS (ESI, m/z): 320 $(M+H)^+$.

Ejemplo 48-4

N-[(1S)-1-{[4-(5-fluoro-2,3-dihidro-1H-indol-1-il)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 29-4, el compuesto del título deseado (171 miligramos, rendimiento del 68 por ciento) se obtuvo a partir del diclorhidrato de (2S)-1-[4-(5-fluoro-2,3-dihidro-1H-

indol-1-il)-piperidin-1-il]-3-metil-1-oxobutan-2-amina (200 miligramos, 0.510 milimoles) como un sólido amarillo.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 12.45 (1H, brs), 10.18 (1H, brs), 8.04-8.01 (1H, m), 7.64-7.39 (3H, m), 6.83-6.72 (2H, m), 6.35-6.30 (1H, m), 5.17-5.07 (1H, m), 4.90-4.86 (1H, m), 4.38 (1H, brs), 3.62-3.56 (1H, m), 3.38-3.21 (3H, m), 2.95 (1H, t, J=6.6 Hz), 2.90 (1H, t, J=6.6 Hz), 2.74 (1H, t, J=10.0 Hz), 2.36-2.28 (1H, m), 2.03-1.60 (4H, m), 1.16-1.09 (6H, m).

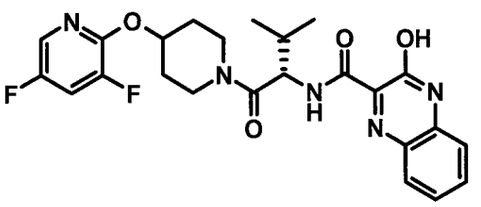
IR (KBr) cm^{-1}: 2960, 1685, 1640, 1490, 1475.

MS (ESI, m/z): 492 $(M+H)^+$, 514 $(M+Na)^+$.

HRMS (ESI, m/z): 492.2422 (Calculado para $C_{27}H_{31}FN_5O_3$: 492.2411).

Análisis calculado para $C_{27}H_{30}FN_5O_3$: C, 65.97; H, 6.15; N, 14.25; F, 3.86. Encontrado:: C, 65.74; H, 5.92; N, 14.07; F, 3.77.

Ejemplo 49



N-[(1S)-1-({4-[(3,5-difluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil}-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 49-1

4-[(3,5-difluoro-piridin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo y 4-[(2,3-difluoro-piridin-5-il)-oxi]-piperidin-1-carboxilato de terbutilo

El 4-hidroxi-piperidin-1-carboxilato de terbutilo (1.38 gramos,

6.63 milimoles) se agregó a una suspensión en N,N-dimetil-formamida (5.5 mililitros) de hidruro de sodio al 60 por ciento (232 miligramos, 6.08 milimoles), a 0°C, y la agitación se llevó a cabo a temperatura ambiente durante 30 minutos. Además, a 0°C, se agregó 2,3,5-trifluoro-piridina (750 miligramos, 5.52 milimoles), y la agitación se llevó a cabo a temperatura ambiente durante 2 horas. Se agregó agua a la solución de la reacción, seguida por extracción con acetato de etilo y el lavado subsiguiente en secuencia con agua y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, para proporcionar el 4-[(3,5-difluoro-piridin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo (654 miligramos, rendimiento del 38 por ciento) como un aceite incoloro, y el 4-[(2,3-difluoro-piridin-5-il)-oxi]-piperidin-1-carboxilato de terbutilo (1.00 gramos, rendimiento del 58 por ciento) como un aceite incoloro.

4-[(3,5-difluoro-piridin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.80 (1H, d, J=2.8 Hz), 7.22-7.17 (1H, m), 5.26-5.20 (1H, m), 3.81-3.75 (2H, m), 3.33-3.27 (2H, m), 2.02-1.96 (2H, m), 1.81-1.73 (2H, m), 1.47 (9H, s).

MS (ESI, m/z): 215 $(M\text{-}Boc+H)^+$.

4-[(2,3-difluoro-piridin-5-il)-oxi]-piperidin-1-carboxilato de terbutilo

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.63 (1H, t, J=2.4 Hz), 7.12-7.07 (1H, m), 4.52-4.46 (1H, m), 3.73-3.67 (2H, m), 3.41-3.34 (2H, m), 1.97-1.90 (2H, m), 1.84-1.76 (2H, m), 1.47 (9H, s).

MS (ESI, m/z): 215 $(M-Boc+H)^+$.

Ejemplo 49-2

[(1S)-1-({4-[(3,5-difluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 29-2, el [(1S)-1-({4-[(3,5-difluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (803 miligramos, rendimiento del 86 por ciento) se obtuvo a partir del 4-[(3,5-difluoro-piridin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo (654 miligramos, 2.08 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.80 (1H, t, J=3.2 Hz), 7.24-7.19 (1H, m), 5.37-5.28 (2H, m), 4.53-4.48 (1H, m), 3.97-3.45 (4H, m), 2.10-1.78 (5H, m), 1.44 (9H, s), 0.98-0.88 (6H, m).

MS (ESI, m/z): 414 $(M+H)^+$.

Ejemplo 49-3

diclorhidrato de (2S)-1-{4-[(3,5-difluoro-piridin-2-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina

De una manera análoga al Ejemplo 29-3, el diclorhidrato de (2S)-1-{4-[(3,5-difluoro-piridin-2-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina (673 miligramos, rendimiento del 90 por ciento) se obtuvo a partir del [(1S)-1-({4-[(3,5-difluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil]-2-metil-propil}-carbamato de terbutilo (803 miligramos, 1.94 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN (CD_3OD, 400 MHz) δ: 7.88 (1H, d, J=2.4 Hz), 7.57-7.51 (1H, m), 5.42-5.34 (1H, m), 4.35 (1H, d, J=5.2 Hz), 4.08-3.45 (4H,

m), 2.25-1.75 (5H, m), 1.11 (3H, d, J=7.0 Hz), 1.03 (3H, d, J=7.0 Hz).

MS (ESI, m/z): 314 $(M+H)^+$.

Ejemplo 49-4

N-[(1S)-1-({4-[(3,5-difluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 29-4, el compuesto del título deseado (148 miligramos, rendimiento del 59 por ciento) se obtuvo a partir del diclorhidrato de (2S)-1-{4-[(3,5-difluoro-piridin-2-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina (200 miligramos, 0.520 milimoles) como un sólido amarillo.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 12.58 (1H, brs), 10.16 (1H, brs), 8.00 (1H, brs), 7.81 (1H, dd, J=7.0 Hz, 2.0 Hz), 7.62-7.19 (4H, m), 5.40-5.33 (1H, m), 5.11-5.08 (1H, m), 4.04-3.66 (4H, m), 2.35-1.88 (5H, m), 1.14-1.10 (6H, m).

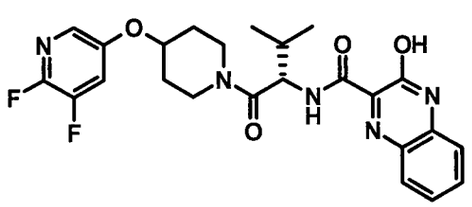
IR (KBr) cm^{-1}: 2965, 1690, 1640, 1470, 1440.

MS (ESI, m/z): 486 $(M+H)^+$, 508 $(M+Na)^+$.

HRMS (ESI, m/z): 486.1979 (Calculado para $C_{24}H_{26}F_2N_5O_4$: 486.1953).

Análisis calculado para $C_{24}H_{25}F_2N_5O_4$: C, 59.38; H, 5.19; N, 14.43; F, 7.83. Encontrado: C, 59.56; H, 5.15; N, 14.41; F, 8.09.

Ejemplo 50



N-[(1S)-1-({4-[(2,3-difluoro-piridin-5-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 50-1

[(1S)-1-({4-[(2,3-difluoro-piridin-5-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 29-2, el [(1S)-1-({4-[(2,3-difluoro-piridin-5-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (1.13 gramos, rendimiento del 89 por ciento) se obtuvo a partir del 4-[(2,3-difluoro-piridin-5-il)-oxi]-piperidin-1-carboxilato de terbutilo (893 miligramos, 2.84 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.66-7.64 (1H, m), 7.10 (1H, td, J=8.0 Hz, 2.8 Hz), 5.33-5.29 (1H, m), 4.63-4.46 (2H, m), 3.90-3.48 (4H, m), 2.06-1.82 (5H, m), 1.44 (9H, s), 0.97 (3H, d, J=6.6 Hz), 0.90 (3H, d, J=6.6 Hz).

MS (ESI, m/z): 314 $(M\text{-}Boc+H)^+$.

Ejemplo 50-2

diclorhidrato de (2S)-1-{4-[(2,3-difluoro-piridin-5-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina

De una manera análoga al Ejemplo 29-3, el diclorhidrato de (2S)-1-{4-[(2,3-difluoro-piridin-5-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina (968 miligramos, rendimiento del 92 por ciento) se obtuvo a partir del [(1S)-1-({4-[(2,3-difluoro-piridin-5-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil}-carbamato de terbutilo (1.13 gramos,

2.73 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN (CD_3OD, 400 MHz) δ: 7.65-7.59 (2H, m), 4.82-4.74 (1H, m), 4.35 (1H, d, J=4.0 Hz), 4.04-3.59 (3H, m), 3.53-3.47 (1H, m), 2.24-2.16 (1H, m), 2.12-1.99 (2H, m), 1.90-1.75 (2H, m), 1.11 (3H, d, J=5.6 Hz), 1.02 (3H, d, J=5.6 Hz).

MS (ESI, m/z): 314 $(M+H)^+$.

Ejemplo 50-3

N-[(1S)-1-({4-[(2,3-difluoro-piridin-5-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 29-4, el compuesto del título deseado (196 miligramos, rendimiento del 78 por ciento) se obtuvo a partir del diclorhidrato de (2S)-1-{4-[(2,3-difluoro-piridin-5-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina (200 miligramos, 0.520 milimoles) como un sólido amarillo.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 12.55 (1H, brs), 10.17 (1H, brs), 8.00 (1H, dd, J=12.6 Hz, 6.6 Hz), 7.66-7.39 (4H, m), 7.16-7.11 (1H, m), 5.07 (1H, q, J=5.7 Hz), 4.67-4.60 (1H, m), 4.12-3.63 (4H, m), 2.36-1.93 (5H, m), 1.15-1.09 (6H, m).

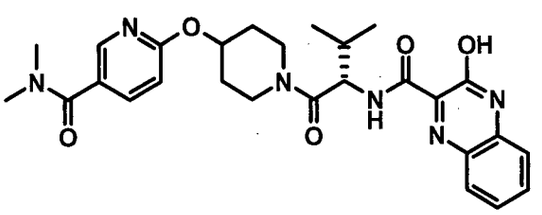
IR (KBr) cm^{-1}: 2965, 1690, 1630, 1525, 1460.

MS (ESI, m/z): 486 $(M+H)^+$, 508 $(M+Na)^+$.

HRMS (ESI, m/z): 486.1944 (Calculado para $C_{24}H_{26}F_2N_5O_4$: 486.1953).

Análisis calculado para $C_{24}H_{25}F_2N_5O_4$: C, 59.38; H, 5.19; N, 14.43; F, 7.83. Encontrado: C, 59.29; H, 5.11; N, 14.42; F, 7.58.

Ejemplo 51



N-{(1S)-1-[(4-{[5-(Dimetil-carbamoil)-piridin-2-il]-oxi}-piperidin-1-il)-carbonil]-2-metil-propil}-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 51-1

6-cloro-N,N-dimetil-nicotinamida

Una solución en tetrahidrofurano (14.2 mililitros, 28.4 milimoles) de N,N-dimetil-amina 2M se agregó a una solución en cloruro de metileno (17 mililitros) de cloruro de 6-cloro-nicotinilo (1.00 gramos, 5.68 milimoles), a 0°C, y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se concentró, y el residuo resultante se diluyó con cloruro de metileno, seguido por lavado en secuencia con agua y una solución salina, y la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, para proporcionar la 6-cloro-N,N-dimetil-nicotinamida (1.02 gramos, rendimiento del 97 por ciento) como un aceite color rojo pálido.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.47 (1H, d, J = 2.4 Hz), 7.75 (1H, dd, J = 8.2 Hz, 2.4 Hz), 7.40 (1H, d, J = 8.2 Hz), 3.13 (3H, s), 3.03 (3H, s).

MS (ESI, m/z): 185 $(M+H)^+$.

Ejemplo 51-2

4-{[5-(dimetil-carbamoil)-piridin-2-il]-oxi}-piperidin-1-carboxilato de terbutilo

El 4-hidroxi-piperidin-1-carboxilato de terbutilo (1.38 gramos, 6.63 milimoles) se agregó a una suspensión en N,N-dimetil-formamida (3.0 mililitros) de hidruro de sodio al 60 por ciento (232 miligramos, 6.08 milimoles), a 0°C, y la agitación se llevó a cabo a temperatura ambiente durante 30 minutos. Además, a 0°C, se agregó una solución en N,N-dimetil-formamida (2.5 mililitros) de 6-cloro-N,N-dimetil-nicotinamida (1.02 gramos, 5.52 milimoles), y la agitación se llevó a cabo a temperatura ambiente durante 3 horas. Se agregó agua a la solución de la reacción, seguida por extracción con acetato de etilo, el extracto se lavó en secuencia con agua y una solución salina, y la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, para proporcionar el 4-{[5-(dimetil-carbamoil)-piridin-2-il]-oxi}-piperidin-1-carboxilato de terbutilo (1.63 gramos, rendimiento del 84 por ciento) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.26-8.25 (1H, m), 7.70-7.67 (1H, m), 6.73 (1H, d, J=8.6 Hz), 5.29-5.22 (1H, m), 3.80-3.76 (2H, m), 3.32-3.26 (2H, m), 3.13-3.03 (6H, m), 2.01-1.96 (2H, m), 1.74-1.60 (2H, m), 1.47 (9H, s).

MS (ESI, m/z): 350 $(M+H)^+$.

Ejemplo 51-3

{(1S)-1-[(4-{[5-(dimetil-carbamoil)-piridin-2-il]-oxi}-piperidin-1-il)-carbonil]-2-metil-propil}-carbamato de terbutilo

De una manera análoga al Ejemplo 29-2, el {(1S)-1-[(4-{[5-(dimetil-carbamoil)-piridin-2-il]-oxi}-piperidin-1-il)-carbonil]-2-metil-propil}-carbamato de terbutilo (1.57 gramos, rendimiento del 78 por ciento) se obtuvo a partir del 4-{[5-(dimetil-carbamoil)-piridin-2-il]-oxi}-piperidin-1-carboxilato de terbutilo (1.56 gramos, 4.46 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.25-8.25 (1H, m), 7.71-7.68 (1H, m), 6.74 (1H, d, J=6.6 Hz), 5.38-5.32 (2H, m), 4.53-4.50 (1H, m), 3.99-3.44 (4H, m), 3.09 (6H, brs), 2.09-1.80 (5H, m), 1.44 (9H, s), 0.98 (3H, d, J=5.6 Hz), 0.89 (3H, d, J=5.2 Hz).

MS (ESI, m/z): 349 $(M\text{-}Boc+H)^+$.

Ejemplo 51-4

Diclorhidrato de N,N-dimetil-6-[(1-L-valil-piperidin-4-il)-oxi]-nicotinamida

De una manera análoga al Ejemplo 29-3, el diclorhidrato de N,N-dimetil-6-[(1-L-valil-piperidin-4-il)-oxi]-nicotinamida (1.61 gramos, rendimiento del 100 por ciento) se obtuvo a partir del {(1S)-1-[(4-{[5-(dimetil-carbamoil)-piridin-2-il]-oxi}-piperidin-1-il)-carbonil]-2-metil-propil}-carbamato de terbutilo (1.57 gramos, 3.50 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN (CD_3OD, 400 MHz) δ: 8.39 (1H, t, J=3.2 Hz), 8.08 (1H, dq, J=8.8 Hz, 2.4 Hz), 7.22 (1H, t, J=8.8 Hz), 5.42-5.32 (1H, m), 4.38

(1H, d, J=4.3 Hz), 4.13-3.44 (4H, m), 3.09 (6H, d, J=10.9 Hz), 2.25-1.81 (5H, m), 1.12 (3H, d, J=7.0 Hz), 1.03 (3H, d, J=6.6 Hz).

MS (ESI, m/z): 349 $(M+H)^+$.

Ejemplo 51-5

N-{(1S)-1-[(4-{[5-(Dimetil-carbamoil)-piridin-2-il]-oxi}-piperidin-1-il)-carbonil]-2-metil-propil}-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 29-4, el compuesto del título deseado (157 miligramos, rendimiento del 64 por ciento) se obtuvo a partir del diclorhidrato de N,N-dimetil-6-[(1-L-valil-piperidin-4-il)-oxi]-nicotinamida (200 miligramos, 0.470 milimoles) como un sólido amarillo.

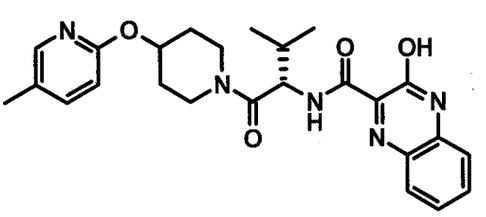
^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 12.73 (1H, brs), 10.19 (1H, brs), 8.27 (1H, s), 8.00 (1H, d, J=7.4 Hz), 7.74-7.27 (4H, m), 6.79-6.73 (1H, m), 5.39 (1H, brs), 5.10 (1H, t, J=7.0 Hz), 4.11-3.60 (4H, m), 3.10 (6H, s), 2.35-1.89 (5H, m), 1.14-1.10 (6H, m);

IR (KBr) cm^{-1}: 3470, 2960, 1690, 1635, 1600, 1475.

MS (ESI, m/z): 521 $(M+H)^+$, 543 $(M+Na)^+$.

HRMS (ESI, m/z): 521.2527 (Calculado para $C_{27}H_{33}N_6O_5$: 521.2512).

Ejemplo 52



3-hidroxi-N-[(1S)-1-({4-[(5-metil-piridin-2-il)-oxi]-piperidin-1-il}-

carbonil)-2-metil-propil]-quinoxalin-2-carboxamida

Una solución al 40 por ciento en tolueno de azodicarboxilato de di-isopropilo (2.10 mililitros, 3.99 milimoles) se agregó a una solución en tolueno (15 mililitros) de {(1S)-1-[(4-hidroxi-piperidin-1-il)-carbonil]-2-metil-propil}-carbamato de terbutilo (1.00 gramos, 3.33 milimoles), 2-hidroxi-5-metil-piridina (400 miligramos, 3.66 milimoles), y trifenil-fosfina (1.05 gramos, 3.99 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, para proporcionar el [(1S)-1-({4-[(5-metil-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (2.06 gramos) como una mezcla con impurezas. Este producto se utilizó como estaba en la siguiente reacción sin mayor purificación.

Se agregó ácido clorhídrico concentrado (1.7 mililitros) a una solución en etanol (3.4 mililitros) de la mezcla resultante (2.06 gramos), a 0°C, y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se concentró, y el residuo resultante se diluyó con agua, y se lavó con acetato de etilo. Se agregó una solución acuosa saturada de carbonato ácido de sodio a la capa acuosa, seguida por extracción con acetato de etilo. La capa orgánica resultante se secó sobre sulfato de sodio anhidro, y entonces se concentró, para proporcionar la (2S)-3-metil-1-{4-[(5-metil-piridin-2-il)-oxi]-piperidin-1-il}-1-oxobutan-2-amina (815 mili-

gramos).

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (157 miligramos, 0.820 milimoles) se agregó a una solución en cloruro de metileno (6.9 mililitros) del compuesto resultante (200 miligramos), ácido 3-hidroxi-quinoxalin-2-carboxílico (135 miligramos, 0.690 milimoles), monohidrato de 1-hidroxi-benzotriazol (102 miligramos, 0.760 milimoles), y N-metil-morfolina (0.226 mililitros, 2.06 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a temperatura ambiente durante la noche. Se agregó agua a la solución de la reacción, seguida por extracción con cloruro de metileno y el lavado subsiguiente en secuencia con una solución acuosa saturada de carbonato ácido de sodio, agua, y una solución salina, y la capa orgánica resultante se secó sobre sulfato de sodio anhidro. Después de que la capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice y tamización molecular, el residuo resultante de la concentración se suspendió en un solvente mixto de etanol/dietil-éter, y la sustancia sólida se recolectó mediante filtración, para proporcionar el compuesto del título deseado (161 miligramos, 10 por ciento) como un sólido amarillo.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 12.59 (1H, brs), 10.05 (1H, brs), 8.00 (1H, d, J=6.6 Hz), 7.95-7.93 (1H, m), 7.62-7.36 (4H, m), 6.64 (1H, dd, J=12.0 Hz, 8.4 Hz), 5.32-5.27 (1H, m), 5.13-5.09 (1H, m), 4.05-3.91 (2H, m), 3.77-3.63 (2H, m), 2.32-1.85 (8H, m), 1.10 (6H, d, J=6.6 Hz).

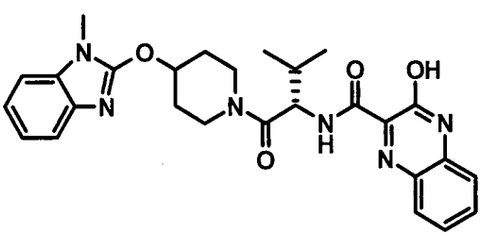
IR (KBr) cm^{-1}: 3440, 2965, 1690, 1640, 1485.

MS (ESI, m/z): 464 $(M+H)^+$, 486 $(M+Na)^+$.

HRMS (ESI, m/z): 464.2319 (Calculado para $C_{25}H_{30}N_5O_4$: 464.2298).

Análisis calculado para $C_{25}H_{29}N_5O_4 \cdot 0.5H_2O$: C, 63.54; H, 6.40; N, 14.82. Encontrado: C, 63.36; H, 6.20; N, 14.72.

Ejemplo 53



3-hidroxi-N-[(1S)-2-metil-1-({4-[(1-metil-1H-bencimidazol-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

Ejemplo 53-1

2-cloro-1-metil-1H-bencimidazol

Se agregó hidruro de sodio (pureza 55 por ciento) (516 miligramos, 12.0 milimoles) a una solución en N,N-dimetil-formamida (8.0 mililitros) de 2-cloro-1H-bencimidazol (1.52 gramos, 10.0 milimoles), a 0°C, bajo una corriente de nitrógeno, y la agitación se llevó a cabo durante 20 minutos. Se agregó yoduro de metilo adicional (0.750 mililitros, 12.0 milimoles), y la agitación se llevó a cabo a temperatura ambiente durante 2 horas. Se agregó agua a la solución de la reacción, y la sustancia sólida resultante se recolectó mediante filtración, para proporcionar el 2-cloro-1-metil-1H-bencimidazol (1.51

gramos, rendimiento del 91 por ciento) como un sólido blanco.

Ejemplo 53-2

4-[(1-metil-1H-bencimidazol-2-il)-oxi]-piperidin-1-carboxilato de terbutilo

Se agregó hidruro de sodio (pureza 55 por ciento) (129 miligramos, 3.00 milimoles) a una solución en N,N-dimetil-formamida (4.0 mililitros) de 2-cloro-1-metil-1H-bencimidazol (333 miligramos, 2.00 milimoles), y 4-hidroxi-piperidin-1-carboxilato de terbutilo (402 miligramos, 2.00 milimoles), a 0°C, bajo una corriente de nitrógeno, y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se vertió en agua, seguido por extracción con acetato de etilo y el lavado subsiguiente en secuencia con agua y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, para proporcionar el 4-[(1-metil-1H-bencimidazol-2-il)-oxi]-piperidin-1-carboxilato de terbutilo (548 miligramos, rendimiento del 83 por ciento) como un sólido blanco.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.53 (1H, m), 7.17 (3H, m), 5.32 (1H, m), 3.77 (2H, m), 3.56 (3H, s), 3.34 (2H, m), 2.11 (2H, m), 1.84 (2H, m), 1.48 (9H, s).

MS (ESI, m/z): 332 $(M+H)^+$.

Ejemplo 53-3

[(1S)-2-metil-1-({4-[(1-metil-1H-bencimidazol-2-il)-oxi]-piperidin-1-il}-

carbonil)-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 29-2, el [(1S)-2-metil-1-({4-[(1-metil-1H-bencimidazol-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (504 miligramos, rendimiento del 71 por ciento) se obtuvo a partir del 4-[(1-metil-1H-bencimidazol-2-il)-oxi]-piperidin-1-carboxilato de terbutilo (548 miligramos, 1.66 milimoles) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.53 (1H, m), 7.17 (3H, m), 5.38 (1H, m), 5.34 (1H, d, J=9.2 Hz), 4.19-3.60 (2H, m), 3.57 y 3.56 (3H, s), 3.47 (2H, m), 2.13 (2H, m), 1.92 (3H, m), 1.44 (9H, s), 0.99 (3H, d, J=6.4 Hz), 0.90 (3H, d, J=6.4 Hz).

MS (ESI, m/z): 431 $(M+H)^+$.

Ejemplo 53-4

3-hidroxi-N-[(1S)-2-metil-1-({4-[(1-metil-1H-bencimidazol-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 1-3, se proporcionó el clorhidrato de (2S)-3-metil-1-{4-[(1-metil-1H-bencimidazol-2-il)-oxi]-piperidin-1-il}-1-oxobutan-2-amina a partir del [(1S)-2-metil-1-({4-[(1-metil-1H-bencimidazol-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (504 miligramos, 1.17 milimoles) como un sólido blanco. El compuesto resultante se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (222 miligramos, 1.17 milimoles), para proporcionar el compuesto del título deseado (524 miligramos, rendimiento del 89 por ciento) como un sólido amarillo pálido.

^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.83 (1H, s), 9.50 (1H, d,

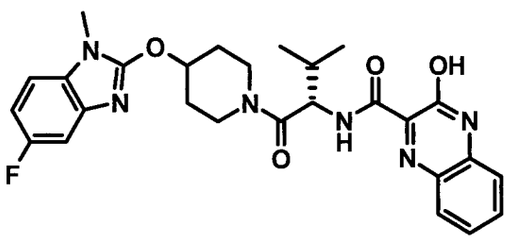
J=8.4 Hz), 7.87 (1H, t, J=6.8 Hz), 7.64 (1H, dt, J=8.0 Hz, 1.6 Hz), 7.41-7.32 (4H, m), 7.12-7.07 (2H, m), 5.31 (1H, m), 4.94 (1H, q, J=7.6 Hz), 3.96-3.28 (4H, m), 3.57 y 3.56 (3H, s), 2.30-1.70 (5H, m), 0.95 (6H, m).

IR (KBr) cm^{-1}: 2965, 1690, 1630, 1530, 1450, 1020.

MS (ESI, m/z): 503 $(M+H)^+$.

HRMS (ESI, m/z): 503.2425 (Calculado para $C_{27}H_{31}N_6O_4$: 503.2407).

Ejemplo 54



N-[(1S)-1-({4-[(5-fluoro-1-metil-1H-bencimidazol-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 54-1

N-metil-4-fluoro-2-nitroanilina

Se agregó carbonato de potasio (2.61 gramos, 18.9 milimoles) a una solución en N,N-dimetil-formamida (20 mililitros) de 2,5-difluoro-nitro-benceno (1.00 gramos, 6.29 milimoles), y clorhidrato de metil-amina (509 miligramos, 7.54 milimoles), bajo una corriente de nitrógeno, y la agitación se llevó a cabo a 120°C durante 1.5 horas. La solución de la reacción se filtró, se agregó agua al filtrado, seguido por extracción con acetato de etilo, y lavado en secuencia

con agua y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., 40+M), para proporcionar la N-metil-4-fluoro-2-nitro-anilina (919 miligramos, rendimiento del 87 por ciento) como un sólido color naranja.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.94 (1H, brs), 7.90 (1H, dd, J=9.4 Hz, 2.9 Hz), 7.31-7.27 (1H, m), 6.83 (1H, dd, J=9.4 Hz, 4.7 Hz), 3.04 (3H, d, J=5.5 Hz).

Ejemplo 54-2

5-fluoro-1-metil-1H-bencimidazol-2-ol

Se agregó un catalizador de paladio al 5 por ciento sobre carbón (1.15 gramos) a una solución en metanol (30 mililitros) de N-metil-4-fluoro-2-nitro-anilina (919 miligramos, 5.40 milimoles), bajo una atmósfera de hidrógeno, y la agitación se llevó a cabo a temperatura ambiente durante 4 horas. Después de que la solución de la reacción se filtró con Celite, el filtrado se concentró, y el residuo resultante se disolvió en una solución de 1,4-dioxano (30 mililitros), y se agregó N,N'-carbonil-di-imidazol (1.31 gramos, 8.10 milimoles), seguido por calentamiento a reflujo durante la noche. La solución de la reacción se enfrió a temperatura ambiente, y se agregó agua, seguida por extracción con acetato de etilo. El extracto se lavó en secuencia con agua y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La

capa orgánica se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., 25+M), para proporcionar el 5-fluoro-1-metil-1H-bencimidazol-2-ol (583 miligramos, rendimiento del 65 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.86 (1H, brs), 7.12-7.06 (1H, m), 6.87-6.82 (2H, m), 3.42 (3H, d, J=6.3 Hz).

MS (EI, m/z): 166 (M^+).

Ejemplo 54-3

4-[(5-fluoro-1-metil-1H-bencimidazol-2-il)-oxi]-piperidin-1-carboxilato de terbutilo

Se agregó oxicloruro de fósforo (5.0 mililitros) al 5-fluoro-1-metil-1H-bencimidazol-2-ol (225 miligramos, 1.35 milimoles), bajo una corriente de nitrógeno, seguido por calentamiento a reflujo durante 5 horas. Se vertió una solución acuosa saturada de carbonato ácido de sodio bajo enfriamiento con hielo en los residuos resultantes de la concentración de la solución de la reacción bajo presión reducida, seguido por extracción con acetato de etilo. El extracto se lavó en secuencia con agua y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el compuesto resultante se disolvió en una solución de N,N-dimetil-formamida (10 mililitros), y a 0°C, se agregaron hidruro de sodio al 63 por ciento (93.0 miligramos, 2.44 milimoles), y 4-hidroxi-piperidin-1-carboxilato de terbutilo (491 miligramos, 2.44 milimoles), seguido por agitación a temperatura

ambiente durante 6 horas. Se agregó agua a la solución de la reacción bajo enfriamiento con hielo, seguida por extracción con acetato de etilo. El extracto se lavó en secuencia con agua, una solución acuosa saturada de carbonato ácido de sodio, agua, y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., 25+M), para proporcionar el 4-[(5-fluoro-1-metil-1H-bencimidazol-2-il)-oxi]-piperidin-1-carboxilato de terbutilo (108 miligramos, rendimiento del 20 por ciento) como un sólido blanco.

^{1}H-RMN ($CDCl_3$) δ: 7.22 (1H, dd, J=9.6 Hz, 2.0 Hz), 7.04 (1H, dd, J=8.0 Hz, 4.7 Hz), 6.89 (1H, ddd, J=10.5 Hz, 8.0 Hz, 2.0 Hz), 5.32-5.26 (1H, m), 3.80-3.78 (2H, m), 3.54 (3H, s), 3.36-3.32 (2H, m), 2.11-2.09 (2H, m), 1.85-1.82 (2H, m), 1.48-1.46 (9H, m).

MS (FAB, m/z): 350 $(M+H)^+$.

Ejemplo 54-4

[(1S)-1-({4-[(5-fluoro-1-metil-1H-bencimidazol-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 29-2, el [(1S)-1-({4-[(5-fluoro-1-metil-1H-bencimidazol-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (128 miligramos, rendimiento del 93 por ciento) se obtuvo a partir del 4-[(5-fluoro-1-metil-1H-bencimidazol-2-il)-oxi]-piperidin-1-carboxilato de terbutilo (108 miligramos, 0.309 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 500 MHz) δ: 7.22 (1H, dd, J=9.6 Hz, 2.0 Hz), 7.04 (1H, dd, J=8.0 Hz, 4.7 Hz), 6.89 (1H, ddd, J=10.5 Hz, 8.0 Hz, 2.0 Hz), 5.37-5.36 (2H, m), 4.52-4.50 (1H, m), 4.07-3.76 (2H, m), 3.68-3.46 (2H, m), 3.55 (3H, d, J=7.3 Hz), 2.24-2.10 (2H, m), 1.96-1.89 (3H, m), 1.44-1.40 (9H, m), 0.98 (3H, t, J=6.6 Hz), 0.91 (3H, t, J=6.6 Hz).

MS (FAB, m/z): 406 $(M+H)^+$.

Ejemplo 54-5

N-[(1S)-1-({4-[(5-fluoro-1-metil-1H-bencimidazol-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 1-3, el clorhidrato de (2S)-1-{4-[(5-fluoro-1-metil-1H-bencimidazol-2-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina (119 miligramos) se obtuvo a partir del [(1S)-1-({4-[(5-fluoro-1-metil-1H-bencimidazol-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (128 miligramos, 0.285 milimoles) como un sólido blanco. El compuesto resultante (119 miligramos, 0.285 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (81.0 miligramos, 0.428 milimoles), para proporcionar el compuesto del título deseado (111 miligramos, rendimiento del 75 por ciento) como un sólido amarillo pálido.

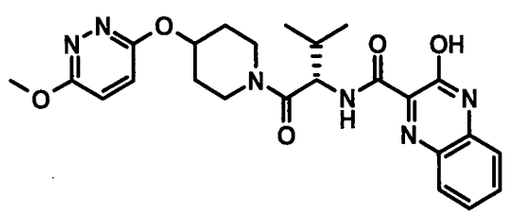
^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.84 (1H, brs), 9.57 (1H, brs), 7.87 (1H, t, J=6.8 Hz), 7.64 (1H, d, J=16.4 Hz), 7.40-7.33 (3H, m), 7.24 (1H, dd, J=9.6 Hz, 2.0 Hz), 6.96 (1H, ddd, J=10.5 Hz, 8.0 Hz, 2.0 Hz), 5.31-5.29 (1H, m), 4.96-4.92 (1H, m), 3.94-3.63 (4H, m), 3.57 (3H, d, J=9.4 Hz), 2.00-1.89 (5H, m), 0.96 (6H, t, J=6.6 Hz).

IR (KBr) cm^{-1}: 2965, 1690, 1640, 1530, 1440, 1140.

MS (ESI, m/z): 521 $(M+H)^+$.

HRMS (ESI, m/z): 521.2320 (Calculado para $C_{27}H_{30}FN_6O_4$: 521.2312).

Ejemplo 55



3-hidroxi-N-[(1S)-1-({4-[(6-metoxi-piridazin-3-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-quinoxalin-2-carboxamida

Ejemplo 55-1

4-[(6-metoxi-piridazin-3-il)-oxi]-piperidin-1-carboxilato de terbutilo

De una manera análoga al Ejemplo 53-2, el 4-[(6-metoxi-piridazin-3-il)-oxi]-piperidin-1-carboxilato de terbutilo (964 miligramos, rendimiento del 78 por ciento) se obtuvo a partir de la 3-cloro-6-metoxi-piridazina (578 miligramos, 4.00 milimoles), y el 4-hidroxi-piperidin-1-carboxilato de terbutilo (924 miligramos, 4.60 milimoles) como un sólido blanco.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 6.94 (1H, d, J=8.8 Hz), 6.89 (1H, d, J=8.8 Hz), 5.32 (1H, m), 4.04 (3H, s), 3.80 (2H, m), 3.22 (2H, m), 2.10 (2H, m), 1.75 (2H, m), 1.47 (9H, s).

MS (ESI, m/z): 310 $(M+H)^+$.

Ejemplo 55-2

[(1S)-1-({4-[(6-metoxi-piridazin-3-il)-oxi]-piperidin-1-il}-carbonil)-2-

metil-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 29-2, el [(1S)-1-({4-[(6-metoxi-piridazin-3-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (157 miligramos, rendimiento del 68 por ciento) se obtuvo a partir del 4-[(6-metoxi-piridazin-3-il)-oxi]-piperidin-1-carboxilato de terbutilo (175 miligramos, 0.566 milimoles) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 6.93 (1H, d, J=9.2 Hz), 6.90 (1H, dd, J=9.2 Hz, 2.4 Hz), 5.40 (1H, m), 5.37 (1H, m), 4.50 (1H, q, J=5.6 Hz), 4.05 (3H, s), 4.05-3.75 (2H, m), 3.55-3.35 (2H, m), 2.20-2.05 (2H, m), 1.95 (1H, m), 1.95-1.75 (2H, m), 1.44 (9H, s), 0.98 (3H, d, J=6.8 Hz), 0.89 (3H, d, J=6.8 Hz).

MS (ESI, m/z): 409 $(M+H)^+$.

Ejemplo 55-3

3-hidroxi-N-[(1S)-1-({4-[(6-metoxi-piridazin-3-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 1-3, el clorhidrato de (2S)-1-{4-[(6-metoxi-piridazin-3-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina se obtuvo a partir del [(1S)-1-({4-[(6-metoxi-piridazin-3-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (156 miligramos, 0.382 milimoles) como un sólido blanco. El compuesto resultante se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (72.6 miligramos, 0.382 milimoles), para proporcionar el compuesto del título deseado (82.7 miligramos, rendimiento del 45 por ciento) como un sólido amarillo pálido.

^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.83 (1H, brs), 9.52 (1H, brs), 7.86 (1H, t, J=6.8 Hz), 7.64 (1H, dt, J=8.0 Hz, 1.6 Hz), 7.41-7.36 (2H, m), 7.22-7.16 (2H, m), 5.31 (1H, m), 4.92 (1H, q, J=7.6 Hz), 4.08-3.28 (4H, m), 3.94 (3H, s), 2.13-2.00 (2H, m), 2.05 (1H, m), 1.79-1.57 (2H, m), 0.95 (6H, t, J=6.4 Hz).

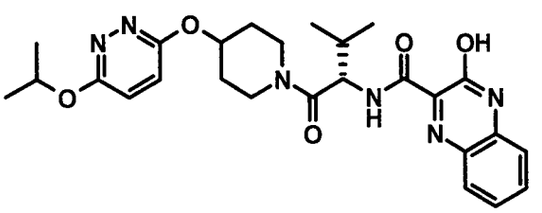
IR (KBr) cm^{-1}: 2960, 1685, 1640, 1670, 1420, 1270, 1015.

MS (ESI, m/z): 481 $(M+H)^+$.

HRMS (ESI, m/z): 481.2206 (Calculado para $C_{24}H_{29}N_6O_5$: 481.2199).

Análisis calculado para $C_{24}H_{28}N_6O_5 \cdot 0.5H_2O$: C, 58.89; H, 5.97; N, 17.17. Encontrado: C, 59.01; H, 5.82; N, 16.77.

Ejemplo 56



3-hidroxi-N-[(1S)-1-({4-[(6-isopropoxi-piridazin-3-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-quinoxalin-2-carboxamida

Ejemplo 56-1

3-cloro-6-isopropoxi-piridazina

Se agregó 2-propanol (0.770 mililitros, 10.0 milimoles) a una solución en N,N-dimetil-formamida (2.0 mililitros) de hidruro de sodio (pureza 55 por ciento) (218 miligramos, 5.00 milimoles), bajo una corriente de nitrógeno, y la agitación se llevó a cabo durante 15 minutos. Además, se agregó 3,6-dicloro-piridazina (745 miligramos,

5.00 milimoles), y la agitación se llevó a cabo a temperatura ambiente durante 1 hora. La solución de la reacción se vertió en una solución acuosa saturada de cloruro de amonio, seguido por extracción con acetato de etilo y el lavado subsiguiente en secuencia con agua y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, para proporcionar la 3-cloro-6-isopropoxi-piridazina (486 miligramos, rendimiento del 56 por ciento) como un sólido blanco.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.33 (1H, d, J=7.2 Hz), 6.87 (1H, d, J=7.2 Hz), 5.18 (1H, m), 1.40 (6H, d, J=6.0 Hz).

Ejemplo 56-2

4-[(6-isopropoxi-piridazin-3-il)-oxi]-piperidin-1-carboxilato de terbutilo

De una manera análoga al Ejemplo 53-2, el 4-[(6-isopropoxi-piridazin-3-il)-oxi]-piperidin-1-carboxilato de terbutilo (631 miligramos, rendimiento del 66 por ciento) se obtuvo a partir de la 3-cloro-6-isopropoxi-piridazina (486 miligramos, 2.86 milimoles), y 4-hidroxi-piperidin-1-carboxilato de terbutilo (790 miligramos, 3.92 milimoles) como un sólido blanco.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 6.87 (2H, s), 5.41 (1H, m), 5.32 (1H, m), 3.80 (2H, brs), 3.22 (2H, m), 2.05 (2H, m), 1.75 (2H, m), 1.46 (9H, s), 1.38 (6H, d, J=6.0 Hz).

Ejemplo 56-3

[(1S)-1-({4-[(6-isopropoxi-piridazin-3-il)-oxi]-piperidin-1-il}-carbonil)-

2-metil-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 29-2, el [(1S)-1-({4-[(6-isopropoxi-piridazin-3-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (586 miligramos, rendimiento del 72 por ciento) se obtuvo a partir del 4-[(6-isopropoxi-piridazin-3-il)-oxi]-piperidin-1-carboxilato de terbutilo (631 miligramos, 1.87 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 6.88 (2H, s), 6.88-5.44 (3H, m), 6.88-5.44 (1H, m), 4.10-3.76 (2H, m), 3.53-3.37 (2H, m), 2.19-1.76 (5H, m), 1.44 (9H, s), 1.39 (6H, d, J=5.9 Hz), 0.99 (3H, d, J=6.8 Hz), 0.89 (3H, d, J=6.8 Hz).

MS (ESI, m/z): 437 $(M+H)^+$.

Ejemplo 56-4

3-hidroxi-N-[(1S)-1-({4-[(6-isopropoxi-piridazin-3-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 1-3, el clorhidrato de (2S)-1-{4-[(6-isopropoxi-piridazin-3-il)-oxi]-piperidin-1-il}-3-metil-1-oxibutan-2-amina se obtuvo a partir del [(1S)-1-({4-[(6-isopropoxi-piridazin-3-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (574 miligramos, 1.31 milimoles) como un sólido blanco. El compuesto resultante se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (249 miligramos, 1.31 milimoles), para proporcionar el compuesto del título deseado (581 miligramos, rendimiento del 87 por ciento) como un sólido amarillo pálido.

^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.83 (1H, brs), 9.51 (1H, m),

7.88 (1H, m), 7.66 (1H, t, J=3.2 Hz), 7.41-7.37 (2H, m), 7.19-7.11 (2H, m), 5.35-5.26 (2H, m), 4.96-4.91 (1H, m), 4.08-3.92 (2H, m), 3.60-3.21 (2H, m), 2.20-2.02 (3H, m), 1.80-1.53 (2H, m), 1.34 (6H, d, J=6.0 Hz), 0.97-0.94 (6H, m).

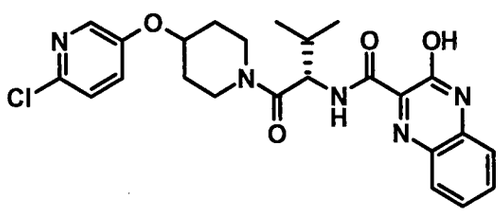
IR (KBr) cm^{-1}: 2970, 1690, 1645, 1630, 1440, 1270.

MS (ESI, m/z): 509 $(M+H)^+$.

HRMS (ESI, m/z): 509.2523 (Calculado para $C_{26}H_{33}N_6O_5$: 509.2512).

Análisis calculado para $C_{26}H_{32}N_6O_5 \cdot 1/2H_2O$: C, 60.34; H, 6.43; N, 16.24. Encontrado: C, 60.43; H, 6.27; N, 16.15.

Ejemplo 57



N-[(1S)-1-({4-[(2-cloro-piridin-5-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 57-1

4-[(2-cloro-piridin-5-il)-oxi]-piperidin-1-carboxilato de terbutilo

De una manera análoga al Ejemplo 53-2, el 4-[(2-cloro-piridin-5-il)-oxi]-piperidin-1-carboxilato de terbutilo (811 miligramos, rendimiento del 86 por ciento) se obtuvo a partir de la 2-cloro-5-fluoro-piridina (393 miligramos, 3.00 milimoles), y 4-hidroxi-piperidin-1-carboxilato de terbutilo (603 miligramos, 3.00 milimoles) como un sólido blanco.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.07 (1H, dd, J=2.8 Hz, 0.8Hz), 7.25 (1H, d, J=8.2 Hz), 7.20 (1H, dd, J=8.8 Hz, 2.8 Hz), 4.49-4.45 (1H, m), 3.73-3.67 (2H, m), 3.38-3.32 (2H, m), 1.97-1.90 (2H, m), 1.79-1.71 (2H, m), 1.47 (9H, s).

Ejemplo 57-2

[(1S)-1-({4-[(2-cloro-piridin-5-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 29-2, el [(1S)-1-({4-[(2-cloro-piridin-5-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (321 miligramos, rendimiento del 52 por ciento) se obtuvo a partir del 4-[(2-cloro-piridin-5-il)-oxi]-piperidin-1-carboxilato de terbutilo (468 miligramos, 1.50 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.08 (1H, d, J=2.8 Hz), 7.26 (1H, d, J=9.4 Hz), 7.21 (1H, dd, J=8.8 Hz, 3.0 Hz), 5.33 (1H, d, J=8.2 Hz), 4.62-4.53 (1H, m), 4.50 (1H, dd, J=9.2 Hz, 5.7 Hz), 3.86-3.47 (4H, m), 2.04-1.78 (5H, m), 1.44 (9H, s), 0.97 (3H, d, J=6.7 Hz), 0.90 (3H, d, J=7.1Hz).

Ejemplo 57-3

N-[(1S)-1-({4-[(2-cloro-piridin-5-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 1-3, el clorhidrato de (2S)-1-{4-[(2-cloro-piridin-5-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina se obtuvo a partir del [(1S)-1-({4-[(2-cloro-piridin-5-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (315

miligramos, 0.766 milimoles) como un sólido blanco. El compuesto resultante se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (146 miligramos, 0.766 milimoles), para proporcionar el compuesto del título deseado (298 miligramos, rendimiento del 80 por ciento) como un sólido amarillo pálido.

^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.85 (1H, brs), 9.51 (1H, brs), 8.19 (1H, dd, J=5.4 Hz, 3.2 Hz), 7.87 (1H, dd, J=7.6 Hz, 4.9 Hz), 7.65 (1H, t, J=7.8 Hz), 7.62-7.57 (1H, m), 7.46 (1H, d, J=8.6 Hz), 7.41-7.37 (2H, m), 4.91 (1H, dd, J=13.8 Hz, 7.7 Hz), 4.81-4.71 (1H, m), 4.04-3.84 (2H, m), 3.58-3.20 (2H, m), 2.12-1.90 (3H, m), 1.76-1.47 (2H, m), 0.96 (3H, d, J=3.9 Hz), 0.94 (3H, d, J=3.9 Hz).

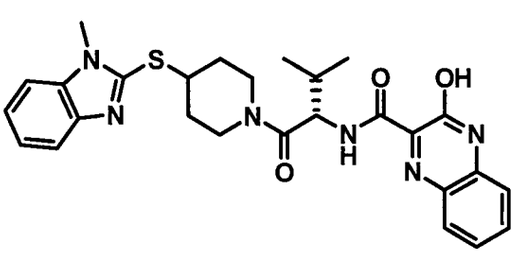
IR (KBr) cm^{-1}: 2960, 1685, 1640, 1450, 1270.

MS (ESI, m/z): 484 $(M+H)^+$.

HRMS (ESI, m/z): 484.1769 (Calculado para $C_{24}H_{27}ClN_5O_4$: 484.1752).

Análisis calculado para $C_{24}H_{26}ClN_5O_4$: C, 59.56; H, 5.42; N, 14.47. Encontrado: C, 59.60; H, 5.42; N, 14.38.

Ejemplo 58



3-hidroxi-N-[(1S)-2-metil-1-({4-[(1-metil-1H-bencimidazol-2-il)-tio]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

Ejemplo 58-1

4-[(1H-bencimidazol-2-il)-tio]-piperidin-1-carboxilato de terbutilo

Se agregó carbonato de potasio (414 miligramos, 3.00 milimoles) a una solución en etanol (10 mililitros) de 4-metan-sulfoniloxi-piperidina (834 miligramos, 3.00 milimoles), y 2-mercapto-bencimidazol (450 miligramos, 3.00 milimoles), a temperatura ambiente, bajo una corriente de nitrógeno, y la agitación se llevó a cabo durante 16 horas bajo calentamiento a reflujo. La solución de la reacción se vertió en una solución acuosa saturada de cloruro de amonio, seguido por extracción con acetato de etilo. El extracto se lavó en secuencia con agua y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se suspendió en un solvente mixto de acetato de etilo-metanol, y el precipitado resultante se recolectó mediante filtración, para proporcionar el 4-[(1H-bencimidazol-2-il)-tio]-piperidin-1-carboxilato de terbutilo (473 miligramos, rendimiento del 47 por ciento) como un sólido blanco.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 9.19 (1H, brs), 7.68 (1H, brs), 7.35 (1H, brs), 7.22 (2H, m), 4.01 (1H, m), 3.39 (2H, m), 3.06 (1H, t, J=10.8 Hz), 2.13 (2H, m), 1.70 (2H, m), 1.46 (9H, s).

Ejemplo 58-2

4-[(1-metil-1H-bencimidazol-2-il)-tio]-piperidin-1-carboxilato de terbutilo

Se agregó butil-litio (solución en hexano 1.58M) (1.08 mililitros,

1.70 milimoles) a una solución en tetrahidrofurano (10 mililitros) de 4-[(1H-bencimidazol-2-il)-tio]-piperidin-1-carboxilato de terbutilo (473 miligramos, 1.42 milimoles), a 0°C, bajo una corriente de nitrógeno, y la agitación se llevó a cabo durante 15 minutos, seguida por otra adición de yoduro de metilo (0.180 mililitros, 2.84 milimoles) y agitación a temperatura ambiente durante 2 horas. La solución de la reacción se vertió en una solución acuosa saturada de cloruro de amonio, seguido por extracción con acetato de etilo. El extracto se lavó en secuencia con agua y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, para proporcionar el 4-[(1-metil-1H-bencimidazol-2-il)-tio]-piperidin-1-carboxilato de terbutilo (493 miligramos, rendimiento del 100 por ciento) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.66 (1H, m), 7.26-7.22 (3H, m), 4.11 (1H, m), 3.95 (2H, m), 3.70 (3H, s), 3.11 (1H, t, J=10.8 Hz), 2.16 (2H, m), 1.71 (2H, m), 1.46 (9H, s).

Ejemplo 58-3

[(1S)-1-({4-[(1-metil-1H-bencimidazol-2-il)-tio]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 29-2, el [(1S)-1-({4-[(1-metil-1H-bencimidazol-2-il)-tio]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (361 miligramos, rendimiento del 57 por ciento) se obtuvo a partir del 4-[(1-metil-1H-bencimidazol-2-il)-

tio]-piperidin-1-carboxilato de terbutilo (493 miligramos, 1.42 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.67 (1H, m), 7.24 (3H, m), 5.34 (1H, d, J=7.2 Hz), 4.48 (1H, dd, J=7.2 Hz, 3.2 Hz), 4.39-4.29 (1H, m), 4.20 (1H, m), 3.93 (1H, t, J=12.0 Hz), 3.70 y 3.69 (3H, s), 3.43-3.33 (1H, m), 3.19-3.08 (1H, m), 2.34-2.20 (2H, m), 1.92 (1H, m), 1.81-1.68 (2H, m), 1.44 (9H, s), 0.97 (3H, t, J=6.4 Hz), 0.89 (3H, d, J=6.4 Hz).

MS (ESI, m/z): 447 $(M+H)^+$.

Ejemplo 58-4

3-hidroxi-N-[(1S)-2-metil-1-({4-[(1-metil-1H-bencimidazol-2-il)-tio]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 1-3, el clorhidrato de (2S)-3-metil-1-{4-[(1-metil-1H-bencimidazol-2-il)-tio]-piperidin-1-il}-1-oxobutan-2-amina se obtuvo a partir del [(1S)-1-({4-[(1-metil-1H-bencimidazol-2-il)-tio]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (361 miligramos, 0.809 milimoles) como un sólido blanco. El compuesto resultante se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (154 miligramos, 0.809 milimoles), para proporcionar el compuesto del título deseado (331 miligramos, rendimiento del 79 por ciento) como un sólido amarillo pálido.

^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.85 (1H, brs), 9.50 (1H, t, J=9.6 Hz), 7.88 (1H, dd, J=8.4 Hz, 1.4 Hz), 7.63 (1H, t, J=17.0 Hz), 7.57 (1H, d, J=16.2 Hz), 7.50 (1H, m), 7.41-7.37 (2H, m), 7.24-7.15 (2H, m), 4.91 (1H, dd, J=13.3 Hz, 7.8 Hz), 4.33-4.06 (3H, m), 3.70

(3H, d, J=7.8 Hz), 3.49-3.38 (1H, m), 3.12-2.99 (1H, m), 2.29-2.15 (2H, m), 2.06 (1H, m), 1.85-1.53 (2H, m), 0.96-0.93 (6H, m).

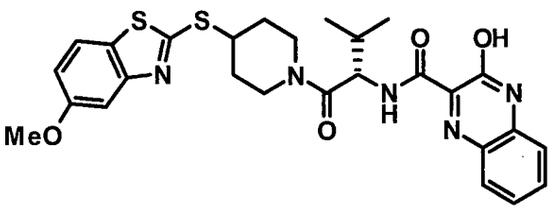
IR (KBr) cm^{-1}: 2960, 1690, 1630, 1530, 1450, 1275.

MS (ESI, m/z): 519 $(M+H)^+$.

HRMS (ESI, m/z): 519.2178 (Calculado para $C_{27}H_{31}N_6O_3S$: 519.2178).

Análisis calculado para $C_{27}H_{30}N_6O_3S$: C, 62.53; H, 5.83; N, 16.20. Encontrado: C, 62.39; H, 5.79; N, 16.09.

Ejemplo 59



3-hidroxi-N-[(1S)-1-({4-[(5-metoxi-benzotiazol-2-il)-tio]-piperidin-1-il}-carbonil)-2-metil-propil]-quinoxalin-2-carboxamida

Ejemplo 59-1

4-[(5-metoxi-benzotiazol-2-il)-tio]-piperidin-1-carboxilato de terbutilo

De una manera análoga al Ejemplo 58-1, el 4-[(5-metoxi-benzotiazol-2-il)-tio]-piperidin-1-carboxilato de terbutilo (922 miligramos, rendimiento del 81 por ciento) se obtuvo a partir de la 5-metan-sulfoniloxi-piperidina (834 miligramos, 3.00 milimoles), y el 2-mercapto-5-metoxi-benzotiazol (592 miligramos, 3.00 milimoles) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.61 (1H, d, J=8.8 Hz), 7.39 (1H,

d, J=2.4 Hz), 6.95 (1H, dd, J=8.8 Hz, 2.4 Hz), 4.06 (1H, m), 3.95 (2H, m), 3.88 (3H, s), 3.12 (2H, t, J=10.8 Hz), 2.20-2.10 (2H, m), 1.76-1.70 (2H, m), 1.47 (9H, s).

Ejemplo 59-2

N-[(1S)-1-({4-[(5-metoxi-benzotiazol-2-il)-tio]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 29-2, el [(1S)-1-({4-[(5-metoxi-benzotiazol-2-il)-tio]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (873 miligramos, rendimiento del 98 por ciento) se obtuvo a partir del 4-[(5-metoxi-benzotiazol-2-il)-tio]-piperidin-1-carboxilato de terbutilo (921 miligramos, 2.42 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.61 (1H, d, J=8.8 Hz), 7.39 (1H, d, J=2.4 Hz), 6.97 (1H, dd, J=8.8 Hz, 2.4 Hz), 5.38 (1H, t, J=7.2 Hz), 4.49 (1H, m), 4.39-4.29 (1H, m), 4.20 (1H, m), 3.88 (3H, s), 3.41-3.14 (3H, m), 2.40-2.20 (2H, m), 1.95 (1H, m), 1.88-1.68 (2H, m), 1.44 (9H, s), 0.97 (3H, t, J=6.4 Hz), 0.89 (3H, d, J=6.4 Hz).

MS (ESI, m/z): 448 $(M+H)^+$.

Ejemplo 59-3

3-hidroxi-N-[(1S)-1-({4-[(5-metoxi-benzotiazol-2-il)-tio]-piperidin-1-il}-carbonil)-2-metil-propil]-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 1-3, el clorhidrato de (2S)-1-{4-[(5-metoxi-benzotiazol-2-il)-tio]-piperidin-1-il}-3-metil-1-oxobutan-2-amina se obtuvo a partir del [(1S)-1-({4-[(5-metoxi-benzotiazol-2-il)-tio]-piperidin-1-il}-carbonil)-2-metil-propil]-

carbamato de terbutilo (873 miligramos, 1.95 milimoles) como un sólido blanco. El compuesto resultante se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (380 miligramos, 2.00 milimoles), para proporcionar el compuesto del título deseado (883 miligramos, rendimiento del 82 por ciento) como un sólido amarillo pálido.

^{1}H-RMN (DMSO-d_6, 500 MHz) δ: 12.83 (1H, s), 9.50 (1H, brs), 7.88 (1H, dd, J=8.8 Hz, 5.3 Hz), 7.86 (1H, t, J=7.5 Hz), 7.64 (1H, t, J=7.5 Hz), 7.45 (1H, brs), 7.39-7.36 (2H, m), 7.04-6.98 (1H, m), 4.89 (1H, dd, J=18.6 Hz, 8.3 Hz), 4.31-4.07 (3H, m), 3.83 (3H, s), 3.49-3.39 (1H, m), 3.13-3.01 (1H, m), 2.31-2.18 (2H, m), 2.06 (1H, m), 1.85-1.56 (2H, m), 0.97-0.94 (6H, m).

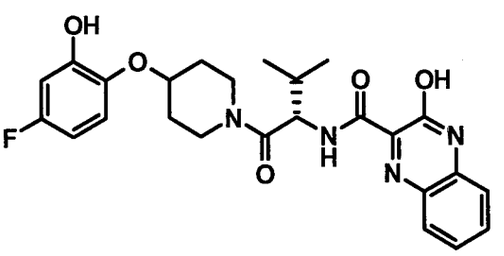
IR (KBr) cm^{-1}: 2960, 1690, 1640, 1450, 1430, 1275.

MS (ESI, m/z): 552 $(M+H)^+$.

HRMS (ESI, m/z): 574.1609 (Calculado para $C_{27}H_{29}N_5NaO_4S_2$: 574.1559).

Análisis calculado para $C_{27}H_{29}N_5O_4S_2 \cdot 0.5H_2O$, C: 57.84, H: 5.39, N: 12.49; Encontrado: C, 57.69; H, 5.13; N, 12.46.

Ejemplo 60



N-[(1S)-1-{[4-(4-fluoro-2-hidroxi-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

460

Ejemplo 60-1

1-[2-(benciloxi)-4-fluoro-fenil]-etanona

Se agregó bromuro de bencilo (1.03 gramos, 6.00 milimoles) a una solución en N,N-dimetil-formamida (5 mililitros) de 1-(4-fluoro-2-hidroxi-fenil)-etanona (770 miligramos, 5.00 milimoles), y carbonato de potasio (860 miligramos, 5.00 milimoles), a temperatura ambiente, bajo una corriente de nitrógeno, y la agitación se llevó a cabo a 70°C durante 1.5 horas. La solución de la reacción se vertió en una solución acuosa de ácido clorhídrico 2N, seguido por extracción con acetato de etilo. El extracto se lavó en secuencia con agua y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, para proporcionar la 1-[2-(benciloxi)-4-fluoro-fenil]-etanona (1.20 gramos, rendimiento del 98 por ciento) como un sólido blanco.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.83 (1H, dd, J=8.0 Hz, 7.2 Hz), 7.44-7.39 (5H, m), 6.76-6.70 (2H, m), 5.15 (2H, s), 2.58 (3H, s).

Ejemplo 60-2

acetato de 2-(benciloxi)-4-fluoro-fenilo

Se agregó ácido m-cloro-perbenzoico (2.54 gramos, 14.7 milimoles) a una solución en cloruro de metileno (20 mililitros) de 1-[2-(benciloxi)-4-fluoro-fenil]-etanona (1.20 gramos, 4.91 milimoles), a temperatura ambiente, bajo una corriente de nitrógeno, y la agitación se llevó a cabo durante 10 horas bajo calentamiento a reflujo. La solución de la reacción se enfrió a temperatura ambiente, la

sustancia sólida se filtró, y entonces se agregó una solución acuosa de tiosulfato de sodio, seguida por agitación durante 15 minutos. La solución se separó, y la capa orgánica resultante se lavó en secuencia con una solución acuosa saturada de carbonato ácido de sodio, agua, y una solución salina, seguido por secado sobre sulfato de sodio anhidro. La capa orgánica se concentró, para proporcionar el acetato de 2-(benciloxi)-4-fluoro-fenilo (1.19 gramos, rendimiento del 93 por ciento) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.40-7.34 (5H, m), 7.01 (1H, dd, J=8.8 Hz, 5.7 Hz), 6.74 (1H, dd, J=10.0 Hz, 3.0 Hz), 6.66 (1H, dt, J=12.1 Hz, 4.2 Hz), 5.07 (2H, s), 2.27 (3H, s).

Ejemplo 60-3

2-(benciloxi)-4-fluoro-fenol

Se agregó metóxido de sodio (494 miligramos, 9.14 milimoles) a una solución en metanol (20 mililitros) de acetato de 2-(benciloxi)-4-fluoro-fenilo (1.19 gramos, 4.57 milimoles), a temperatura ambiente, bajo una corriente de nitrógeno, y la agitación se llevó a cabo durante 1.5 horas. La solución de la reacción se concentró, seguido por vertido en una solución acuosa de ácido clorhídrico 2N y extracción con acetato de etilo, y el extracto se lavó en secuencia con agua y solución salina saturada. La capa orgánica resultante se secó sobre sulfato de sodio anhidro, y entonces el residuo resultante de la concentración se purificó mediante cromatografía en gel de sílice, para proporcionar el 2-(benciloxi)-4-fluoro-fenol (900 miligramos, rendimiento del 90 por ciento) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.42-7.34 (5H, m), 6.87 (1H, dd, J=8.8 Hz, 5.7 Hz), 6.69 (1H, dd, J=10.0 Hz, 3.0 Hz), 6.60 (1H, dt, J=12.1 Hz, 4.2 Hz), 5.41 (1H, s), 5.08 (2H, s).

Ejemplo 60-4

[(1S)-1-{[4-(2-benciloxi-4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 1-2, el [(1S)-1-{[4-(2-benciloxi-4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo (1.18 gramos) se obtuvo a partir del [(1S)-1-{(4-hidroxi-piperidin-1-il)-carbonil}-2-metil-propil]-carbamato de terbutilo (1.24 gramos, 4.12 milimoles), y el 2-(benciloxi)-4-fluoro-fenol (900 miligramos, 4.12 milimoles) como una mezcla de aceite incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.40-7.34 (5H, m), 6.90 (1H, m), 6.70 (1H, m), 6.60 (1H, m), 5.36 (1H, d, J=8.8 Hz), 5.41 (1H, s), 5.07 (2H, s), 4.48 (1H, m), 4.38 (1H, m), 4.10-3.40 (4H, m), 1.93-1.81 (5H, m), 1.44 (9H, s), 0.97 (3H, d, J=6.4 Hz), 0.89 (3H, d, J=6.4 Hz).

MS (ESI, m/z): 501 $(M+H)^+$.

Ejemplo 60-5

[(1S)-1-{[4-(4-fluoro-2-hidroxi-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo

Se agregó el catalizador de paladio al 10 por ciento sobre carbón (120 miligramos) al [(1S)-1-{[4-(2-benciloxi-4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo (1.18 gramos, 2.36 milimoles), y la agitación se llevó a cabo a temperatura

ambiente durante 2 horas bajo una corriente de hidrógeno. La solución de la reacción se filtró con Celite, el filtrado se concentró, y el residuo resultante se purificó mediante cromatografía en gel de sílice, para proporcionar el [(1S)-1-{[4-(4-fluoro-2-hidroxi-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo (478 miligramos, rendimiento del 49 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 6.81(1H, dd, J=9.0 Hz, 5.1 Hz), 6.71 (1H, dd, J=9.2 Hz, 2.9 Hz), 6.58-6.53 (1H, m), 5.75 (1H, d, J=4.3 Hz), 5.33 (1H, t, J=8.0 Hz), 4.52-4.42 (2H, m), 4.10-3.75 (2H, m), 3.58-3.31 (2H, m), 2.11-1.72 (5H, m), 1.44 (9H, s), 0.97 (3H, t, J=6.0 Hz), 0.90 (3H, d, J=6.7 Hz).

MS (ESI, m/z): 411 $(M+H)^+$.

Ejemplo 60-6

N-[(1S)-1-{[4-(4-fluoro-2-hidroxi-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 1-3, el clorhidrato de (2S)-1-[4-(4-fluoro-2-hidroxi-fenoxi)-piperidin-1-il]-3-metil-1-oxobutan-2-amina se obtuvo a partir del [(1S)-1-{[4-(4-fluoro-2-hidroxi-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo (478 miligramos, 1.16 milimoles) como un sólido blanco. El compuesto resultante se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (220 miligramos, 1.16 milimoles), para proporcionar el compuesto del título deseado (411 miligramos, rendimiento del 73 por ciento) como un sólido amarillo pálido.

^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.84 (1H, s), 9.50 (1H, t, J=8.0 Hz), 9.46 (1H, s), 7.88 (1H, dd, J=7.8 Hz, 4.3 Hz), 7.65 (1H, t, J=7.6 Hz), 7.39 (2H, t, J=6.5 Hz), 7.04-7.00 (1H, m), 6.82 (1H, dt, J=10.0 Hz, 3.2 Hz), 6.57-6.52 (1H, m), 4.92 (1H, t, J=7.0 Hz), 4.48-4.47 (1H, m), 4.00-3.86 (2H, m), 3.54-3.25 (2H, m), 2.09-1.52 (5H, m), 0.96 (3H, d, J=6.8 Hz), 0.93 (3H, d, J=6.8 Hz).

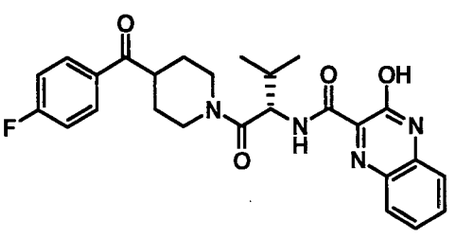
IR (KBr) cm^{-1}: 2965, 1690, 1630, 1525, 1505, 1230.

MS (ESI, m/z): 483 $(M+H)^+$.

HRMS (ESI, m/z): 505.1882 (Calculado para $C_{25}H_{27}FN_4NaO_5$: 505.1863).

Análisis calculado para $C_{25}H_{27}FN_4O_5 \cdot H_2O$: C, 59.99; H, 5.84; N, 11.19. Encontrado: C, 60.23; H, 5.57; N, 11.00.

Ejemplo 61



N-[(1S)-1-{[4-(4-fluoro-benzoil)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 61-1

[(1S)-1-{[4-(4-fluoro-benzoil)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 2-1, el [(1S)-1-{[4-(4-fluoro-benzoil)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo (3.88 gramos, rendimiento del 96 por ciento) se obtuvo a partir del

clorhidrato de 4-(4-fluoro-benzoil)-piperidina (2.44 gramos, 10.0 milimoles), y la N-(terbutoxi-carbonil)-L-valina (2.17 gramos, 10.0 milimoles) como una sustancia amorfa incolora.

Ejemplo 61-2

[(1S)-1-{[4-(4-fluoro-benzoil)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 2-2, el clorhidrato de (4-fluoro-fenil)-(1-L-valil-piperidin-4-il)-metanona (3.17 gramos, rendimiento del 97 por ciento) se obtuvo a partir del [(1S)-1-{[4-(4-fluoro-benzoil)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo (3.88 gramos, 9.55 milimoles) como una sustancia amorfa incolora. El compuesto resultante (200 miligramos, 0.580 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (110 miligramos, 0.580 milimoles), para proporcionar el compuesto del título deseado (143 miligramos, rendimiento del 51 por ciento) como un sólido amarillo pálido.

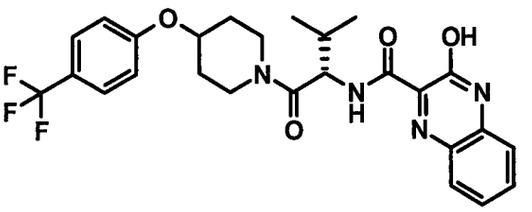
^{1}H-RMN ($CDCl_3$ 400 MHz) δ: 12.90 y 10.21 (1H, brs), 8.05-7.97 (2H, m), 7.61 (1H, d, J=6.8 Hz), 7.58 (1H, m), 7.37 (1H, brs), 7.21-7.13 (2H, m), 5.14-5.07 (1H, m), 4.68 y 4.59 (1H, m), 4.34 (1H, d, J=11.7 Hz), 3.60-3.35 (2H, m), 3.10-2.96 (1H, m), 3.10-2.96 (1H, m), 2.38-2.29 (1H, m), 2.11-0.96 (5H, m), 1.12-1.09 (6H, m).

IR (ATR) cm^{-1}: 1680, 1630, 1595, 1525, 1505, 1475.

MS (ESI, m/z): 479 $(M+H)^+$.

Análisis calculado para $C_{26}H_{27}FN_4O_4 \cdot 0.5H_2O$: C, 64.05; H, 5.79; N, 11.49. Encontrado: C, 64.20; H, 5.58; N, 11.34.

Ejemplo 62



3-hidroxi-N-[(1S)-2-metil-1-({4-[4-(trifluoro-metil)-fenoxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

Ejemplo 62-1

[(1S)-2-metil-1-({4-[4-(trifluoro-metil)-fenoxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 2-1, el [(1S)-2-metil-1-({4-[4-(trifluoro-metil)-fenoxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (1.41 gramos, rendimiento del 98 por ciento) se obtuvo a partir del clorhidrato de 4-[4-(trifluoro-metil)-fenoxi]-piperidina (913 miligramos, 3.24 milimoles), y N-(terbutoxi-carbonil)-L-valina (704 miligramos, 3.24 milimoles) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$ 400 MHz) δ: 7.55 (2H, d, J=8.5 Hz), 6.97 (2H, d, J=8.5 Hz), 5.33 (1H, d, J=8.8 Hz), 4.68-4.60 (1H, m), 4.49 (1H, dd, J=8.1 Hz, 6.4 Hz), 3.90-3.49 (4H, m), 2.04-1.80 (5H, m), 1.44 (9H, s), 0.98 (3H, d, J=6.8 Hz), 0.90 (3H, d, J=6.8 Hz).

IR (ATR) cm^{-1}: 2965, 1705, 1635, 1615, 1515, 1440, 1320, 1250.

MS (ESI, m/z): 445 $(M+H)^+$.

Ejemplo 62-2

3-hidroxi-N-[(1S)-2-metil-1-({4-[4-(trifluoro-metil)-fenoxi]-piperidin-1-

il}-carbonil)-propil]-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 2-2, el clorhidrato de (2S)-3-metil-1-oxo-1-{4-[4-(trifluoro-metil)-fenoxi]-piperidin-1-il}-butan-2-amina (1.14 gramos, rendimiento del 95 por ciento) se obtuvo a partir del [(1S)-2-metil-1-({4-[4-(trifluoro-metil)-fenoxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (1.41 gramos, 3.16 milimoles) como una sustancia amorfa. El compuesto resultante (220 miligramos, 0.580 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (110 miligramos, 0.580 milimoles), para proporcionar el compuesto del título deseado (132 miligramos, rendimiento del 45 por ciento) como un sólido blanco.

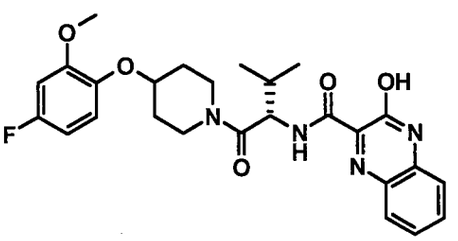
^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 12.57 y 10.15 (1H, brs), 7.98 (1H, d, J=4.6 Hz), 7.65-7.53 (4H, m), 7.37 (1H, brs), 6.99 (2H, d, J=8.6 Hz), 5.07 (1H, t, J=7.3 Hz), 4.72-4.65 (1H, m), 4.03-3.62 (5H, m), 2.36-2.10 (2H, m), 2.02-1.80 (3H, m), 1.12 (3H, d, J=6.8 Hz), 1.11 (3H, d, J=6.8 Hz).

IR (ATR) cm^{-1}: 1685, 1630, 1610, 1515, 1445, 1320, 1250.

MS (ESI, m/z): 517 $(M+H)^+$.

Análisis calculado para $C_{26}H_{27}F_3N_4O_4$: C, 60.46; H, 5.27; N, 10.85. Encontrado: C, 60.23; H, 5.23; N, 10.82.

Ejemplo 63



N-[(1S)-1-{[4-(4-fluoro-2-metoxi-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 63-1

[(1S)-1-{[4-(4-fluoro-2-metoxi-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo

Una solución al 40 por ciento en tolueno de azodicarboxilato de di-isopropilo (0.930 mililitros, 1.83 milimoles) se agregó a una solución en tolueno (15 mililitros) de {(1S)-1-[(4-hidroxi-piperidin-1-il)-carbonil]-2-metil-propil}-carbamato de terbutilo (500 miligramos, 1.66 milimoles), 4-fluoro-2-metoxi-fenol (260 miligramos, 1.83 milimoles), y trifenil-fosfina (480 miligramos, 1.83 milimoles), a temperatura ambiente, bajo una corriente de nitrógeno, y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Yamazen Corporation, W-Prep 2XY), para proporcionar el [(1S)-1-{[4-(4-fluoro-2-metoxi-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo (520 miligramos, rendimiento del 74 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 6.89 y 6.87 (1H, d, J=8.8 Hz), 6.65 (1H, m), 6.66 y 6.65 (1H, d, J=2.4 Hz), 6.58 y 6.57 (1H, dd, J=8.8 Hz, 2.4 Hz), 5.36 (1H, d, J=9.2 Hz), 4.50 (1H, dd, J=9.2 Hz, 5.4 Hz), 3.92-3.78 (5H, m), 3.63-3.39 (2H, m), 1.98-1.75 (5H, m), 1.44 y 1.43 (9H, s), 0.97 (3H, t, J=7.3 Hz), 0.89 (3H, dd, J=6.4 Hz).

MS (ESI, m/z): 425 $(M+H)^+$.

Ejemplo 63-2

N-[(1S)-1-{[4-(4-fluoro-2-metoxi-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Se agregó ácido clorhídrico concentrado (5.0 mililitros) a una solución en etanol (10 mililitros) de [(1S)-1-{[4-(4-fluoro-2-metoxi-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo (400 miligramos, 0.940 milimoles), bajo una corriente de nitrógeno, y la mezcla se dejó reaccionar a temperatura ambiente durante la noche. La solución de la reacción se concentró, para proporcionar el clorhidrato de (2S)-1-[4-(4-fluoro-2-metoxi-fenoxi)-piperidin-1-il]-3-metil-1-oxobutan-2-amina (340 miligramos) como una sustancia amorfa incolora.

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (270 miligramos, 1.41 milimoles), monohidrato de 1-hidroxi-benzotriazol (150 miligramos, 1.13 milimoles), y N-metil-morfolina (0.410 mililitros, 3.77 milimoles), se agregaron a una solución en cloruro de metileno (10 mililitros) del compuesto resultante (340 miligramos, 0.940 milimoles), y ácido 3-hidroxi-quinoxalin-2-carboxílico (180 miligramos, 0.940 milimoles), a temperatura ambiente, bajo una corriente de nitrógeno, y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se lavó en secuencia con agua, una solución acuosa saturada de carbonato ácido de sodio, agua, y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio

anhidro. La capa orgánica se concentró, el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Yamazen Corporation, W-Prep 2XY), el residuo resultante de la concentración se suspendió en dietil-éter, y la sustancia sólida se recolectó mediante filtración, para proporcionar el compuesto del título deseado (459 miligramos, rendimiento del 98 por ciento) como un sólido amarillo pálido.

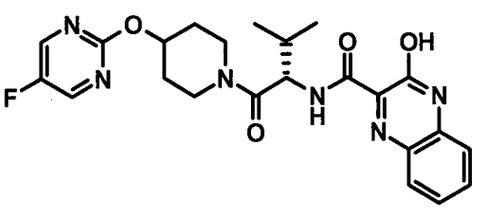
^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.86 (1H, brs), 9.55 (1H, brs), 7.89 (1H, d, J=8.3 Hz), 7.66 (1H, t, J=7.2 Hz), 7.43-7.37 (2H, m), 7.11-7.06 (1H, m), 6.98-6.93 (1H, m), 6.78-6.73 (1H, m), 4.93 (1H, q, J=7.8 Hz), 4.51-4.43 (1H, m), 3.99-3.87 (2H, m), 3.81 (3H, d, J=6.8 Hz), 3.58-3.45 (2H, m), 2.11-1.84 (3H, m), 1.75-1.49 (2H, m), 0.98 (3H, d, J=6.8 Hz), 0.97 (3H, d, J=6.8 Hz).

IR (KBr) cm^{-1}: 2960, 1685, 1640, 1500, 1450, 1215, 1190, 1150, 1030.

MS (ESI, m/z): 497 $(M+H)^+$.

Análisis calculado para $C_{26}H_{29}FN_4O_5 \cdot 1/4H_2O$: C, 62.33; H, 5.93; N, 11.18; F, 3.79. Encontrado: C, 62.07; H, 6.02; N, 11.04; F, 3.68.

Ejemplo 64



N-[(1S)-1-({4-[(5-fluoro-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 64-1

[(1S)-1-({4-[(5-fluoro-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo

Se agregó hidruro de sodio al 63 por ciento (278 miligramos, 7.32 milimoles) a una solución en N,N-dimetil-formamida (20 mililitros) de 2-cloro-5-fluoro-pirimidina (452 miligramos, 3.66 milimoles), y N-{(1S)-1-[(4-hidroxi-piperidin-1-il)-carbonil]-2-metil-propil}-carbamato de terbutilo (1.00 gramos, 3.32 milimoles), a 0°C, bajo una corriente de nitrógeno, y la agitación se llevó a cabo a temperatura ambiente durante la noche. Se agregó agua a la solución de la reacción bajo enfriamiento con hielo, seguida por extracción con acetato de etilo. El extracto se lavó en secuencia con agua, una solución acuosa saturada de carbonato ácido de sodio, agua, y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., 25+M), para proporcionar el [(1S)-1-({4-[(5-fluoro-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (568 miligramos, rendimiento del 43 por ciento) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.36 (2H, s), 5.41 (1H, d, J=9.0 Hz), 5.26-5.16 (1H, m), 4.53-4.47 (1H, m), 4.06-3.78 (2H, m), 3.74-3.45 (2H, m), 2.02-1.92 (5H, m), 1.50-1.39 (9H, m), 0.98 (3H, t, J=6.8

Hz), 0.86 (3H, t, J=6.8 Hz).

MS (FAB, m/z): 397 $(M+H)^+$.

Ejemplo 64-2

N-[(1S)-1-({4-[(5-fluoro-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 1-3, el clorhidrato de (2S)-1-{4-[(5-fluoro-pirimidin-2-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina (163 miligramos) se obtuvo a partir del [(1S)-1-({4-[(5-fluoro-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (194 miligramos, 0.489 milimoles) como un sólido blanco. El compuesto resultante (163 miligramos, 0.489 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (139 miligramos, 0.734 milimoles), para proporcionar el compuesto del título deseado (90.0 miligramos, rendimiento del 39 por ciento) como un sólido amarillo pálido.

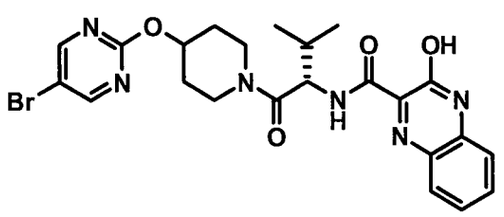
^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.80 (1H, brs), 9.46 (1H, brs), 8.68 (1H, d, J=3.1 Hz), 8.60 (1H, d, J=3.1 Hz), 7.84 (1H, d, J=8.2 Hz), 7.62 (1H, t, J=7.6 Hz), 7.37-7.35 (2H, m), 4.92-4.85 (2H, m), 3.95-3.90 (2H, m), 3.55-3.19 (2H, m), 2.07-1.55 (5H, m), 0.94-0.92 (6H, m).

IR (KBr) cm^{-1} : 2960, 1685, 1640, 1530, 1430, 1275.

MS (FAB, m/z): 469 $(M+H)^+$.

HRMS (ESI, m/z): 469.2001 (Calculado para $C_{23}H_{26}FN_6O_4$: 469.1999).

Ejemplo 65



N-[(1S)-1-({4-[(5-bromo-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 65-1

[(1S)-1-({4-[(5-bromo-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 64-1, el N-[(1S)-1-({4-(5-bromo-pirimidin-2-il)-oxi}-piperidin-1-il)-carbonil]-2-metil-propil]-carbamato de terbutilo (1.74 gramos, rendimiento del 57 por ciento) se obtuvo a partir del 5-bromo-2-cloro-pirimidina (1.42 gramos, 7.32 milimoles), y {(1S)-1-[(4-hidroxi-piperidin-1-il)-carbonil]-2-metil-propil}-carbamato de terbutilo (2.00 gramos, 6.66 milimoles) como un sólido blanco.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.53 (2H, s), 5.36-5.35 (1H, m), 5.27-5.18 (1H, m), 4.51-4.49 (1H, m), 4.02-3.68 (3H, m), 3.59-3.44 (1H, m), 2.10-1.82 (5H, m), 1.44 (9H, brs), 0.97 (3H, d, J=6.6 Hz), 0.89 (3H, d, J=6.6 Hz).

MS (FAB, m/z): 457 $(M+H)^+$.

Ejemplo 65-2

N-[(1S)-1-({4-[(5-bromo-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 1-3, el clorhidrato de (2S)-1-{4-[(5-bromo-pirimidin-2-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina (1.50 gramos) se obtuvo a partir del [(1S)-1-({4-[(5-bromo-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (1.74 gramos, 3.80 milimoles) como un sólido blanco. El compuesto resultante (200 miligramos, 0.508 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (145 miligramos, 0.762 milimoles), para proporcionar el compuesto del título deseado (136 miligramos, rendimiento del 51 por ciento) como un sólido amarillo pálido.

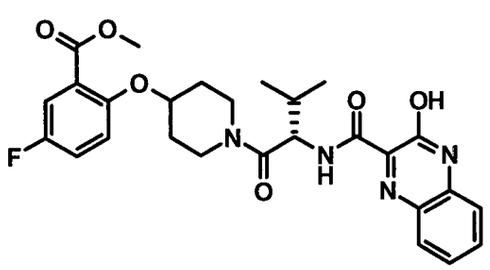
^{1}H-RMN (DMSO-d_6, 500 MHz) δ: 12.83 (1H, brs), 9.55 (1H, brs), 8.77 (2H, d, J=3.9 Hz), 7.86 (1H, d, J=7.8 Hz), 7.63 (1H, t, J=7.8 Hz), 7.38-7.36 (2H, m), 5.19 (1H, brs), 4.91 (1H, q, J=7.8 Hz), 4.04-3.91 (2H, m), 3.59-3.22 (2H, m), 2.06-2.01 (3H, m), 1.78-1.57 (2H, m), 0.96-0.95 (6H, m).

IR (KBr) cm^{-1}: 2965, 1690, 1630, 1540, 1425, 1320.

MS (ESI, m/z): 529 $(M+H)^+$.

HRMS (ESI, m/z): 529.1197 (Calculado para $C_{23}H_{26}BrN_6O_4$: 529.1198).

Ejemplo 66



5-fluoro-2-[(1-{N-[(3-hidroxi-quinoxalin-2-il)-carbonil]-L-valil}-piperidin-4-il)-oxi]-benzoato de metilo

Ejemplo 66-1

4-[4-fluoro-2-(metoxi-carbonil)-fenoxi]-piperidin-1-carboxilato de terbutilo

De una manera análoga al Ejemplo 23-1, el 4-[4-fluoro-2-(metoxi-carbonil)-fenoxi]-piperidin-1-carboxilato de terbutilo (2.39 gramos, rendimiento del 91 por ciento) se obtuvo a partir del 4-hidroxi-piperidin-1-carboxilato de terbutilo (1.50 gramos, 7.45 milimoles), y 5-fluoro-2-hidroxi-benzoato de metilo (1.40 gramos, 8.20 milimoles) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.52-7.49 (1H, m), 7.17-7.12 (1H, m), 6.95 (1H, dd, J=9.4 Hz, 4.3 Hz), 4.52-4.48 (1H, m), 3.90 (3H, s), 3.66-3.60 (2H, m), 3.48-3.42 (2H, m), 1.91-1.78 (4H, m), 1.49-1.43 (9H, m).

MS (FAB, m/z): 354 $(M+H)^+$.

Ejemplo 66-2

2-({1-[N-(terbutoxi-carbonil)-L-valil]-piperidin-4-il}-oxi)-5-fluoro-benzoato de metilo

De una manera análoga al Ejemplo 23-2, el clorhidrato de 5-fluoro-2-[(piperidin-4-il)-oxi]-benzoato de metilo (1.87 gramos, rendimiento del 95 por ciento) se obtuvo a partir del 4-[4-fluoro-2-(metoxi-carbonil)-fenoxi]-piperidin-1-carboxilato de terbutilo (2.39 gramos, 6.76 milimoles) como un sólido blanco. El compuesto resultante (1.87 gramos, 6.45 milimoles) se condensó con N-

(terbutoxi-carbonil)-L-valina (1.54 gramos, 7.10 milimoles), para proporcionar el 2-({1-[N-(terbutoxi-carbonil)-L-valil]-piperidin-4-il}-oxi)-5-fluoro-benzoato de metilo (2.62 gramos, rendimiento del 90 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.53 (1H, dd, J=8.6 Hz, 4.3 Hz), 7.18-7.16 (1H, m), 6.94 (1H, dd, J=9.0 Hz, 4.3 Hz), 5.36-5.34 (1H, m), 4.62-4.60 (1H, m), 4.50 (1H, dd, J=9.0 Hz, 5.5 Hz), 3.97 (3H, s), 3.89-3.54 (4H, m), 1.97-1.83 (5H, m), 1.44 (9H, s), 0.98 (3H, d, J=6.8 Hz), 0.89 (3H, d, J=6.8 Hz).

MS (FAB, m/z): 453 $(M+H)^+$.

Ejemplo 66-3

5-fluoro-2-[(1-{N-[(3-hidroxi-quinoxalin-2-il)-carbonil]-L-valil}-piperidin-4-il)-oxi]-benzoato de metilo

De una manera análoga al Ejemplo 23-3, el clorhidrato de 5-fluoro-2-[(1-L-valil-piperidin-4-il)-oxi]-benzoato de metilo (1.72 gramos) se obtuvo a partir del 2-({1-[N-(terbutoxi-carbonil)-L-valil]-piperidin-4-il}-oxi)-5-fluoro-benzoato de metilo (1.86 gramos, 5.79 milimoles) como un sólido blanco. El compuesto resultante (1.00 gramos, 2.57 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (734 miligramos, 3.86 milimoles), para proporcionar el compuesto del título deseado (1.09 gramos, rendimiento del 74 por ciento) como un sólido amarillo pálido.

^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.83 (1H, s), 9.49 (1H, d, J=8.2 Hz), 7.87 (1H, d, J=8.2 Hz), 7.65 (1H, t, J=8.2 Hz), 7.50-7.29 (5H, m), 4.92 (1H, q, J=7.4 Hz), 4.78 (1H, brs), 3.81 (3H, s), 3.71-

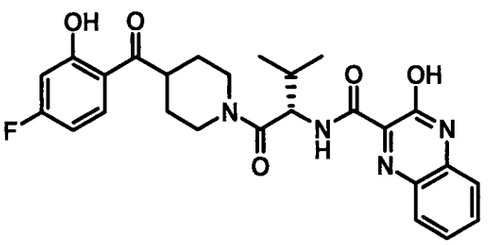
3.69 (4H, m), 2.09-1.67 (5H, m), 0.97-0.95 (6H, m).

IR (KBr) cm^{-1}: 2960, 1685, 1640, 1495, 1270, 1185.

MS (FAB, m/z): 525 $(M+H)^+$.

HRMS (ESI, m/z): 525.2127 (Calculado para $C_{27}H_{30}FN_4O_6$: 525.2149).

Ejemplo 67



N-[(1S)-1-{[4-(4-fluoro-2-hidroxi-benzoil)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 67-1

[(1S)-1-{[4-(6-fluoro-1,2-bencisoxazol-3-il)-piperidin-1-il]-carbonil}-2-metil-propil}-carbamato de terbutilo

De una manera análoga al Ejemplo 2-1, el 6-fluoro-3-(piperidin-4-il)-1,2-bencisoxazol (2.00 gramos, 9.08 milimoles) se condensó con N-(terbutoxi-carbonil)-L-valina (2.17 gramos, 9.99 milimoles), para proporcionar el [(1S)-1-{[4-(6-fluoro-1,2-bencisoxazol-3-il)-piperidin-1-il]-carbonil}-2-metil-propil}-carbamato de terbutilo (3.70 gramos, rendimiento del 97 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.71-7.61 (1H, m), 7.29-7.25 (1H, m), 7.09-7.04 (1H, m), 5.35 (1H, dd, J=17.8 Hz, 9.2 Hz), 4.67-4.55 (2H, m), 4.19-4.09 (1H, m), 3.42-3.27 (2H, m), 3.02-2.92 (1H, m),

2.24-1.82 (5H, m), 1.48-1.46 (9H, m), 1.00 (3H, t, J=6.6 Hz), 0.90 (3H, t, J=6.6 Hz).

MS (FAB, m/z): 420 $(M+H)^+$.

Ejemplo 67-2

N-[(1S)-1-{[4-(6-fluoro-1,2-bencisoxazol-3-il)-piperidin-1-il]-carbonil}-2-metil-propil}-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 1-3, el clorhidrato de (2S)-1-[4-(6-fluoro-1,2-bencisoxazol-3-il)-piperidin-1-il]-3-metil-1-oxobutan-2-amina (3.20 gramos) se obtuvo a partir del [(1S)-1-{[4-(6-fluoro-1,2-bencisoxazol-3-il)-piperidin-1-il]-carbonil}-2-metil-propil}-carbamato de terbutilo (3.70 gramos, 8.78 milimoles) como un sólido blanco. El compuesto resultante (400 miligramos, 1.12 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (319 miligramos, 1.68 milimoles), para proporcionar la N-[(1S)-1-{[4-(6-fluoro-1,2-bencisoxazol-3-il)-piperidin-1-il]-carbonil}-2-metil-propil}-3-hidroxi-quinoxalin-2-carboxamida (220 miligramos, rendimiento del 40 por ciento) como un sólido amarillo pálido.

^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 9.50 (1H, t, J=7.6 Hz), 8.07-8.03 (1H, m), 7.88-7.61 (3H, m), 7.42-7.21 (3H, m), 4.95-4.91 (1H, m), 4.51 (1H, t, J=12.1 Hz), 4.27 (1H, d, J=12.1 Hz), 3.53-3.51 (1H, m), 3.41-3.25 (1H, m), 3.00-2.93 (2H, m), 2.11-1.75 (5H, m), 0.97 (6H, t, J=6.8 Hz).

IR (KBr) cm^{-1}: 2960, 1685, 1635, 1530, 1450, 1275, 1120.

MS (FAB, m/z): 492 $(M+H)^+$.

HRMS (ESI, m/z): 492.2035 (Calculado para $C_{26}H_{27}FN_5O_4$:

492.2047).

Ejemplo 67-3

N-[(1S)-1-{[4-(4-fluoro-2-hidroxi-benzoil)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Se agregó un catalizador de paladio al 5 por ciento sobre carbón (50.0 miligramos) a una solución en metanol (3.0 mililitros) de N-[(1S)-1-{[4-(6-fluoro-1,2-bencisoxazol-3-il)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida (150 miligramos, 0.305 milimoles), y la agitación se llevó a cabo a temperatura ambiente durante 3 horas bajo una atmósfera de hidrógeno. La solución de la reacción se filtró con Celite, y el filtrado se concentró. El residuo resultante se disolvió en una solución en tetrahidrofurano (3.0 mililitros), y se agregó una solución acuosa de hidróxido de sodio 2N (3.0 mililitros), seguido por reacción a temperatura ambiente durante la noche. Bajo enfriamiento con hielo, la solución de la reacción se vertió en una solución acuosa de ácido clorhídrico 2N, seguido por extracción con acetato de etilo, y lavado en secuencia con agua y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, para proporcionar el compuesto del título deseado (122 miligramos, rendimiento del 81 por ciento) como un sólido amarillo pálido.

^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.83 (1H, brs), 12.25 (1H, d, J=6.3 Hz), 9.48 (1H, dd, J=16.2 Hz, 8.8 Hz), 8.11-8.07 (1H, m), 7.87 (1H, dd, J=8.8 Hz, 4.0 Hz), 7.65 (1H, t, J=7.8 Hz), 7.40-7.38 (2H, m),

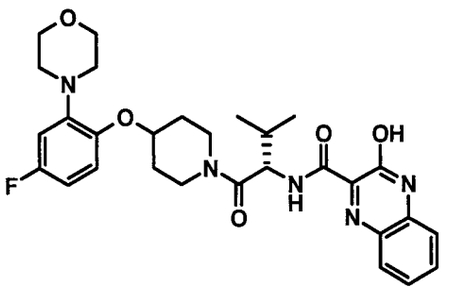
6.86-6.84 (2H, m), 4.93-4.92 (1H, m), 4.49-4.46 (1H, m), 4.22-4.20 (1H, m), 3.81-3.79 (1H, m), 3.33-3.30 (1H, m), 2.83 (1H, m), 2.05-1.88 (3H, m), 1.67-1.40 (2H, m), 0.96 (6H, t, J=6.8 Hz).

IR (KBr) cm^{-1}: 2965, 1685, 1635, 1530, 1200.

MS (ESI, m/z): 517 $(M+Na)^+$.

HRMS (ESI, m/z): 517.1827 (Calculado para $C_{26}H_{27}FN_4NaO_5$: 517.1863).

Ejemplo 68



N-[(1S)-1-({4-[4-fluoro-2-(morfolin-4-il)-fenoxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 68-1

4-(2-bromo-4-fluoro-fenoxi)-piperidin-1-carboxilato de terbutilo

De una manera análoga al Ejemplo 1-2, el 4-(2-bromo-4-fluoro-fenoxi)-piperidin-1-carboxilato de terbutilo (2.45 gramos, rendimiento del 88 por ciento) se obtuvo a partir del 4-hidroxi-piperidin-1-carboxilato de terbutilo (1.50 gramos, 7.45 milimoles), y terbutil-2-bromo-4-fluoro-fenol (1.57 gramos, 8.20 milimoles) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.31-7.27 (1H, m), 6.99-6.93 (1H, m), 6.91-6.86 (1H, m), 4.47-4.43 (1H, m), 3.69-3.62 (2H, m), 3.47-

3.44 (2H, m), 1.91-1.78 (4H, m), 1.47-1.43 (9H, m).

MS (FAB, m/z): 374 $(M+H)^+$.

Ejemplo 68-2

4-[4-fluoro-2-(morfolin-4-il)-fenoxi]-piperidin-1-carboxilato de terbutilo

Se agregaron en secuencia terbutóxido de sodio (77.0 miligramos, 0.801 milimoles), 2,2'-bis-(difenil-fosfino)-1,1'-binaftilo (200 miligramos, 0.320 milimoles), y tris-(dibenciliden-acetona)-dipaladio (61.0 miligramos, 0.107 milimoles) a una solución en tolueno (5 mililitros) de 4-(2-bromo-4-fluoro-fenoxi)-piperidin-1-carboxilato de terbutilo (910 miligramos, 3.67 milimoles), y morfolina (0.0700 mililitros, 0.801 milimoles), a temperatura ambiente, bajo una corriente de nitrógeno, seguido por calentamiento a reflujo durante 10 horas. La solución de la reacción se vertió en agua helada, seguido por extracción con acetato de etilo, el extracto se lavó en secuencia con una solución acuosa saturada de carbonato ácido de sodio, agua, y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., 25+M), para proporcionar el 4-[4-fluoro-2-(morfolin-4-il)-fenoxi]-piperidin-1-carboxilato de terbutilo (154 miligramos, rendimiento del 76 por ciento) como una sustancia oleosa amarilla.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 6.83-6.80 (1H, m), 6.63-6.61 (2H, m), 4.47-4.42 (1H, m), 3.84 (4H, t, J=4.7 Hz), 3.73-3.67 (2H, m), 3.35-3.31 (2H, m), 3.08 (4H, t, J=4.7 Hz), 1.91-1.84 (2H, m), 1.77-

1.69 (2H, m), 1.51-1.43 (9H, m).

MS (FAB, m/z): 381 $(M+H)^+$.

Ejemplo 68-3

[(1S)-1-{[4-(4-fluoro-2-morfolin-4-il-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 23-2, el clorhidrato de 4-{5-fluoro-2-[(piperidin-4-il)-oxi]-fenil}-morfolina (128 miligramos, rendimiento del 100 por ciento) se obtuvo a partir del 4-[4-fluoro-2-(morfolin-4-il)-fenoxi]-piperidin-1-carboxilato de terbutilo (154 miligramos, 0.405 milimoles) como un sólido blanco. El compuesto resultante (128 miligramos, 0.405 milimoles) se condensó con N-(terbutoxi-carbonil)-L-valina (132 miligramos, 0.607 milimoles), para proporcionar el [(1S)-1-({4-[4-fluoro-2-(morfolin-4-il)-fenoxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (199 miligramos, rendimiento del 100 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 6.85-6.81 (1H, m), 6.66-6.62 (2H, m), 5.35 (1H, t, J=4.5 Hz), 4.53-4.51 (2H, m), 3.85-3.43 (4H, m), 3.84 (4H, t, J=4.7 Hz), 3.08 (4H, t, J=4.7 Hz), 1.99-1.76 (5H, m), 1.43-1.41 (9H, m), 1.00 (3H, t, J=6.8 Hz), 0.90 (3H, t, J=6.8 Hz).

MS (FAB, m/z): 480 $(M+H)^+$.

Ejemplo 68-4

N-[(1S)-1-({4-[4-fluoro-2-(morfolin-4-il)-fenoxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 2-2, el clorhidrato de (2S)-

1-{4-[4-fluoro-2-(morfolin-4-il)-fenoxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina (223 miligramos) se obtuvo a partir del [(1S)-1-({4-[4-fluoro-2-(morfolin-4-il)-fenoxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (195 miligramos, 0.405 milimoles) como un sólido blanco. El compuesto resultante (223 miligramos, 0.405 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (116 miligramos, 0.608 milimoles), para proporcionar el compuesto del título deseado (133 miligramos, rendimiento del 57 por ciento) como un sólido amarillo pálido.

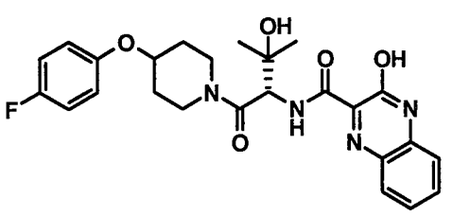
^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.81 (1H, s), 9.51 (1H, d, J=7.4 Hz), 7.86 (1H, d, J=7.4 Hz), 7.64-7.63 (1H, m), 7.39-7.37 (2H, m), 7.05-7.02 (1H, m), 6.75-6.73 (2H, m), 4.91 (1H, dd, J=14.5 Hz, 4.5 Hz), 4.60 (1H, brs), 3.85-3.57 (8H, m), 3.01 (4H, t, J=4.7 Hz), 2.07-1.59 (5H, m), 0.97-0.93 (6H, m).

IR (KBr) cm^{-1}: 2965, 1685, 1630, 1495, 1215, 1120.

MS (FAB, m/z): 552 $(M+H)^+$.

HRMS (ESI, m/z): 552.2600 (Calculado para $C_{29}H_{35}FN_5O_5$: 552.2622).

Ejemplo 69



N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-hidroxi-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 69-1

[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-hidroxi-2-metil-propil]-carbamato de terbutilo

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (115 miligramos, 0.600 milimoles), monohidrato de 1-hidroxi-benzotriazol (81.0 miligramos, 0.600 milimoles), y N-metil-morfolina (0.440 mililitros, 2.00 milimoles) se agregaron a una solución en cloruro de metileno (2.0 mililitros) de clorhidrato de 4-(4-fluoro-fenoxi)-piperidina (116 miligramos, 0.500 milimoles), y ácido N-(terbutoxi-carbonil)-(S)-2-amino-3-hidroxi-3-metil-butanoico (117 miligramos, 0.500 milimoles), a 0°C, bajo una corriente de nitrógeno, y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se diluyó con cloruro de metileno, seguido por lavado en secuencia con una solución acuosa saturada de carbonato ácido de sodio, una solución acuosa saturada de cloruro de amonio, agua, y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en gel de sílice, para proporcionar el [(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-hidroxi-2-metil-propil]-carbamato de terbutilo (89.0 miligramos, rendimiento del 44 por ciento) como una sustancia amorfa incolora.

Mayor: ^{1}H-RMN ($CDCl_3$, 500 MHz) δ: 7.00-6.96 (2H, m), 6.86-6.85 (2H, m), 5.50 (1H, d, J=8.4 Hz), 4.72 (1H, s), 4.50-4.48

(1H, m), 4.45 (1H, s), 3.81-3.79 (2H, m), 3.66-3.64 (2H, m), 1.99-1.84 (4H, m), 1.44 (9H, s), 1.25 (6H, s).

Menor: ^{1}H-RMN ($CDCl_3$, 500 MHz) δ: 7.00-6.96 (2H, m), 6.86-6.85 (2H, m), 5.52 (1H, d, J=8.4 Hz), 4.79 (1H, s), 4.45-4.43 (1H, m), 4.43 (1H, s), 3.96-3.94 (2H, m), 3.82-3.79 (2H, m), 1.99-1.84 (4H, m), 1.44 (9H, s), 1.21 (6H, s).

MS (FAB, m/z): 410 $(M+H)^+$.

Ejemplo 69-2

N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-hidroxi-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Se agregaron agua (0.5 mililitros) y ácido clorhídrico concentrado (0.5 mililitros) a una solución en 1,4-dioxano (2.0 mililitros) de [(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-hidroxi-2-metil-propil]-carbamato de terbutilo (86.0 miligramos, 0.210 milimoles), y la mezcla se dejó reaccionar a temperatura ambiente durante la noche. La solución de la reacción se concentró, para proporcionar el clorhidrato de (3S)-3-amino-4-[4-(4-fluoro-fenoxi)-piperidin-1-il]-2-metil-4-oxobutan-2-ol como un aceite incoloro. Este producto se utilizó como estaba en la siguiente reacción sin purificación.

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (48.0 miligramos, 0.250 milimoles), monohidrato de 1-hidroxi-benzotriazol (34.0 miligramos, 0.250 milimoles), y N-metil-morfolina (0.0930 mililitros, 0.840 milimoles), se agregaron a una solución en cloruro de metileno (4.0 mililitros) del compuesto resultante y ácido

3-hidroxi-quinoxalin-2-carboxílico (40.0 miligramos, 0.210 milimoles), a temperatura ambiente, bajo una corriente de nitrógeno, y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se vertió en una solución acuosa de ácido clorhídrico 2N, seguido por extracción con acetato de etilo. El extracto se lavó en secuencia con agua y una solución salina, y entonces se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, el residuo resultante se purificó mediante cromatografía en gel de sílice, el residuo resultante se suspendió en dietil-éter, y entonces la sustancia sólida se recolectó mediante filtración, para proporcionar el compuesto del título deseado (62.0 miligramos, rendimiento del 62 por ciento) como un sólido amarillo pálido.

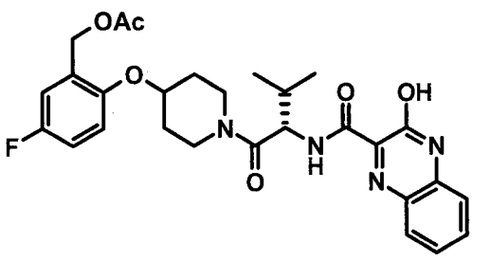
^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.86 (1H, s), 9.74 (1H, m), 7.88 (1H, dd, J=8.8 Hz, 1.6 Hz), 7.41-7.38 (2H, m), 7.15-7.10 (2H, m), 7.04-7.01 (2H, m), 5.11 (1H, m), 4.93 (1H, s), 4.62-4.58 (1H, m), 4.02-3.93 (2H, m), 3.57-3.53 (1H, m), 3.32-3.30 (1H, m), 2.01-1.98 (1H, m), 1.93-1.89 (1H, m), 1.70-1.68 (1H, m), 1.53-1.49 (1H, m), 1.24 (3H, s), 1.17 (3H, s).

IR (KBr) cm^{-1}: 2975, 1685, 1625, 1505, 1205.

HRMS (ESI, m/z): 483.2050 (Calculado para $C_{25}H_{28}FN_4O_5$: 483.2043).

Análisis calculado para $C_{24}H_{27}FN_4O_5 \cdot 0.2H_2O$: C, 61.77; H, 5.68; N, 11.53; F, 3.91. Encontrado: C, 61.73; H, 5.51; N, 11.59; F, 4.14.

Ejemplo 70



Acetato de 5-fluoro-2-[(1-{N-[(3-hidroxi-quinoxalin-2-il)-carbonil]-L-valil}-piperidin-4-il)-oxi]-bencilo

Ejemplo 70-1

Acetato de 2-({1-[N-(terbutoxi-carbonil)-L-valil]-piperidin-4-il}-oxi)-5-fluoro-bencilo

Una solución en tolueno de hidruro de di-isobutil-aluminio (0.990 M, 13.6 mililitros, 13.5 milimoles) se agregó lentamente por goteo a una solución en tetrahidrofurano (50 mililitros) de 4-(4-fluoro-2-metoxi-carbonil-fenoxi)-piperidin-1-carboxilato de terbutilo (1.59 gramos, 4.50 milimoles), a 0°C, bajo una corriente de nitrógeno, y la agitación se llevó a cabo a 0°C durante 1 hora. Después de completarse la reacción, se agregaron en secuencia una solución acuosa de sal de Rochelle y acetato de etilo, y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se extrajo con acetato de etilo, y entonces el extracto se lavó en secuencia con una solución acuosa saturada de carbonato ácido de sodio, agua y solución salina. La capa orgánica resultante se secó sobre sulfato de sodio anhidro, y entonces el residuo

resultante de la concentración se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., 25+M), para proporcionar el 4-(4-fluoro-2-hidroxi-metil-fenoxi)-piperidin-1-carboxilato de terbutilo (1.13 gramos, rendimiento del 77 por ciento) como un aceite incoloro.

Se agregó anhídrido acético (0.304 mililitros, 3.24 milimoles) a una solución en piridina (5 mililitros) del compuesto resultante (350 miligramos, 1.08 milimoles), bajo una corriente de nitrógeno, y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se concentró, para proporcionar el 4-(2-acetoxi-metil-4-fluoro-fenoxi)-piperidin-1-carboxilato de terbutilo (396 miligramos) como un aceite incoloro.

De una manera análoga al Ejemplo 23-2, el clorhidrato de acetato de 5-fluoro-2-[(piperidin-4-il)-oxi]-bencilo (328 miligramos) se obtuvo a partir del compuesto resultante (396 miligramos, 1.08 milimoles) como un sólido blanco. El compuesto resultante (328 miligramos, 1.08 milimoles) se condensó con N-(terbutoxi-carbonil)-L-valina (352 miligramos, 1.62 milimoles), para proporcionar el acetato de 2-({1-[N-(terbutoxi-carbonil)-L-valil]-piperidin-4-il}-oxi)-5-fluoro-bencilo (475 miligramos, rendimiento del 94 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.08 (1H, dd, J=9.0 Hz, 2.9 Hz), 6.99-6.96 (1H, m), 6.82 (1H, dd, J=9.0 Hz, 4.3 Hz), 5.35 (1H, d, J=9.0 Hz), 5.14 (2H, d, J=8.6 Hz), 4.58-4.48 (2H, m), 3.88-3.48 (4H, m), 2.11 (3H, s), 1.99-1.81 (5H, m), 1.47-1.44 (9H, m), 0.97 (3H, d,

J=6.6 Hz), 0.89 (3H, d, J=6.6 Hz).

MS (FAB, m/z): 467 $(M+H)^+$.

Ejemplo 70-2

Acetato de 5-fluoro-2-[(1-{N-[(3-hidroxi-quinoxalin-2-il)-carbonil]-L-valil}-piperidin-4-il)-oxi]-bencilo

De una manera análoga al Ejemplo 23-3, el clorhidrato de acetato de 5-fluoro-2-[(1-valil-piperidin-4-il)-oxi]-bencilo (410 miligramos) se obtuvo a partir del acetato de 2-({1-[N-(terbutoxi-carbonil)-L-valil]-piperidin-4-il}-oxi)-5-fluoro-bencilo (475 miligramos, 1.02 milimoles) como un sólido blanco. El compuesto resultante (230 miligramos, 0.571 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (163 miligramos, 0.856 milimoles), para proporcionar el compuesto del título deseado (240 miligramos, rendimiento del 78 por ciento) como un sólido amarillo pálido.

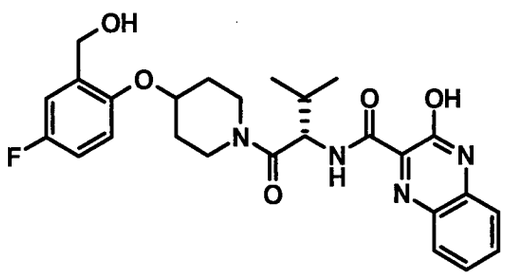
^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 9.57 (1H, d, J=9.0 Hz), 7.86-7.85 (1H, m), 7.64-7.62 (1H, m), 7.38 (2H, d, J=7.8 Hz), 7.19-7.15 (3H, m), 5.07 (2H, d, J=8.6 Hz), 4.91 (1H, m), 4.71 (1H, brs), 4.10 (1H, brs), 3.70-3.54 (4H, m), 2.08-1.60 (8H, m), 0.95 (6H, t, J=5.9 Hz).

IR (KBr) cm^{-1}: 2960, 1685, 1640, 1495, 1225, 1030.

MS (ESI, m/z): 539 $(M+H)^+$, 561 $(M+Na)^+$.

HRMS (ESI, m/z): 561.2138 (Calculado para $C_{28}H_{31}FN_4NaO_6$: 561.2125).

Ejemplo 71



N-[(1S)-1-({4-[4-fluoro-2-(hidroxi-metil)-fenoxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Una solución acuosa de hidróxido de sodio 2N (3 mililitros) se agregó a una solución en tetrahidrofurano (3.0 mililitros) de 5-fluoro-2-[(1-{N-[(3-hidroxi-quinoxalin-2-il)-carbonil]-L-valil}-piperidin-4-il)-oxi]-benzoato de metilo (120 miligramos, 0.223 milimoles), y la agitación se llevó a cabo a temperatura ambiente durante la noche. Bajo enfriamiento con hielo, la solución de la reacción se vertió en una solución acuosa de ácido clorhídrico 2N, seguido por extracción con acetato de etilo, y el extracto se lavó en secuencia con agua y solución salina. La capa orgánica resultante se secó sobre sulfato de sodio anhidro, y entonces se concentró, para proporcionar el compuesto del título deseado (84.0 miligramos, rendimiento del 76 por ciento) como un sólido amarillo pálido.

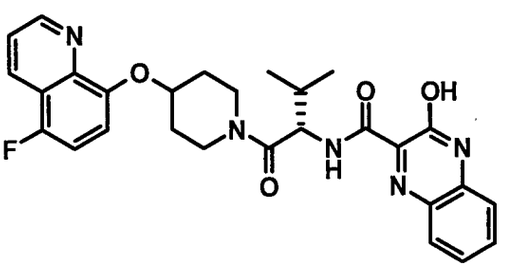
^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.82 (1H, s), 9.52 (1H, d, J=8.8 Hz), 7.87 (1H, d, J=7.8 Hz), 7.64 (1H, m), 7.39-7.37 (2H, m), 7.18-7.16 (1H, m), 7.07-6.98 (2H, m), 5.19-5.18 (1H, m), 4.92 (1H, dd, J=14.7 Hz, 6.5 Hz), 4.64 (1H, brs), 4.53-4.51 (2H, m), 3.85-3.37 (4H, m), 2.10-1.58 (5H, m), 0.95 (6H, t, J=5.9 Hz).

IR (KBr) cm^{-1}: 2960, 1685, 1635, 1490, 1195, 1045.

MS (ESI, m/z): 497 $(M+H)^+$.

HRMS (ESI, m/z): 519.2026 (Calculado para $C_{26}H_{29}FN_4NaO_5$: 519.2019).

Ejemplo 72



N-[(1S)-1-({4-[(5-fluoro-quinolin-8-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 72-1

4-[(5-fluoro-quinolin-8-il)-oxi]-piperidin-1-carboxilato de terbutilo

De una manera análoga al Ejemplo 23-1, el 4-[(5-fluoro-quinolin-8-il)-oxi]-piperidin-1-carboxilato de terbutilo (1.14 gramos, rendimiento del 90 por ciento) se obtuvo a partir del 4-hidroxi-piperidin-1-carboxilato de terbutilo (740 miligramos, 3.68 milimoles), y 5-fluoro-8-hidroxi-quinolina (600 miligramos, 3.68 milimoles) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 500 MHz) δ: 8.99 (1H, dd, J=4.2 Hz, 1.5 Hz), 8.40 (1H, dd, J=8.3 Hz, 1.5 Hz), 7.49 (1H, dd, J=8.8 Hz, 4.2 Hz), 7.12 (1H, t, J=8.8 Hz), 7.06 (1H, dd, J=8.3 Hz, 4.9 Hz), 4.72-4.67 (1H, m), 3.95 (2H, brs), 3.22-3.17 (2H, m), 2.09-2.05 (2H, m), 1.94-1.91 (2H, m), 1.47-1.45 (9H, m).

MS (FAB, m/z): 347 $(M+H)^+$.

Ejemplo 72-2

[(1S)-1-({4-[(5-fluoro-quinolin-8-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 23-2, el clorhidrato de 5-fluoro-8-[(piperidin-4-il)-oxi]-quinolina (1.02 gramos) se obtuvo a partir del 4-[(5-fluoro-quinolin-8-il)-oxi]-piperidin-1-carboxilato de terbutilo (1.14 gramos, 3.29 milimoles) como un sólido blanco. El compuesto resultante (720 miligramos, 2.26 milimoles) se condensó con N-(terbutoxi-carbonil)-L-valina (588 miligramos, 2.71 milimoles), para proporcionar el [(1S)-1-({4-[(5-fluoro-quinolin-8-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (772 miligramos, rendimiento del 77 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.99 (1H, dd, J=4.2 Hz, 1.5 Hz), 8.42 (1H, dd, J=8.4 Hz, 1.5 Hz), 7.51 (1H, dd, J=8.4 Hz, 4.2 Hz), 7.17-7.06 (2H, m), 5.38-5.36 (1H, m), 4.82-4.80 (1H, m), 4.55-4.52 (1H, m), 4.15-4.09 (1H, m), 4.02-3.94 (1H, m), 3.56-3.42 (2H, m), 2.18-1.93 (5H, m), 1.45-1.45 (9H, m), 0.99 (3H, t, J=6.8 Hz), 0.90 (3H, t, J=6.8 Hz).

MS (FAB, m/z): 445 $(M+H)^+$.

Ejemplo 72-3

N-[(1S)-1-({4-[(5-fluoro-quinolin-8-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 23-3, el diclorhidrato de (2S)-1-{4-[(5-fluoro-quinolin-8-il)-oxi]-piperidin-1-il}-3-metil-1-

oxobutan-2-amina (725 miligramos) se obtuvo a partir del [(1S)-1-({4-[(5-fluoro-quinolin-8-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (772 miligramos, 1.73 milimoles) como un sólido blanco. El compuesto resultante (200 miligramos, 0.478 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (136 miligramos, 0.717 milimoles), para proporcionar el compuesto del título deseado (160 miligramos, rendimiento del 65 por ciento) como un sólido amarillo pálido.

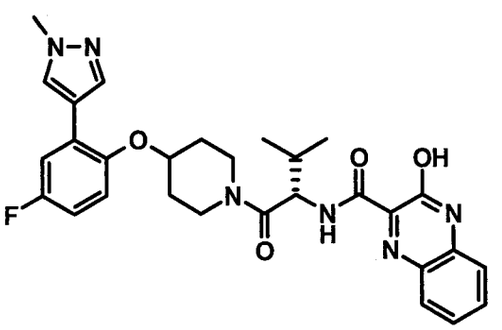
^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.81 (1H, brs), 9.66 (1H, brs), 8.98 (1H, dd, J=4.2 Hz, 1.5 Hz), 8.45 (1H, dd, J=8.4 Hz, 1.5 Hz), 7.85 (1H, dd, J=8.4 Hz, 4.2 Hz), 7.66-7.63 (2H, m), 7.38-7.36 (4H, m), 4.95-4.91 (2H, m), 4.03-4.01 (2H, m), 3.59-3.33 (2H, m), 2.09-1.68 (5H, m), 0.97 (6H, t, J=7.0 Hz).

IR (KBr) cm^{-1}: 2960, 1685, 1630, 1530, 1475, 1255, 1090.

MS (ESI, m/z): 518 $(M+H)^+$.

HRMS (ESI, m/z): 518.2191 (Calculado para $C_{28}H_{28}FN_5O_4$: 518.2203).

Ejemplo 73



N-[(1S)-1-({4-[4-fluoro-2-(1-metil-1H-pirazol-4-il)-fenoxi]-piperidin-1-

il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 73-1

4-[4-fluoro-2-(1-metil-1H-pirazol-4-il)-fenoxi]-piperidin-1-carboxilato de terbutilo

Se agregaron en secuencia carbonato de potasio (775 miligramos, 5.61 milimoles), y tetraquis-(trifenil-fosfina)-paladio (108 miligramos, 0.0935 milimoles) a una solución mixta en 1,2-dimetoxietano/agua (5.0 mililitros, 4:4, volumen/volumen) de 4-(2-bromo-4-fluoro-fenoxi)-piperidin-1-carboxilato de terbutilo (350 miligramos, 0.935 milimoles), y 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaboran-2-il)-1H-pirazol (233 miligramos, 1.12 milimoles), bajo una corriente de nitrógeno, y la agitación se llevó a cabo durante la noche bajo calentamiento a reflujo. Después de completarse la reacción, la solución de la reacción se enfrió a temperatura ambiente, y se vertió en agua helada, seguido por extracción con acetato de etilo. El extracto se lavó en secuencia con agua y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., 25+M), para proporcionar el 4-[4-fluoro-2-(1-metil-1H-pirazol-4-il)-fenoxi]-piperidin-1-carboxilato de terbutilo (253 miligramos, rendimiento del 72 por ciento) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.83 (1H, d, J=15.2 Hz), 7.75 (1H, d, J=11.3 Hz), 7.20-7.16 (1H, m), 6.91-6.83 (2H, m), 4.45-4.43 (1H,

m), 3.95 (3H, s), 3.74-3.72 (2H, m), 3.28-3.21 (2H, m), 1.94-1.88 (2H, m), 1.74-1.69 (2H, m), 1.47-1.46 (9H, m).

MS (FAB, m/z): 376 $(M+H)^+$.

Ejemplo 73-2

[(1S)-1-({4-[4-fluoro-2-(1-metil-1H-pirazol-4-il)-fenoxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 23-2, el clorhidrato de 4-[4-fluoro-2-(1-metil-1H-pirazol-4-il)-fenoxi]-piperidina (210 miligramos, rendimiento del 100 por ciento) se obtuvo a partir del 4-[4-fluoro-2-(1-metil-1H-pirazol-4-il)-fenoxi]-piperidin-1-carboxilato de terbutilo como un sólido blanco. El compuesto resultante (210 miligramos, 0.674 milimoles) se condensó con N-(terbutoxi-carbonil)-L-valina (176 miligramos, 0.809 milimoles), para proporcionar el [(1S)-1-({4-[4-fluoro-2-(1-metil-1H-pirazol-4-il)-fenoxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (158 miligramos, rendimiento del 49 por ciento) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.83 (1H, d, J=15.2 Hz), 7.75 (1H, d, J=11.3 Hz), 7.20-7.15 (1H, m), 6.91-6.84 (2H, m), 5.33 (1H, t, J=8.6 Hz), 4.53-4.47 (2H, m), 3.95 (3H, s), 3.79-3.60 (2H, m), 3.47-3.40 (2H, m), 2.05-1.80 (5H, m), 1.45-1.42 (9H, m), 0.96 (3H, d, J=6.8 Hz), 0.89 (3H, d, J=6.8 Hz).

MS (FAB, m/z): 475 $(M+H)^+$.

Ejemplo 73-3

N-[(1S)-1-({4-[4-fluoro-2-(1-metil-1H-pirazol-4-il)-fenoxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 23-3, el clorhidrato de (2S)-1-{4-[4-fluoro-2-(1-metil-1H-pirazol-4-il)-fenoxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina (137 miligramos) se obtuvo a partir del [(1S)-1-({4-[4-fluoro-2-(1-metil-1H-pirazol-4-il)-fenoxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (158 miligramos, 0.333 milimoles) como un sólido blanco. El compuesto resultante (70.0 miligramos, 0.170 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (49.0 miligramos, 0.256 milimoles), para proporcionar el compuesto del título deseado (92.0 miligramos, rendimiento del 99 por ciento) como un sólido amarillo pálido.

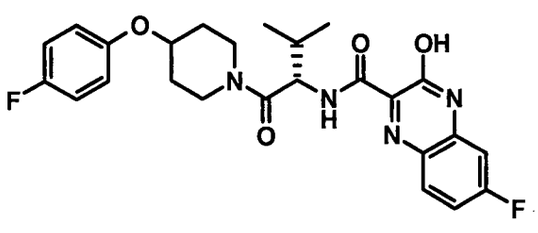
^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.80 (1H, brs), 9.54 (1H, d, J=8.2 Hz), 8.13 (1H, d, J=5.9 Hz), 7.93 (1H, d, J=5.5 Hz), 7.84 (1H, dd, J=16.0 Hz, 7.6 Hz), 7.63 (1H, t, J=7.6 Hz), 7.44 (1H, dd, J=10.0 Hz, 2.9 Hz), 7.39-7.37 (2H, m), 7.18-7.16 (1H, m), 7.01-6.97 (1H, m), 4.94-4.91 (1H, m), 4.71-4.68 (1H, m), 4.02-3.87 (2H, m), 3.86 (3H, d, J=12.9 Hz), 3.53-3.16 (2H, m), 2.18-1.54 (5H, m), 1.05-0.85 (6H, m).

IR (KBr) cm^{-1}: 2960, 1685, 1640, 1530, 1495, 1450, 1210.

MS (ESI, m/z): 569 $(M+Na)^+$.

HRMS (ESI, m/z): 569.2304 (Calculado para $C_{29}H_{31}FN_6NaO_4$: 569.2288).

Ejemplo 74



N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-6-fluoro-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 74-1

6-fluoro-3-hidroxi-quinoxalin-2-carboxilato de etilo

La 4-fluoro-2-nitro-anilina (672 miligramos, 4.31 milimoles), y ceto-malonato de dietilo (500 miligramos, 2.87 milimoles) se disolvieron en etanol (30 mililitros), bajo una corriente de nitrógeno, y la agitación se llevó a cabo a temperatura ambiente durante 1.5 horas. Subsiguientemente, se agregó dihidrato de cloruro de estaño (II) (1.62 gramos, 7.18 milimoles), y se llevó a cabo una agitación adicional durante la noche. La solución de la reacción se concentró hasta 5.0 mililitros bajo presión reducida, y se vertió en una solución acuosa de ácido clorhídrico 2N, seguido por extracción con cloruro de metileno, el extracto se lavó en secuencia con agua y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., 25+M), para proporcionar el 6-fluoro-3-oxo-1,2,3,4-tetrahidro-quinoxalin-2-carboxilato de etilo (105 miligramos, rendimiento del 16 por ciento) como un sólido amarillo pálido.

Se agregó 2,3-dicloro-5,6-diciano-benzoquinona (66.0 miligramos, 0.290 milimoles) a una solución en cloruro de metileno (3.0 mililitros) del compuesto resultante (59.0 miligramos, 0.248 milimoles), a temperatura ambiente, bajo una corriente de nitrógeno,

y la agitación se llevó a cabo a temperatura ambiente durante 3 horas. Después de completarse la reacción, la solución de la reacción se vertió en agua helada, seguido por extracción con acetato de etilo, y el extracto se lavó en secuencia con agua y una solución salina, y entonces se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., 25+M), para proporcionar el 6-fluoro-3-hidroxi-quinoxalin-2-carboxilato de etilo (52.0 miligramos, rendimiento del 90 por ciento) como un sólido blanco.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.68 (1H, d, J=8.0 Hz), 7.45-7.43 (2H, m), 4.57 (2H, q, J=7.0 Hz), 1.49 (3H, t, J=7.0 Hz).

MS (FAB, m/z): 237 $(M+H)^+$.

Ejemplo 74-2

N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-6-fluoro-3-hidroxi-quinoxalin-2-carboxamida

Se agregó monohidrato de hidróxido de litio (32.0 miligramos, 0.773 milimoles) a una solución acuosa (2.0 mililitros) de 6-fluoro-3-hidroxi-quinoxalin-2-carboxilato de etilo (73.0 miligramos, 0.309 milimoles), bajo una corriente de nitrógeno, y la mezcla se dejó reaccionar a temperatura ambiente durante 2.5 horas. Bajo enfriamiento con hielo, la solución de la reacción se vertió en una solución acuosa de ácido clorhídrico 2N, y el sólido precipitado se recolectó mediante filtración, seguido por secado, para proporcionar el ácido 6-fluoro-3-hidroxi-2-quinoxalin-carboxílico (52.0 miligramos,

rendimiento del 81 por ciento) como un sólido amarillo pálido.

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (72.0 miligramos, 0.375 milimoles), y el monohidrato de 1-hidroxi-benzotriazol (51.0 miligramos, 0.375 milimoles) se agregaron a una solución en cloruro de metileno (5.0 mililitros) del compuesto resultante (52.0 miligramos, 0.250 milimoles), y (2S)-1-[4-(4-fluoro-fenoxi)-piperidin-1-il]-3-metil-1-oxobutan-2-amina (74.0 miligramos, 0.250 milimoles), a temperatura ambiente, bajo una corriente de nitrógeno, y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se vertió en una solución acuosa de ácido clorhídrico 2N, seguido por extracción con acetato de etilo, y el extracto se lavó en secuencia con agua, una solución acuosa saturada de carbonato ácido de sodio, agua, y una solución salina, y entonces se secó sobre sulfato de sodio anhidro. Después de que la capa orgánica se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., 25+M), el residuo resultante de la concentración se suspendió en un solvente mixto de cloruro de metileno/dietil-éter, y la sustancia sólida se recolectó mediante filtración, para proporcionar el compuesto del título deseado (90.0 miligramos, rendimiento del 74 por ciento) como un sólido amarillo pálido.

^{1}H-RMN (DMSO-d_6, 500 MHz) δ: 12.86 (1H, brs), 9.46 (1H, brs), 7.72 (1H, t, J=7.2 Hz), 7.57-7.55 (1H, m), 7.40 (1H, dd, J=9.3 Hz, 4.6 Hz), 7.13-7.11 (2H, m), 7.04-7.00 (2H, m), 4.90 (1H, dd,

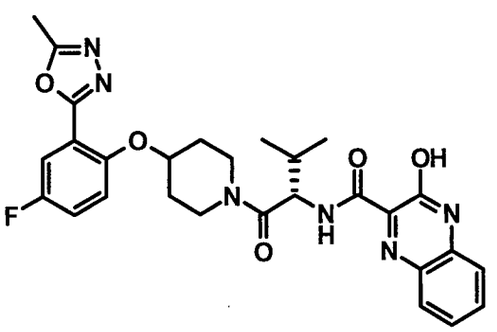
J=13.2 Hz, 7.3 Hz), 4.60-4.59 (1H, m), 3.93-3.90 (2H, m), 3.49-3.31 (2H, m), 2.09-1.91 (3H, m), 1.66-1.55 (2H, m), 0.94 (6H, t, J=6.8 Hz).

IR (KBr) cm^{-1}: 2965, 1690, 1640, 1505, 1245, 1205.

MS (ESI, m/z): 507 $(M+Na)^+$.

HRMS (ESI, m/z): 507.1804 (Calculado para $C_{25}H_{26}F_2N_4NaO_4$: 507.1819).

Ejemplo 75



N-[(1S)-1-({4-[4-fluoro-2-(5-metil-1,3,4-oxadiazol-2-il)-fenoxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 75-1

2-[(1-{N-[(benciloxi-carbonil)-amino]-L-valil}-piperidin-4-il)-oxi]-5-fluoro-benzoato de metilo

De una manera análoga al Ejemplo 23-2, el clorhidrato de 5-fluoro-2-[(piperidin-4-il)-oxi]-benzoato de metilo (985 miligramos, rendimiento del 100 por ciento) se obtuvo a partir del 4-[4-fluoro-2-(metoxi-carbonil)-fenoxi]-piperidin-1-carboxilato de terbutilo (1.20 gramos, 3.40 milimoles) como un sólido blanco. El compuesto resultante (985 miligramos, 3.40 milimoles) se condensó con N-

(benciloxi-carbonil)-L-valina (1.02 gramos, 4.07 milimoles), para proporcionar el 2-[(1-{N-[(benciloxi-carbonil)-amino]-L-valil}-piperidin-4-il)-oxi]-5-fluoro-benzoato de metilo (1.49 gramos, rendimiento del 90 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.53 (1H, dd, J=8.6 Hz, 3.0 Hz), 7.35-7.32 (5H, m), 7.19-7.14 (1H, m), 6.93 (1H, dd, J=8.6 Hz, 4.3 Hz), 5.62 (1H, t, J=8.0 Hz), 5.10-5.09 (2H, m), 4.62-4.55 (2H, m), 4.01-3.98 (1H, m), 3.88 (3H, s), 3.88-3.53 (3H, m), 1.93-1.89 (5H, m), 0.99 (3H, d, J=6.6 Hz), 0.89 (3H, d, J=6.6 Hz).

MS (FAB, m/z): 487 $(M+H)^+$.

Ejemplo 75-2

{(1S)-1-[(4-{2-[(2-acetil-hidrazino)-carbonil]-4-fluoro-fenoxi}-piperidin-1-il)-carbonil]-2-metil-propil}-carbamato de bencilo

Una solución acuosa de hidróxido de sodio 2N (30 mililitros) se agregó a una solución en tetrahidrofurano (30 mililitros) de 2-[(1-{N-[(benciloxi-carbonil)-amino]-L-valil}-piperidin-4-il)-oxi]-5-fluoro-benzoato de metilo (1.23 gramos, 2.53 milimoles), y la mezcla se dejó reaccionar a temperatura ambiente durante la noche. Bajo enfriamiento con hielo, la solución de la reacción se vertió en una solución acuosa de ácido clorhídrico 2N, seguido por extracción con acetato de etilo. El extracto se lavó en secuencia con agua y una solución salina, y se secó sobre sulfato de sodio anhidro, y entonces se concentró, para proporcionar el ácido 2-[(1-{N-[(benciloxi-carbonil)-amino]-L-valil}-piperidin-4-il)-oxi]-5-fluoro-benzoico (840 miligramos).

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (512 miligramos, 2.67 milimoles), y el monohidrato de 1-hidroxi-benzotriazol (361 miligramos, 2.67 milimoles) se agregaron a una solución en tetrahidrofurano (25 mililitros) del compuesto resultante (840 miligramos, 1.78 milimoles), y acetohidrazida (198 miligramos, 2.67 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se vertió en una solución acuosa de ácido clorhídrico 2N, seguido por extracción con acetato de etilo, el extracto se lavó en secuencia con agua, una solución acuosa saturada de carbonato ácido de sodio, agua, y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., 25+M), para proporcionar el {(1S)-1-[(4-{2-[(2-acetil-hidrazino)-carbonil]-4-fluoro-fenoxi}-piperidin-1-il)-carbonil]-2-metil-propil}-carbamato de bencilo (854 miligramos, rendimiento del 91 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 10.82-10.74 (1H, m), 9.33-9.23 (1H, m), 7.90 (1H, dd, J=8.6 Hz, 3.0 Hz), 7.35-7.33 (5H, m), 7.21-7.18 (1H, m), 6.99 (1H, dd, J=8.6 Hz, 4.3 Hz), 5.67 (1H, m), 5.11-5.10 (2H, m), 4.73-4.70 (1H, m), 4.58-4.56 (1H, m), 4.11-3.95 (2H, m), 3.55-3.46 (2H, m), 2.12 (3H, d, J=7.4 Hz), 1.97-1.79 (5H, m), 1.01 (3H, t, J=6.6 Hz), 0.91 (3H, t, J=6.6 Hz).

Ejemplo 75-3

[(1S)-1-({4-[4-fluoro-2-(5-metil-1,3,4-oxadiazol-2-il)-fenoxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de bencilo

Se agregaron cloruro de p-toluen-sulfonilo (420 miligramos, 0.874 milimoles), y trietil-amina (0.244 mililitros, 1.75 milimoles), a una solución en cloruro de metileno (15 mililitros) de {(1S)-1-[(4-{2-[(2-acetil-hidrazino)-carbonil]-4-fluoro-fenoxi}-piperidin-1-il)-carbonil]-2-metil-propil}-carbamato de bencilo (420 miligramos, 0.795 milimoles), bajo una corriente de nitrógeno, y la agitación se llevó a cabo a temperatura ambiente durante la noche. Bajo enfriamiento con hielo, la solución de la reacción se vertió en una solución acuosa de ácido clorhídrico 2N, seguido por extracción con acetato de etilo, el extracto se lavó en secuencia con agua y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., 25+M), para proporcionar el [(1S)-1-({4-[4-fluoro-2-(5-metil-1,3,4-oxadiazol-2-il)-fenoxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de bencilo (227 miligramos, rendimiento del 56 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.69-7.63 (1H, m), 7.36-7.31 (5H, m), 7.19-7.16 (1H, m), 7.00 (1H, dd, J=8.6 Hz, 4.3 Hz), 5.60 (1H, d, J=8.6 Hz), 5.09 (2H, s), 4.72-4.67 (1H, m), 4.56 (1H, dd, J=8.6 Hz, 5.7 Hz), 4.07-3.49 (4H, m), 2.60 (3H, s), 1.97-1.91 (5H, m), 0.99 (3H,

t, J=6.6 Hz), 0.89 (3H, t, J=6.6 Hz).

Ejemplo 75-4

N-[(1S)-1-({4-[4-fluoro-2-(5-metil-1,3,4-oxadiazol-2-il)-fenoxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Se agregó un catalizador de paladio al 5 por ciento sobre carbón (193 miligramos) a una solución en metanol (10 mililitros) de [(1S)-1-({4-[4-fluoro-2-(5-metil-1,3,4-oxadiazol-2-il)-fenoxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de bencilo (464 miligramos, 0.909 milimoles), y la agitación se llevó a cabo a temperatura ambiente durante 3 horas bajo una atmósfera de hidrógeno. La solución de la reacción se filtró con Celite, y el filtrado se concentró, para proporcionar la (2S)-1-{4-[4-fluoro-2-(5-metil-1,3,4-oxadiazol-2-il)-fenoxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina (334 miligramos, rendimiento del 98 por ciento) como cristales blancos.

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (126 miligramos, 0.657 milimoles), y el monohidrato de 1-hidroxi-benzotriazol (89.0 miligramos, 0.657 milimoles) se agregaron a una solución en cloruro de metileno (5.0 mililitros) del compuesto resultante (165 miligramos, 0.438 milimoles), y ácido 3-hidroxi-quinoxalin-2-carboxílico (125 miligramos, 0.657 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se vertió en una solución acuosa de ácido clorhídrico 2N, seguido por extracción con acetato de etilo, el extracto se lavó en secuencia con agua, una

solución acuosa saturada de carbonato ácido de sodio, agua, y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., 25+M), el residuo resultante de la concentración se suspendió en un solvente mixto de cloruro de metileno/dimetil-éter, y la sustancia sólida se recolectó mediante filtración, para proporcionar el compuesto del título deseado (217 miligramos, rendimiento del 90 por ciento) como un sólido amarillo pálido.

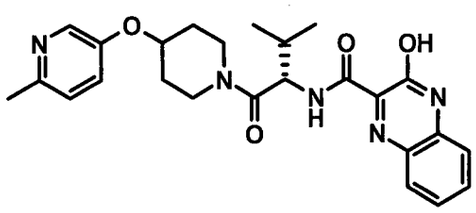
^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.82 (1H, brs), 9.50 (1H, d, J=9.0 Hz), 7.86 (1H, t, J=7.0 Hz), 7.65-7.63 (2H, m), 7.49-7.36 (4H, m), 4.94-4.85 (2H, m), 3.71-3.61 (4H, m), 2.55 (3H, d, J=12.9 Hz), 1.96-1.84 (5H, m), 0.97-0.93 (6H, m).

IR (KBr) cm^{-1}: 2965, 1685, 1640, 1540, 1480, 1265.

MS (ESI, m/z): 571 $(M+Na)^+$.

HRMS (ESI, m/z): 571.2075 (Calculado para $C_{28}H_{29}FN_6NaO_5$: 571.2081).

Ejemplo 76



3-hidroxi-N-[(1S)-2-metil-1-({4-[(6-metil-piridin-3-il)-oxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

Ejemplo 76-1

[(1S)-2-metil-1-({4-[(6-metil-piridin-3-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo

Una solución al 40 por ciento en tolueno de azodicarboxilato de di-isopropilo (2.10 mililitros, 3.99 milimoles) se agregó a una solución en tolueno (15 mililitros) de [(1S)-4-(4-hidroxi-piperidin-1-carbonil)-2-metil-propil]-carbamato de terbutilo (1.00 gramos, 3.33 milimoles), 5-hidroxi-2-metil-piridina (404 miligramos, 3.66 milimoles), y trifenil-fosfina (1.05 gramos, 3.99 milimoles), a temperatura ambiente, y la agitación se llevó a cabo durante 4 días. La solución de la reacción se concentró bajo presión reducida, y el residuo resultante se diluyó con acetato de etilo, seguido por lavado en secuencia con una solución acuosa de hidróxido de sodio 1N, agua, y una solución salina, y entonces la capa orgánica resultante se extrajo con ácido clorhídrico 1N. Se utilizó una solución acuosa de hidróxido de sodio 5N para hacer básica la capa acuosa, seguido por extracción con acetato de etilo. La capa orgánica resultante se secó sobre sulfato de sodio anhidro, y la capa orgánica se concentró, para proporcionar el [(1S)-2-metil-1-({4-[(6-metil-piridin-3-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (980 miligramos, rendimiento del 72 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$) δ: 8.20 (1H, s), 7.14-7.07 (2H, m), 5.34 (1H, d, J=7.8 Hz), 4.56-4.48 (2H, m), 3.82-3.46 (4H, m), 2.50 (3H, s), 1.99-1.80 (5H, m), 1.44 (9H, s), 0.97 (3H, d, J = 6.6 Hz), 0.89 (3H, d, J = 6.6 Hz).

|MS (ESI, m/z): 392 $(M+H)^+$.

Ejemplo 76-2

Diclorhidrato de (2S)-3-metil-1-{4-[(6-metil-piridin-3-il)-oxi]-piperidin-1-il}-1-oxobutan-2-amina

De una manera análoga al Ejemplo 29-3, el diclorhidrato de (2S)-3-metil-1-{4-[(6-metil-piridin-3-il)-oxi]-piperidin-1-il}-1-oxobutan-2-amina (907 miligramos, rendimiento del 100 por ciento) se obtuvo a partir del [(1S)-2-metil-1-({4-[(6-metil-piridin-3-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (980 miligramos, 2.50 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN (CD_3OD) δ: 8.52 (1H, s), 8.21-8.18 (1H, m), 7.85 (1H, d, J=9.0 Hz), 4.96 (1H, s), 4.38 (1H, d, J=4.3 Hz), 4.12-3.43 (4H, m), 2.71 (3H, s), 2.24-2.03 (3H, m), 1.93-1.74 (2H, m), 1.11 (3H, d, J=6.6 Hz), 1.02 (3H, d, J=6.6 Hz).

MS (ESI, m/z): 292 $(M+H)^+$.

Ejemplo 76-3

3-hidroxi-N-[(1S)-2-metil-1-({4-[(6-metil-piridin-3-il)-oxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 29-4, el compuesto del título deseado (228 miligramos, rendimiento del 90 por ciento) se obtuvo a partir del diclorhidrato de (2S)-3-metil-1-{4-[(6-metil-piridin-3-il)-oxi]-piperidin-1-il}-1-oxobutan-2-amina (200 miligramos, 0.549 milimoles) como un sólido amarillo.

^{1}H-RMN ($CDCl_3$) δ: 12.73 (1H, br s), 10.04 (1H, br s), 8.23 (1H, dd, J=8.8 Hz, 2.9 Hz), 8.00 (1H, t, J=7.0 Hz), 7.63 (1H, t, J=7.4 Hz),

7.55 (1H, br s), 7.41-7.37 (1H, m), 7.17-7.13 (1H, m), 7.09 (1H, dd, J=8.6 Hz, 4.7 Hz), 5.10-5.05 (1H, m), 4.63-4.57 (1H, m), 4.03-3.68 (4H, m), 2.51 (3H, d, J=2.3 Hz), 2.40-1.87 (5H, m), 1.14-1.09 (6H, m).

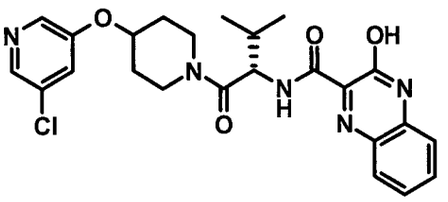
IR (KBr) cm^{-1}: 3440, 2960, 1685, 1635, 1525.

MS (ESI, m/z): 464 $(M+H)^+$.

HRMS (ESI, m/z): 464.2316 (Calculado para $C_{25}H_{30}N_5O_4$: 464.2298).

Análisis calculado para $C_{25}H_{29}N_5O_4 \cdot 1/2H_2O$: C, 63.54; H, 6.40; N, 14.82. Encontrado: C, 63.76; H, 6.13; N, 14.80.

Ejemplo 77



N-[(1S)-1-({4-[(5-cloro-piridin-3-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 77-1

[(1S)-1-({4-[(5-cloro-piridin-3-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 1-2, el [(1S)-1-({4-[(5-cloro-piridin-3-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (253 miligramos, rendimiento del 18 por ciento) se obtuvo a partir del [(1S)-1-(4-hidroxi-piperidin-1-carbonil)-2-metil-propil]-carbamato de terbutilo (1.00 gramos, 3.33 milimoles), y 3-cloro-5-

hidroxi-piridina (474 miligramos, 3.66 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$) δ: 8.21 (2H, s), 7.24-7.22 (1H, m), 5.34-5.32 (1H, m), 4.64-4.48 (2H, m), 3.87-3.53 (4H, m), 2.05-1.86 (5H, m), 1.44 (9H, s), 0.97 (3H, d, J=6.6 Hz), 0.90 (3H, d, J=6.6 Hz).

MS (ESI, m/z): 412 $(M+H)^+$.

Ejemplo 77-2

Diclorhidrato de (2S)-1-{4-[(5-cloro-piridin-3-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina

De una manera análoga al Ejemplo 29-3, el diclorhidrato de (2S)-1-{4-[(5-cloro-piridin-3-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina (236 miligramos, rendimiento del 100 por ciento) se obtuvo a partir del [(1S)-1-({4-[(5-cloro-piridin-3-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (253 miligramos, 0.614 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN (CD_3OD) δ: 8.56-8.51 (2H, m), 8.21-8.19 (1H, m), 4.97 (1H, s), 4.38 (1H, s), 4.10-3.45 (4H, m), 2.23-1.77 (5H, m), 1.12 (3H, d, J=6.6 Hz), 1.02 (3H, d, J=6.6 Hz).

MS (ESI, m/z): 312 $(M+H)^+$.

Ejemplo 77-3

N-[(1S)-1-({4-[(5-cloro-piridin-3-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 29-4, el compuesto del título deseado (189 miligramos, rendimiento del 64 por ciento) se obtuvo a partir del diclorhidrato de (2S)-1-{4-[(5-cloro-piridin-3-il)-

oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina (236 miligramos, 0.613 milimoles) como un sólido amarillo.

^{1}H-RMN ($CDCl_3$) δ: 12.35 (1H, br s), 10.18 (1H, br s), 8.25-8.22 (2H, m), 8.04-8.00 (1H, m), 7.64-7.22 (4H, m), 5.10-5.05 (1H, m), 4.68-4.62 (1H, m), 4.03-3.66 (4H, m), 2.35-1.88 (5H, m), 1.14-1.09 (6H, m).

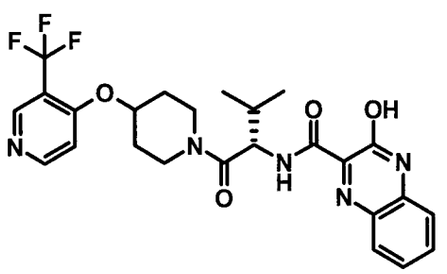
IR (KBr) cm^{-1}: 2965, 1685, 1640, 1520, 1420.

MS (ESI, m/z): 484 $(M+H)^+$.

HRMS (ESI, m/z): 506.1579 (Calculado para $C_{24}H_{26}ClN_5NaO_4$: 506.1571).

Análisis calculado para $C_{24}H_{26}ClN_5O_4$: C, 59.56; H, 5.42; N, 14.47; Cl, 7.33. Encontrado: C, 59.63; H, 5.32; N, 14.51; Cl, 7.64.

Ejemplo 78



3-hidroxi-N-{(1S)-2-metil-1-[(4-{[3-(trifluoro-metil)-piridin-4-il]-oxi}-piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida

Ejemplo 78-1

4-{[3-(trifluoro-metil)-piridin-4-il]-oxi}-piperidin-1-carboxilato de terbutilo

El 4-hidroxi-piperidin-1-carboxilato de terbutilo (1.30 gramos, 5.78 milimoles) se agregó a una suspensión en N,N-dimetil-

formamida (4.8 mililitros) de hidruro de sodio al 60 por ciento (404 miligramos, 10.6 milimoles), a 0°C, y la agitación se llevó a cabo a temperatura ambiente durante 30 minutos. Además, a 0°C, se agregó clorhidrato de 4-cloro-3-(trifluoro-metil)-piridina (1.00 gramos, 4.82 milimoles, y la agitación se llevó a cabo a temperatura ambiente durante 5 horas. Se agregó agua a la solución de la reacción, y se utilizó ácido clorhídrico 1N para hacerla ácida, seguido por lavado con acetato de etilo. Se utilizó una solución acuosa de hidróxido de sodio 1N para hacer básica la capa acuosa, seguida por extracción con acetato de etilo, y entonces el extracto se lavó con agua y solución salina saturada. La capa orgánica resultante se secó sobre sulfato de sodio anhidro, y subsiguientemente se concentró para proporcionar el 4-{[3-(trifluoro-metil)-piridin-4-il]-oxi}-piperidin-1-carboxilato de terbutilo (884 miligramos, rendimiento del 53 por ciento) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ: 8.70 (1H, s), 8.61 (1H, d, J=4.7 Hz), 6.90 (1H, d, J=4.7 Hz), 4.79-4.76 (1H, m), 3.65-3.60 (2H, m), 3.50-3.46 (2H, m), 1.92-1.87 (4H, m), 1.47 (9H, s).

MS (ESI, m/z): 347 $(M+H)^+$.

Ejemplo 78-2

{(1S)-2-metil-1-[(4-{[3-(trifluoro-metil)-piridin-4-il]-oxi}-piperidin-1-il)-carbonil]-propil}-carbamato de terbutilo

De una manera análoga al Ejemplo 29-2, el {(1S)-2-metil-1-[(4-{[3-(trifluoro-metil)-piridin-4-il]-oxi}-piperidin-1-il)-carbonil]-propil}-carbamato de terbutilo (610 miligramos, rendimiento del 54 por

ciento) se obtuvo a partir del 4-{[3-(trifluoro-metil)-piridin-4-il]-oxi}-piperidin-1-carboxilato de terbutilo (884 miligramos, 2.55 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.72 (1H, s), 8.64 (1H, d, J=4.7 Hz), 6.90 (1H, d, J=4.7 Hz), 5.32 (1H, d, J=7.4 Hz), 4.89-4.84 (1H, m), 4.49 (1H, dd, J=7.2 Hz, 4.5 Hz), 4.22-3.98 (1H, m), 3.76-3.29 (3H, m), 2.02-1.91 (5H, m), 1.44 (9H, s), 0.99-0.88 (6H, m).

MS (ESI, m/z): 446 $(M+H)^+$.

Ejemplo 78-3

Diclorhidrato de (2S)-3-metil-1-oxo-1-(4-{[3-(trifluoro-metil)-piridin-4-il]-oxi}-piperidin-1-il)-butan-2-amina

De una manera análoga al Ejemplo 29-3, el diclorhidrato de (2S)-3-metil-1-oxo-1-(4-{[3-(trifluoro-metil)-piridin-4-il]-oxi}-piperidin-1-il)-butan-2-amina (583 miligramos, rendimiento del 100 por ciento) se obtuvo a partir del {(1S)-2-metil-1-[(4-{[3-(trifluoro-metil)-piridin-4-il]-oxi}-piperidin-1-il)-carbonil]-propil}-carbamato de terbutilo (610 miligramos, 1.37 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN (CD_3OD) δ: 9.10 (1H, s), 8.95 (1H, d, J=7.0 Hz), 8.02 (1H, dd, J=10.2 Hz, 7.0 Hz), 5.46-5.37 (1H, m), 4.40 (1H, t, J=5.5 Hz), 4.07-3.52 (4H, m), 2.24-1.90 (5H, m), 1.14-1.02 (6H, m).

MS (ESI, m/z): 346 $(M+H)^+$.

Ejemplo 78-4

3-hidroxi-N-{(1S)-2-metil-1-[(4-{[3-(trifluoro-metil)-piridin-4-il]-oxi}-piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 29-4, el compuesto del

título deseado (152 miligramos, rendimiento del 61 por ciento) se obtuvo a partir del diclorhidrato de (2S)-3-metil-1-oxo-1-(4-{[3-(trifluoro-metil)-piridin-4-il]-oxi}-piperidin-1-il)-butan-2-amina (200 miligramos, 0.478 milimoles) como un sólido incoloro.

^{1}H-RMN ($CDCl_3$) δ: 12.21 (1H, brs), 10.16 (1H, brs), 8.74-8.64 (2H, m), 8.06-8.00 (1H, m), 7.63-7.22 (3H, m), 6.92 (1H, d, J=5.9 Hz), 5.10-5.03 (1H, m), 4.93-4.88 (1H, m), 4.41-3.33 (4H, m), 2.34-2.01 (5H, m), 1.15-1.10 (6H, m).

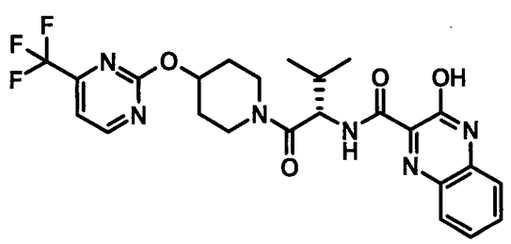
IR (KBr) cm^{-1}: 3430, 2965, 1690, 1645, 1600.

MS (ESI, m/z): 518 $(M+H)^+$.

HRMS (ESI, m/z): 540.1825 (Calculado para $C_{25}H_{26}F_3N_5NaO_4$: 540.1835).

Análisis calculado para $C_{25}H_{26}F_3N_5O_4$: C, 58.02; H, 5.06; N, 13.53; F, 11.01. Encontrado: C, 57.77; H, 4.93; N, 13.48; F, 11.19.

Ejemplo 79



3-hidroxi-N-{(1S)-2-metil-1-[(4-{[4-(trifluoro-metil)-pirimidin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida

Ejemplo 79-1

{(1S)-2-metil-1-[(4-{[4-(trifluoro-metil)-pirimidin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-carbamato de terbutilo

De una manera análoga al Ejemplo 64-1, el {(1S)-2-metil-1-[(4-{[4-(trifluoro-metil)-pirimidin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-carbamato de terbutilo (2.74 gramos, rendimiento del 92 por ciento) se obtuvo a partir de la 2-cloro-4-(trifluoro-metil)-pirimidina (0.883 mililitros, 7.32 milimoles), y {(1S)-1-[(4-hidroxi-piperidin-1-il)-carbonil]-2-metil-propil}-carbamato de terbutilo (2.00 gramos, 6.66 milimoles) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 500 MHz) δ: 8.80 (1H, d, J=4.8 Hz), 7.31 (1H, d, J=4.8 Hz), 5.41-5.33 (2H, m), 4.53 (1H, dd, J=8.8 Hz, 6.0 Hz), 4.04-3.49 (4H, m), 2.16-1.89 (5H, m), 1.47 (9H, s), 1.00 (3H, d, J=6.8 Hz), 0.92 (3H, d, J=6.8 Hz).

MS (FAB, m/z): 447 $(M+H)^+$.

Ejemplo 79-2

3-hidroxi-N-{(1S)-2-metil-1-[(4-{[4-(trifluoro-metil)-pirimidin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 1-3, el clorhidrato de (2S)-3-metil-1-oxo-1-(4-{[4-(trifluoro-metil)-pirimidin-2-il]-oxi}-piperidin-1-il)-butan-2-amina (2.48 gramos) se obtuvo a partir del {(1S)-2-metil-1-[(4-{[4-(trifluoro-metil)-pirimidin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-carbamato de terbutilo (2.74 gramos, 6.14 milimoles) como un sólido blanco. El compuesto resultante (200 miligramos, 0.522 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (136 miligramos, 0.784 milimoles), para proporcionar el compuesto del título deseado (240 miligramos, rendimiento del 92 por ciento) como un sólido amarillo pálido.

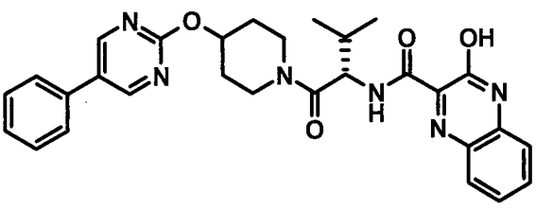
^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.86 (1H, brs), 9.56 (1H, brs), 9.03 (1H, t, J=4.0 Hz), 7.89 (1H, dd, J=6.4 Hz, 3.2 Hz), 7.67-7.66 (2H, m), 7.42-7.40 (2H, m), 5.33-5.32 (1H, m), 4.95 (1H, q, J=8.0 Hz), 4.05-3.90 (2H, m), 3.59-3.40 (2H, m), 2.06-1.74 (5H, m), 1.12-0.97 (6H, m).

IR (KBr) cm^{-1}: 2965, 1690, 1645, 1425, 1155.

MS (ESI, m/z): 519 $(M+H)^+$.

HRMS (ESI, m/z): 519.1956 (Calculado para $C_{24}H_{26}F_3N_6O_4$: 519.1967).

Ejemplo 80



3-hidroxi-N-[(1S)-2-metil-1-({4-[(5-fenil-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

Ejemplo 80-1

4-[(5-bromo-pirimidin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo

De una manera análoga al Ejemplo 64-1, el 4-[(5-bromo-pirimidin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo (2.10 gramos, rendimiento del 44 por ciento) se obtuvo a partir de la 5-bromo-2-cloro-pirimidina (2.84 gramos, 13.3 milimoles), y 4-hidroxi-piperidin-1-carboxilato de terbutilo (2.68 gramos, 13.3 milimoles) como un sólido blanco.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.48 (2H, s), 5.10-5.06 (1H, m),

3.76-3.75 (2H, m), 3.29-3.23 (2H, m), 1.94-1.94 (2H, brm), 1.77-1.74 (2H, m), 1.42 (9H, s).

MS (EI, m/z): 355 $(M)^+$.

Ejemplo 80-2

4-[(5-fenil-pirimidin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo

Se agregaron en secuencia carbonato de potasio (1.73 gramos, 12.5 milimoles), y tetraquis-(trifenil-fosfina)-paladio (242 miligramos, 0.0209 milimoles) a una solución mixta en 1,2-dimetoxi-etano/agua (5.0 mililitros, 4:1, volumen/volumen) de 4-[(5-bromo-pirimidin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo (750 miligramos, 2.09 milimoles), y ácido fenil-borónico (382 miligramos, 3.14 milimoles), bajo una corriente de nitrógeno, y la agitación se llevó a cabo durante la noche bajo calentamiento a reflujo. Después de completarse la reacción, la solución de la reacción se enfrió a temperatura ambiente, y se agregó agua, seguida por extracción con acetato de etilo. El extracto se lavó en secuencia con agua, una solución acuosa saturada de carbonato ácido de sodio, agua, y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., 40+M), para proporcionar el 4-[(5-fenil-pirimidin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo (584 miligramos, rendimiento del 79 por ciento) como un sólido blanco.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.68 (2H, s), 7.45-7.40 (5H, m),

5.23-5.18 (1H, m), 3.80-3.79 (2H, m), 3.33-3.26 (2H, m), 2.01-1.99 (2H, m), 1.83-1.80 (2H, m), 1.41 (9H, s).

MS (FAB, m/z): 455 $(M+H)^+$.

Ejemplo 80-3

[(1S)-2-metil-1-({4-[(5-fenil-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 23-2, el clorhidrato de 5-fenil-2-[(piperidin-4-il)-oxi]-pirimidina (0.476 miligramos) se obtuvo a partir del 4-[(5-fenil-pirimidin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo (580 miligramos, 1.63 milimoles) como un sólido incoloro. El compuesto resultante (476 miligramos, 1.63 milimoles) se condensó con N-(terbutoxi-carbonil)-L-valina (532 miligramos, 2.45 milimoles), para proporcionar el [(1S)-2-metil-1-({4-[(5-fenil-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (740 miligramos, rendimiento del 100 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.68 (2H, s), 7.48-7.40 (5H, m), 5.32 (2H, s), 4.49 (1H, dd, J=7.2 Hz, 3.6 Hz), 3.76-3.62 (4H, m), 2.02-1.89 (5H, m), 1.41 (9H, s), 0.94 (3H, d, J=6.8 Hz), 0.86 (3H, d, J=6.8 Hz).

MS (FAB, m/z): 397 $(M+H)^+$.

Ejemplo 80-4

3-hidroxi-N-[(1S)-2-metil-1-({4-[(5-fenil-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 1-3, el clorhidrato de (2S)-

3-metil-1-oxo-1-{4-[(5-fenil-pirimidin-2-il)-oxi]-piperidin-1-il}-butan-2-amina (0.636 miligramos) se obtuvo a partir del [(1S)-2-metil-1-({4-[(5-fenil-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (740 miligramos, 1.63 milimoles) como un sólido blanco. El compuesto resultante (200 miligramos, 0.512 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (136 miligramos, 0.784 milimoles), para proporcionar el compuesto del título deseado (130 miligramos, rendimiento del 48 por ciento) como un sólido amarillo pálido.

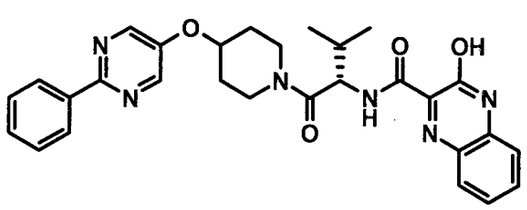
^{1}H-RMN (DMSO-d_6, 500 MHz) δ: 12.86 (1H, brs), 9.60 (1H, brs), 8.97 (2H, d, J=4.4 Hz), 7.90 (1H, d, J=7.6 Hz), 7.76 (2H, d, J=7.6 Hz), 7.66 (1H, t, J=7.6 Hz), 7.54 (2H, t, J=7.6 Hz), 7.45-7.40 (3H, m), 5.34-5.32 (1H, br m), 4.96 (1H, q, J=7.6 Hz), 4.11-3.99 (2H, m), 3.65-3.28 (2H, m), 2.06-1.75 (5H, m), 1.07 (3H, d, J=6.8 Hz), 0.99 (3H, d, J=6.8 Hz).

IR (KBr) cm^{-1}: 2960, 1685, 1635, 1525, 1440, 1370.

MS (ESI, m/z): 527 $(M+H)^+$.

HRMS (ESI, m/z): 527.2422 (Calculado para $C_{29}H_{31}N_6O_4$: 527.2406).

Ejemplo 81



3-hidroxi-N-[(1S)-2-metil-1-({4-[(2-fenil-pirimidin-5-il)-oxi]-piperidin-1-

il}-carbonil)-propil]-quinoxalin-2-carboxamida

Ejemplo 81-1

[(1S)-1-({4-[(2-cloro-pirimidin-5-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 64-1, el [(1S)-1-({4-[(2-cloro-pirimidin-5-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (575 miligramos, rendimiento del 42 por ciento) se obtuvo a partir de la 2-cloro-5-fluoro-pirimidina (452 miligramos, 3.66 milimoles), y 4-hidroxi-piperidin-1-carboxilato de terbutilo (1.00 gramos, 3.32 milimoles) como un sólido blanco.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.29 (2H, s), 5.33 (1H, d, J=9.2 Hz), 4.65-4.60 (1H, m), 4.45 (1H, dd, J=9.2 Hz, 5.6 Hz), 3.75-3.57 (4H, m), 1.96-1.88 (5H, m), 1.40 (9H, s), 0.94 (3H, d, J=6.8 Hz), 0.87 (3H, d, J=6.8 Hz).

MS (FAB, m/z): 413 $(M+H)^+$.

Ejemplo 81-2

[(1S)-2-metil-1-({4-[(2-fenil-pirimidin-5-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 80-2, el [(1S)-2-metil-1-({4-[(2-fenil-piperidin-5-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (297 miligramos, rendimiento del 94 por ciento) se obtuvo a partir del [(1S)-1-({4-[(2-cloro-pirimidin-5-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (280 miligramos, 8.92 milimoles), y ácido fenil-borónico (163 miligramos, 1.34 milimoles) como un sólido blanco.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.47 (2H, s), 8.34-8.32 (2H, m), 7.47-7.45 (3H, m), 5.32 (1H, d, J=9.2 Hz), 4.70-4.64 (1H, m), 4.48 (1H, dd, J=9.2 Hz, 5.6 Hz), 3.89-3.47 (4H, m), 2.09-1.87 (5H, m), 1.43 (9H, s), 0.97 (3H, d, J=6.8 Hz), 0.88 (3H, d, J=6.8 Hz).

MS (FAB, m/z): 455 $(M+H)^+$.

Ejemplo 81-3

3-hidroxi-N-[(1S)-2-metil-1-({4-[(2-fenil-pirimidin-5-il)-oxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 1-3, el clorhidrato de (2S)-3-metil-1-oxo-1-{4-[(2-fenil-pirimidin-5-il)-oxi]-piperidin-1-il}-butan-2-amina (255 miligramos) se obtuvo a partir del [(1S)-2-metil-1-({4-[(2-fenil-piperidin-5-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (297 miligramos, 0.653 milimoles) como un sólido blanco.

El compuesto resultante (127 miligramos, 0.325 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (93.0 miligramos, 0.487 milimoles) bajo una corriente de nitrógeno, para proporcionar el compuesto del título deseado (80.0 miligramos, rendimiento del 47 por ciento) como un sólido amarillo pálido.

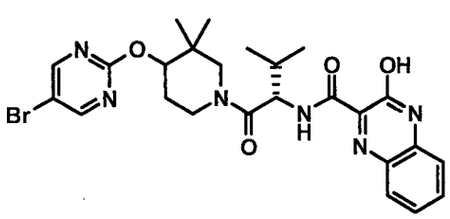
^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.86 (1H, brs), 9.66 (1H, brs), 8.75 (2H, d, J=5.6 Hz), 8.34 (2H, d, J=7.6 Hz), 7.88 (1H, t, J=6.8 Hz), 7.66 (1H, t, J=7.6 Hz), 7.53-7.52 (3H, m), 7.41-7.39 (2H, m), 4.96-4.93 (2H, m), 4.05-3.95 (2H, m), 3.63-3.27 (2H, m), 2.11-2.07 (3H, m), 1.79-1.63 (2H, m), 0.99-0.98 (6H, m).

IR (KBr) cm^{-1}: 2965, 1690, 1645, 1525, 1435, 1270.

MS (ESI, m/z): 527 $(M+H)^+$.

HRMS (ESI, m/z): 527.2406 (Calculado para $C_{29}H_{31}N_6O_4$: 527.2406).

Ejemplo 82



N-[(1S)-1-({4-[(5-bromo-pirimidin-2-il)-oxi]-3,3-dimetil-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 82-1

3,3-dimetil-4-oxo-piperidin-1-carboxilato de terbutilo

Se agregaron yoduro de metilo (2.75 mililitros, 44.2 milimoles), e hidruro de sodio al 63 por ciento (2.29 gramos, 60.2 milimoles) a una solución en tetrahidrofurano (80 mililitros) de 4-oxo-piperidin-1-carboxilato de terbutilo (4.00 gramos, 20.1 milimoles), a 0°C, bajo una corriente de nitrógeno, y la agitación se llevó a cabo a 60°C durante 5 horas. Se agregó agua a la solución de la reacción bajo enfriamiento con hielo, seguida por extracción con acetato de etilo, y lavado en secuencia con agua, una solución acuosa saturada de carbonato ácido de sodio, agua, y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., Si, 40+M), para proporcionar el

3,3-dimetil-4-oxo-piperidin-1-carboxilato de terbutilo (2.17 gramos, rendimiento del 48 por ciento) como un sólido blanco.

^{1}H-RMN ($CDCl_3$, 500 MHz) δ: 3.76-3.74 (2H, brm), 3.47-3.45 (2H, brm), 2.52 (2H, t, J=6.4 Hz), 1.53 (9H, s), 1.14 (6H, s).

MS (FAB, m/z): 228 $(M+H)^+$.

Ejemplo 82-2

4-[(5-bromo-pirimidin-2-il)-oxi]-3,3-dimetil-piperidin-1-carboxilato de terbutilo

Se agregó borohidruro de sodio (433 miligramos, 11.5 milimoles) a una solución en metanol (50 mililitros) de 3,3-dimetil-4-oxo-piperidin-1-carboxilato de terbutilo (2.17 gramos, 9.55 milimoles), a 0°C, bajo una corriente de nitrógeno, y la agitación se llevó a cabo a temperatura ambiente durante 3 horas. Se agregó agua a la solución de la reacción bajo enfriamiento con hielo, seguida por extracción con acetato de etilo, y lavado en secuencia con agua, una solución acuosa saturada de carbonato ácido de sodio, agua, y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, para proporcionar el 4-hidroxi-3,3-dimetil-piperidin-1-carboxilato de terbutilo (2.19 gramos) como un aceite incoloro.

De una manera análoga al Ejemplo 64-1, el 4-[(5-bromo-pirimidin-2-il)-oxi]-3,3-dimetil-piperidin-1-carboxilato de terbutilo (1.41 gramos, rendimiento del 67 por ciento) se obtuvo a partir del compuesto resultante (1.25 gramos, 5.45 milimoles), y 5-bromo-2-cloro-pirimidina (1.58 gramos, 8.18 milimoles) como un sólido blanco.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.54 (2H, s), 4.90 (1H, dd, J=7.6 Hz, 4.0 Hz), 3.78 (1H, brs), 3.56 (1H, brs), 3.36-3.31 (1H, m), 3.05 (1H, d, J=13.6 Hz), 1.98 (1H, brs), 1.78 (1H, brs), 1.49 (9H, s), 1.07 (3H, s), 1.03 (3H, s).

MS (FAB, m/z): 411 $(M+H)^+$.

Ejemplo 82-3

[(1S)-1-({4-[(5-bromo-pirimidin-2-il)-oxi]-3,3-dimetil-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 23-2, el clorhidrato de 5-bromo-2-[(3,3-dimetil-piperidin-4-il)-oxi]-pirimidina (0.251 miligramos) se obtuvo a partir del 4-[(5-bromo-pirimidin-2-il)-oxi]-3,3-dimetil-piperidin-1-carboxilato de terbutilo (300 miligramos, 0.777 milimoles) como un sólido blanco. El compuesto resultante (251 miligramos, 0.777 milimoles) se condensó con N-(terbutoxi-carbonil)-L-valina (253 miligramos, 1.16 milimoles), para proporcionar el [(1S)-1-({4-[(5-bromo-pirimidin-2-il)-oxi]-3,3-dimetil-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (322 miligramos, rendimiento del 85 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.49 (2H, s), 5.31-5.23 (1H, m), 4.90-4.85 (1H, m), 4.51-4.45 (1H, m), 4.09-4.05 (1H, m), 3.54-3.21 (3H, m), 2.09-1.74 (3H, m), 1.40 (9H, s), 1.05-0.85 (12H, m);

MS (FAB, m/z): 485 $(M+H)^+$.

Ejemplo 82-4

N-[(1S)-1-({4-[(5-bromo-pirimidin-2-il)-oxi]-3,3-dimetil-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 1-3, el clorhidrato de (2S)-1-{4-[(5-bromo-pirimidin-2-il)-oxi]-3,3-dimetil-piperidin-1-il}-3-metil-1-oxobutan-2- (280 miligramos) se obtuvo a partir del [(1S)-1-({4-[(5-bromo-pirimidin-2-il)-oxi]-3,3-dimetil-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (322 miligramos, 0.663 milimoles) como un sólido blanco. El compuesto resultante (140 miligramos, 0.332 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (95.0 miligramos, 0.497 milimoles), para proporcionar el compuesto del título deseado (70.0 miligramos, rendimiento del 38 por ciento) como un sólido amarillo pálido.

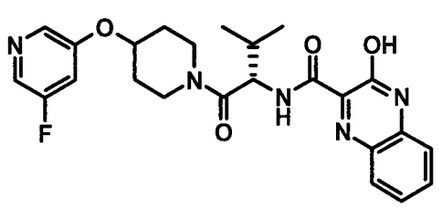
^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.80 (1H, brs), 9.50 (1H, brs), 8.72 (2H, s), 7.83-7.82 (1H, m), 7.60 (1H, t, J=7.6 Hz), 7.35-7.34 (2H, m), 4.92-4.88 (2H, m), 3.73-3.01 (4H, m), 2.07-1.99 (3H, m), 0.95-0.90 (12H, m).

IR (KBr) cm^{-1}: 2965, 1690, 1640, 1540, 1425, 1325.

MS (ESI, m/z): 579 $(M+Na)^+$.

HRMS (ESI, m/z): 579.1329 (Calculado para $C_{25}H_{29}BrN_6NaO_4$: 579.1331).

Ejemplo 83



N-[(1S)-1-({4-[(5-fluoro-piridin-3-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 83-1

4-[(5-fluoro-piridin-3-il)-oxi]-piperidin-1-carboxilato de terbutilo

El 4-hidroxi-piperidin-1-carboxilato de terbutilo (1.04 gramos, 5.00 milimoles) se agregó a una suspensión en N,N-dimetil-formamida (5.0 mililitros) de hidruro de sodio al 60 por ciento (229 miligramos, 6.00 milimoles), a 0°C, y la agitación se llevó a cabo a temperatura ambiente durante 30 minutos. Además, a 0°C, se agregó 3,5-difluoro-piridina (645 miligramos, 5.50 milimoles), y la agitación se llevó a cabo durante 16.5 horas. Se agregó agua a la solución de la reacción, seguida por extracción con acetato de etilo. El extracto se lavó en secuencia con agua y una solución salina, y entonces se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, para proporcionar el 4-[(5-fluoro-piridin-3-il)-oxi]-piperidin-1-carboxilato de terbutilo (1.48 gramos, rendimiento del 99 por ciento) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.16-8.11 (2H, m), 6.96 (1H, dt, J=10.2, 2.3 Hz), 4.52-4.47 (1H, m), 3.73-3.67 (2H, m), 3.39-3.33 (2H, m), 1.99-1.73 (4H, m), 1.47 (9H, s).

MS (ESI, m/z): 297 $(M+H)^+$.

Ejemplo 83-2

[(1S)-1-({4-[(5-fluoro-piridin-3-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo

Se agregó ácido clorhídrico concentrado (5.0 mililitros) a una solución en etanol (10 mililitros) de 4-[(5-fluoro-piridin-3-il)-oxi]-

piperidin-1-carboxilato de terbutilo (1.48 gramos, 4.99 milimoles), a 0°C, y la agitación se llevó a cabo a temperatura ambiente durante 16 horas. La solución de la reacción se concentró, para proporcionar el clorhidrato de 3-fluoro-5-(piperidin-4-iloxi)-piridina. Este producto se utilizó como estaba en la siguiente reacción sin purificación.

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (1.44 gramos, 7.49 milimoles) se agregó a una solución en cloruro de metileno (50 mililitros) del compuesto resultante, N-(terbutoxi-carbonil)-L-valina (1.09 gramos, 4.99 milimoles), monohidrato de 1-hidroxi-benzotriazol (810 miligramos, 5.99 milimoles), y N-metil-morfolina (2.75 mililitros, 25.0 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a temperatura ambiente durante la noche. Se agregó agua a la solución de la reacción, seguida por extracción con cloruro de metileno, lavado en secuencia con una solución acuosa saturada de carbonato ácido de sodio, agua, y una solución salina, y se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, para proporcionar el [(1S)-1-({4-[(5-fluoro-piridin-3-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (1.89 gramos, rendimiento del 96 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.16 (1H, s), 8.13 (1H, d, J=2.3 Hz), 6.96 (1H, dt, J=10.2, 2.3 Hz), 5.34-5.30 (1H, m), 4.64-4.55 (1H, m), 4.51-4.47 (1H, m), 3.87-3.48 (4H, m), 2.04-1.81 (5H, m), 1.44 (9H, s), 0.98 (3H, d, J=7.0 Hz), 0.90 (3H, d, J=6.6 Hz).

MS (ESI, m/z): 396 $(M+H)^+$.

Ejemplo 83-3

Diclorhidrato de (2S)-1-{4-[(5-fluoro-piridin-3-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina

Se agregó ácido clorhídrico concentrado (4.8 mililitros) a una solución en etanol (9.6 mililitros) de [(1S)-1-({4-[(5-fluoro-piridin-3-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (1.89 gramos, 4.78 milimoles), a 0°C, y la agitación se llevó a cabo a temperatura ambiente durante 2 días. La solución de la reacción se concentró, para proporcionar el diclorhidrato de (2S)-1-{4-[(5-fluoro-piridin-3-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina (1.85 gramos, rendimiento del 100 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN (CD_3OD, 400 MHz) δ: 8.65-8.63 (2H, m), 8.34 (1H, dt, J=10.3, 2.2 Hz), 5.06-4.94 (1H, m), 4.40 (1H, d, J=5.1 Hz), 4.13-3.45 (4H, m), 2.23-1.80 (5H, m), 1.13-1.02 (6H, m).

MS (ESI, m/z): 296 $(M+H)^+$.

Ejemplo 83-4

N-[(1S)-1-({4-[(5-fluoro-piridin-3-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (156 miligramos, 0.815 milimoles) se agregó a una solución en cloruro de metileno (5.4 mililitros) de diclorhidrato de (2S)-1-{4-[(5-fluoro-piridin-3-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina (200

miligramos, 0.543 milimoles), ácido 3-hidroxi-quinoxalin-2-carboxílico (106 miligramos, 0.543 milimoles), monohidrato de 1-hidroxi-benzotriazol (88.1 miligramos, 0.652 milimoles), y N-metil-morfolina (0.299 mililitros, 2.72 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a temperatura ambiente durante la noche. Se agregó agua a la solución de la reacción, seguida por extracción con cloruro de metileno, y el extracto se lavó en secuencia con una solución acuosa saturada de carbonato ácido de sodio, agua, y una solución salina, y se secó sobre sulfato de sodio anhidro. Después de que la capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, el residuo resultante se suspendió en un solvente mixto de etanol/dietil-éter, y la sustancia sólida se recolectó mediante filtración, para proporcionar el compuesto del título deseado (160 miligramos, rendimiento del 63 por ciento) como un sólido amarillo.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 12.56 (1H, brs), 10.12 (1H, brs), 8.20-7.99 (3H, m), 7.66-7.31 (3H, m), 7.02-6.96 (1H, m), 5.10-5.05 (1H, m), 4.70-4.61 (1H, m), 4.03-3.67 (4H, m), 2.39-1.89 (5H, m), 1.15-1.10 (6H, m).

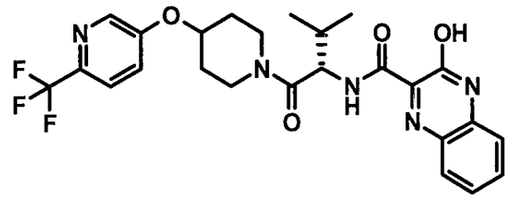
IR (KBr) cm^{-1}: 2960, 1690, 1640, 1530, 1430.

MS (ESI, m/z): 468 $(M+H)^+$.

HRMS (ESI, m/z): 490.1857 (Calculado para $C_{24}H_{26}FN_5NaO_4$: 490.1867).

Análisis calculado para $C_{24}H_{26}FN_5O_4$: C, 61.66; H, 5.61; N, 14.98; F, 4.06. Encontrado: C, 61.44; H, 5.71; N, 14.87; F, 4.21.

Ejemplo 84



3-hidroxi-N-{(1S)-2-metil-1-[(4-{[6-(trifluoro-metil)-piridin-3-il]-oxi}-piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida

Ejemplo 84-1

{(1S)-2-metil-1-[(4-{[6-(trifluoro-metil)-piridin-3-il]-oxi}-piperidin-1-il)-carbonil]-propil}-carbamato de terbutilo

Una solución al 40 por ciento en tolueno de azodicarboxilato de di-isopropilo (2.10 mililitros, 3.99 milimoles) se agregó a una solución en tolueno (15 mililitros) de {(1S)-1-[(4-hidroxi-piperidin-1-il)-carbonil]-2-metil-propil}-carbamato de terbutilo (1.00 gramos, 3.33 milimoles), 2-(trifluoro-metil)-piridin-5-ol (597 miligramos, 3.33 milimoles), y trifenil-fosfina (1.05 gramos, 3.99 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a la misma temperatura durante 2 días. La solución de la reacción se concentró, y el residuo resultante se diluyó con acetato de etilo, seguido por lavado en secuencia con una solución acuosa de hidróxido de sodio 1N, agua, y una solución salina, y la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, para proporcionar el {(1S)-2-metil-1-[(4-{[6-(trifluoro-metil)-

piridin-3-il]-oxi}-piperidin-1-il)-carbonil]-propil}-carbamato de terbutilo (1.11 gramos, rendimiento del 75 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.39 (1H, s), 7.63 (1H, d, J=8.6 Hz), 7.30 (1H, dd, J=8.6 Hz, 2.7 Hz), 5.31 (1H, d, J=8.2 Hz), 4.74-4.66 (1H, m), 4.51-4.48 (1H, m), 3.86-3.54 (4H, m), 2.06-1.84 (5H, m), 1.44 (9H, s), 0.98 (3H, d, J=6.6 Hz), 0.90 (3H, d, J=6.6 Hz).

MS (ESI, m/z): 346 $(M+H)^+$.

Ejemplo 84-2

Diclorhidrato de (2S)-3-metil-1-oxo-1-(4-{[6-(trifluoro-metil)-piridin-3-il]-oxi}-piperidin-1-il)-butan-2-amina

Se agregó ácido clorhídrico concentrado (2.5 mililitros) a una solución en etanol (5.0 mililitros) de {(1S)-2-metil-1-[(4-{[6-(trifluoro-metil)-piridin-3-il]-oxi}-piperidin-1-il)-carbonil]-propil}-carbamato de terbutilo (1.11 gramos, 2.49 milimoles), a 0°C, y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se concentró, para proporcionar el diclorhidrato de (2S)-3-metil-1-oxo-1-(4-{[6-(trifluoro-metil)-piridin-3-il]-oxi}-piperidin-1-il)-butan-2-amina (970 miligramos, rendimiento del 100 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN (CD_3OD, 400 MHz) δ: 8.39 (1H, dd, J=9.0 Hz, 2.7 Hz), 7.76 (1H, d, J=9.0 Hz), 7.61 (1H, d, J=8.6 Hz), 4.35 (1H, d, J=4.7 Hz), 4.09-3.46 (5H, m), 2.21-1.77 (5H, m), 1.11 (3H, d, J=7.0 Hz), 1.02 (3H, dd, J=6.8 Hz, 1.4 Hz).

MS (ESI, m/z): 346 $(M+H)^+$.

Ejemplo 84-3

3-hidroxi-N-{(1S)-2-metil-1-[(4-{[6-(trifluoro-metil)-piridin-3-il]-oxi}-piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (137 miligramos, 0.717 milimoles) se agregó a una solución en cloruro de metileno (4.8 mililitros) de diclorhidrato de (2S)-3-metil-1-oxo-1-(4-{[6-(trifluoro-metil)-piridin-3-il]-oxi}-piperidin-1-il)-butan-2-amina (200 miligramos, 0.478 milimoles), ácido 3-hidroxi-quinoxalin-2-carboxílico (93.7 miligramos, 0.478 milimoles), monohidrato de 1-hidroxi-benzotriazol (77.5 miligramos, 0. 574 milimoles), y N-metil-morfolina (0.263 mililitros, 2.39 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a temperatura ambiente durante la noche. Se agregó agua a la solución de la reacción, seguida por extracción con cloruro de metileno, y el extracto se lavó en secuencia con una solución acuosa saturada de carbonato ácido de sodio, agua, y una solución salina, y se secó sobre sulfato de sodio anhidro. Después de que la capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, el residuo resultante se suspendió en un solvente mixto de etanol/dietil-éter, y entonces la sustancia sólida se recolectó mediante filtración, para proporcionar el compuesto del título deseado (145 miligramos, rendimiento del 59 por ciento) como un sólido amarillo.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 12.08 (1H, brs), 10.15 (1H, brs), 8.41 (1H, dd, J=10.6 Hz, 2.7 Hz), 8.02 (1H, brs), 7.66-7.30 (5H, m),

5.09-5.04 (1H, m), 4.78-4.70 (1H, m), 4.10-3.64 (4H, m), 2.35-1.95 (5H, m), 1.14-1.09 (6H, m).

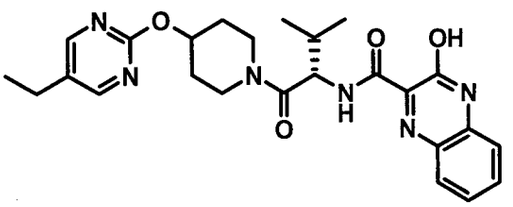
IR (KBr) cm^{-1}: 2965, 1685, 1640, 1530, 1340.

MS (ESI, m/z): 518 $(M+H)^+$.

HRMS (ESI, m/z): 518.2016 (Calculado para $C_{25}H_{27}F_3N_5O_4$: 518.2015).

Análisis calculado para $C_{25}H_{26}F_3N_5O_4 \cdot 0.5H_2O$:C, 57.03; H, 5.17; N, 13.30; F, 10.83. Encontrado: C, 56.82; H, 4.98; N, 13.03; F, 10.89.

Ejemplo 85



N-[(1S)-1-({4-[(5-etil-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 85-1

4-[(5-etil-pirimidin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo

Se agregó 4-hidroxi-piperidin-1-carboxilato de terbutilo (1.04 gramos, 5.00 milimoles) a una suspensión en N,N-dimetil-formamida (5.0 mililitros) de hidruro de sodio al 60 por ciento (229 miligramos, 6.00 milimoles), a 0°C, y la agitación se llevó a cabo a temperatura ambiente durante 30 minutos. Se agregó 2-cloro-5-etil-pirimidina (0.689 mili-litros, 5.50 milimoles) a la solución de la reacción, a 0°C, y la agitación se llevó a cabo durante 1 hora adicional. Se agregó agua a la solución de la reacción, seguida por extracción con acetato

de etilo, y el extracto se lavó en secuencia con agua y una solución salina, y se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, para proporcionar el 4-[(5-etil-pirimidin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo (1.03 gramos, rendimiento del 67 por ciento) como un sólido blanco.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.33 (2H, s), 5.18-5.12 (1H, m), 3.83-3.77 (2H, m), 3.34-3.27 (2H, m), 2.58 (2H, q, J=7.6 Hz), 2.02-1.97 (2H, m), 1.84-1.76 (2H, m), 1.47 (9H, s), 1.25 (3H, t, J=7.6 Hz).

MS (ESI, m/z): 308 $(M+H)^+$, 252 $(M+H-tBu)^+$, 208 $(M+H-BOC)^+$.

Ejemplo 85-2

[(1S)-1-({4-[(5-etil-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo

Se agregó ácido clorhídrico concentrado (3.4 mililitros) a una solución en etanol (6.8 mililitros) de 4-[(5-etil-pirimidin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo (1.03 gramos, 3.35 milimoles), a 0°C, y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se concentró, para proporcionar el diclorhidrato de 5-etil-2-(piperidin-4-iloxi)-pirimidina. Este producto se utilizó como estaba en la siguiente reacción sin purificación.

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (964 miligramos, 5.03 milimoles) se agregó a una solución en cloruro de metileno (34 mililitros) del compuesto resultante, N-(terbutoxi-carbonil)-L-valina (728 miligramos, 3.35 milimoles), monohidrato de 1-hidroxi-benzotriazol (543 miligramos, 4.02 milimoles), y N-metil-

morfolina (1.11 mililitros, 10.1 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a temperatura ambiente durante 6 días. Se agregó agua a la solución de la reacción, seguida por extracción con acetato de etilo, y el extracto se lavó en secuencia con una solución acuosa saturada de carbonato ácido de sodio, agua, y una solución salina, y se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, para proporcionar el [(1S)-1-({4-[(5-etil-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (1.20 gramos, rendimiento del 88 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.34 (2H, s), 5.38-5.35 (1H, m), 5.29-5.22 (1H, m), 4.53-4.49 (1H, m), 4.00-3.44 (4H, m), 2.59 (2H, q, J=7.6 Hz), 2.10-1.84 (5H, m), 1.44 (9H, s), 1.25 (3H, t, J=7.6 Hz), 0.97 (3H, dd, J=6.8 Hz, 2.2 Hz), 0.90-0.88 (3H, m).

MS (ESI, m/z): 407 $(M+H)^+$.

Ejemplo 85-3

Diclorhidrato de (2S)-1-{4-[(5-etil-pirimidin-2-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina

Se agregó ácido clorhídrico concentrado (3.0 mililitros) a una solución en etanol (6.0 mililitros) de [(1S)-1-({4-[(5-etil-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (1.20 gramos, 2.95 milimoles), a 0°C, y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se concentró, para proporcionar el diclorhidrato de (2S)-1-{4-[(5-etil-

pirimidin-2-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina (1.20 gramos, rendimiento del 100 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN (CD_3OD, 400 MHz) δ: 8.75-8.69 (2H, m), 5.54-5.47 (1H, m), 4.38 (1H, d, J=4.7 Hz), 4.07-3.48 (4H, m), 2.75-2.69 (2H, m), 2.21-1.86 (5H, m), 1.29 (3H, t, J=7.4 Hz), 1.12 (3H, d, J=7.0 Hz), 1.03 (3H, d, J=6.6 Hz).

MS (ESI, m/z): 307 $(M+H)^+$.

Ejemplo 85-4

N-[(1S)-1-({4-[(5-etil-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (152 miligramos, 0.633 milimoles) se agregó a una solución en cloruro de metileno (5.3 mililitros) de diclorhidrato de (2S)-1-{4-[(5-etil-pirimidin-2-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina (200 miligramos, 0.527 milimoles), ácido 3-hidroxi-quinoxalin-2-carboxílico (103 miligramos, 0.527 milimoles), monohidrato de 1-hidroxi-benzotriazol (85.5 miligramos, 0.633 milimoles), y N-metil-morfolina (0.174 mililitros, 2.11 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a temperatura ambiente durante la noche. Se agregó agua a la solución de la reacción, seguida por extracción con cloruro de metileno, y el extracto se lavó en secuencia con una solución acuosa saturada de carbonato ácido de sodio, agua, y una solución salina, y se secó sobre sulfato de sodio anhidro. Después de que la capa orgánica se concentró, y el residuo resultante se

purificó mediante cromatografía en columna de gel de sílice, el residuo resultante se suspendió en un solvente mixto de etanol/dietil-éter, y subsiguientemente la sustancia sólida se recolectó mediante filtración, para proporcionar el compuesto del título deseado (206 miligramos, rendimiento del 82 por ciento) como un sólido amarillo.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 12.82-12.64 (1H, m), 10.19 (1H, brs), 8.36 (2H, d, J=6.3 Hz), 8.02 (1H, t, J=9.2 Hz), 7.62-7.27 (3H, m), 5.32-5.07 (2H, m), 4.02-3.68 (4H, m), 2.63-2.56 (2H, m), 2.34-1.96 (5H, m), 1.29-1.24 (3H, m), 1.14-1.09 (6H, m).

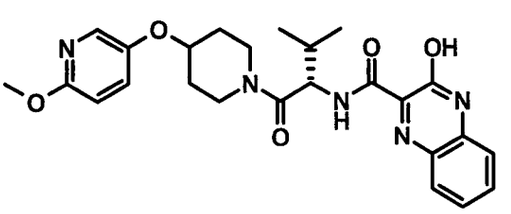
IR (KBr) cm^{-1}: 2965, 1690, 1630, 1525, 1435.

MS (ESI, m/z): 479 $(M+H)^+$.

HRMS (ESI, m/z): 501.2226 (Calculado para $C_{25}H_{30}N_6ONaO_4$: 501.2219).

Análisis calculado para $C_{25}H_{30}N_6O_4$: C, 62.75; H, 6.32; N, 17.56. Encontrado: C, 62.78; H, 6.30; N, 17.45.

Ejemplo 86



3-hidroxi-N-[(1S)-1-({4-[(6-metoxi-piridin-3-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-quinoxalin-2-carboxamida

Ejemplo 86-1

[(1S)-1-({4-[(6-metoxi-piridin-3-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo

Una solución al 40 por ciento en tolueno de azodicarboxilato de di-isopropilo (0.690 mililitros, 1.31 milimoles) se agregó a una solución en tolueno (5.0 mililitros) de {(1S)-1-[(4-hidroxi-piperidin-1-il)-carbonil]-2-metil-propil}-carbamato de terbutilo (329 miligramos, 1.09 milimoles), 6-metoxi-piridin-3-ol (137 miligramos, 1.09 milimoles), y trifenil-fosfina (345 miligramos, 1.31 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a temperatura ambiente durante 6 días. La solución de la reacción se concentró, y el residuo resultante se diluyó con acetato de etilo, seguido por lavado en secuencia con una solución acuosa de hidróxido de sodio 1N, agua, y una solución salina, y se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, para proporcionar el [(1S)-1-({4-[(6-metoxi-piridin-3-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (273 miligramos, rendimiento del 61 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.84 (1H, d, J=2.7 Hz), 7.23 (1H, dd, J=9.0, 2.7 Hz), 6.70 (1H, d, J=9.0 Hz), 5.34 (1H, d, J=9.0 Hz), 4.51-4.38 (2H, m), 3.90 (3H, s), 3.88-3.42 (4H, m), 2.02-1.78 (5H, m), 1.44 (9H, s), 0.98-0.88 (6H, m).

MS (ESI, m/z): 408 $(M+H)^+$.

Ejemplo 86-2

Diclorhidrato de (2S)-1-{4-[(6-metoxi-piridin-3-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina

Se agregó ácido clorhídrico concentrado (1.0 mililitros) a una

solución en etanol (2.0 mililitros) de [(1S)-1-({4-[(6-metoxi-piridin-3-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (273 miligramos, 0.669 milimoles), a 0°C, y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se concentró, para proporcionar el diclorhidrato de (2S)-1-{4-[(6-metoxi-piridin-3-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina (270 miligramos, rendimiento del 100 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN (CD_3OD, 400 MHz) δ: 8.19-8.13 (2H, m), 7.51-7.48 (1H, m), 4.82-4.73 (1H, m), 4.37 (1H, d, J=5.1 Hz), 4.16 (3H, s), 4.09-3.43 (4H, m), 2.21-1.75 (5H, m), 1.11 (3H, d, J=7.0 Hz), 1.02 (3H, d, J=6.6 Hz).

MS (ESI, m/z): 308 $(M+H)^+$.

Ejemplo 86-3

3-hidroxi-N-[(1S)-1-({4-[(6-metoxi-piridin-3-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-quinoxalin-2-carboxamida

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (193 miligramos, 1.00 milimoles) se agregó a una solución en cloruro de metileno (6.7 mililitros) de diclorhidrato de (2S)-1-{4-[(6-metoxi-piridin-3-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina (255 miligramos, 0.669 milimoles), ácido 3-hidroxi-quinoxalin-2-carboxílico (131 miligramos, 0.669 milimoles), monohidrato de 1-hidroxi-benzotriazol (109 miligramos, 0.803 milimoles), y N-metil-morfolina (0.221 mililitros, 2.68 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a temperatura ambiente durante 3 días. Se

agregó agua a la solución de la reacción, seguida por extracción con cloruro de metileno, y el extracto se lavó en secuencia con una solución acuosa saturada de carbonato ácido de sodio, agua, y una solución salina, y se secó sobre sulfato de sodio anhidro. Después de que la capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, el residuo resultante se suspendió en un solvente mixto de etanol/dietil-éter, y subsiguientemente la sustancia sólida se recolectó mediante filtración, para proporcionar el compuesto del título deseado (253 miligramos, rendimiento del 79 por ciento) como un sólido amarillo.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 12.54 (1H, brs), 10.16 (1H, brs), 8.02-7.98 (1H, m), 7.86 (1H, dd, J=7.4 Hz, 2.7 Hz), 7.61-7.22 (4H, m), 6.71 (1H, dd, J=8.8 Hz, 5.3 Hz), 5.10-5.05 (1H, m), 4.49-4.44 (1H, m), 3.91-3.74 (7H, m), 2.36-1.90 (5H, m), 1.26-1.09 (6H, m).

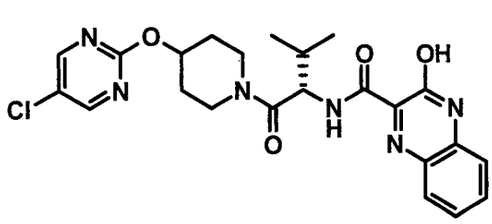
IR (KBr) cm^{-1}: 3430, 2945, 1685, 1640, 1490.

MS (ESI, m/z): 480 $(M+H)^+$.

HRMS (ESI, m/z): 502.2078 (Calculado para $C_{25}H_{29}N_5NaO_5$: 502.2066).

Análisis calculado para $C_{25}H_{29}N_5O_5$: C, 62.62; H, 6.10; N, 14.60. Encontrado: C, 62.42; H, 6.07; N, 14.58.

Ejemplo 87



N-[(1S)-1-({4-[(5-cloro-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 87-1

[(1S)-1-({4-[(5-cloro-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo

Una solución al 40 por ciento en tolueno de azodicarboxilato de di-isopropilo (2.10 mililitros, 3.99 milimoles) se agregó a una solución en tolueno (15 mililitros) de {(1S)-1-[(4-hidroxi-piperidin-1-il)-carbonil]-2-metil-propil}-carbamato de terbutilo (1.00 gramos, 3.33 milimoles), clorhidrato de 5-cloro-2-hidroxi-pirimidina (612 miligramos, 3.66 milimoles), y trifenil-fosfina (1.05 gramos, 3.99 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a temperatura ambiente durante 2 días. La solución de la reacción se concentró, y el residuo resultante se diluyó con acetato de etilo, y entonces la capa orgánica se lavó en secuencia con una solución acuosa de hidróxido de sodio 1N, agua, y una solución salina, y se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, para proporcionar el [(1S)-1-({4-[(5-cloro-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (517 miligramos, rendimiento del 38 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.45 (2H, s), 5.36-5.18 (2H, m), 4.52-4.48 (1H, m), 3.98-3.50 (4H, m), 2.10-1.83 (5H, m), 1.44 (9H, s), 0.97 (3H, d, J=6.3 Hz), 0.89 (3H, dd, J=6.6 Hz, 2.7 Hz).

MS (ESI, m/z): 413 $(M+H)^+$.

Ejemplo 87-2

Diclorhidrato de (2S)-1-{4-[(5-cloro-pirimidin-2-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina

Se agregó ácido clorhídrico concentrado (1.3 mililitros) a una solución en etanol (2.6 mililitros) de [(1S)-1-({4-[(5-cloro-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (517 miligramos, 1.25 milimoles), a 0°C, y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se concentró, para proporcionar el diclorhidrato de (2S)-1-{4-[(5-cloro-pirimidin-2-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina (456 miligramos, rendimiento del 94 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN (CD_3OD, 400 MHz) δ: 8.59 (2H, d, J=1.6 Hz), 5.36-5.28 (1H, m), 4.35 (1H, d, J=5.1 Hz), 4.07-3.46 (4H, m), 2.23-1.77 (5H, m), 1.11 (3H, d, J=7.0 Hz), 1.02 (3H, d, J=7.0 Hz).

MS (ESI, m/z): 313 $(M+H)^+$.

Ejemplo 87-3

N-[(1S)-1-({4-[(5-cloro-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (149 miligramos, 0.778 milimoles) se agregó a una solución en cloruro de metileno (5.2 mililitros) de diclorhidrato de (2S)-1-{4-[(5-cloro-pirimidin-2-il)-oxi]-piperidin-1-il}-3-metil-1-oxobutan-2-amina (200 miligramos, 0.519 milimoles), ácido 3-hidroxi-quinoxalin-2-

carboxílico (102 miligramos, 0.519 milimoles), monohidrato de 1-hidroxi-benzotriazol (84.1 miligramos, 0.622 milimoles), y N-metil-morfolina (0.285 mililitros, 2.59 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a temperatura ambiente durante la noche. Se agregó agua a la solución de la reacción, seguida por extracción con cloruro de metileno, y el extracto se lavó en secuencia con una solución acuosa saturada de carbonato ácido de sodio, agua, y una solución salina, y se secó sobre sulfato de sodio anhidro. Después de que la capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, el residuo resultante se suspendió en un solvente mixto de etanol/dietil-éter, y entonces la sustancia sólida se recolectó mediante filtración, para proporcionar el compuesto del título deseado (198 miligramos, rendimiento del 79 por ciento) como un sólido amarillo.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 12.52 (1H, brs), 10.17 (1H, brs), 8.47-8.46 (2H, m), 8.05-8.00 (1H, m), 7.63-7.26 (3H, m), 5.30-5.06 (2H, m), 4.08-3.63 (4H, m), 2.35-1.91 (5H, m), 1.14-1.09 (6H, m).

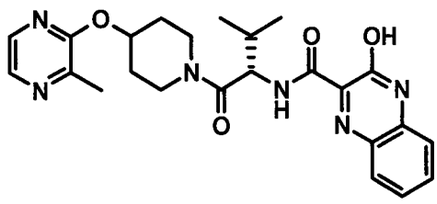
IR (KBr) cm^{-1}: 2965, 1690, 1630, 1425.

MS (ESI, m/z): 485 $(M+H)^+$.

HRMS (ESI, m/z): 507.1532 (Calculado para $C_{23}H_{25}ClN_6NaO_4$: 507.1524).

Análisis calculado para $C_{23}H_{25}ClN_6O_4 \cdot 0.1H_2O$: C, 56.76; H, 5.22; N, 17.27; F, 7.28. Encontrado: C, 56.56; H, 5.07; N, 17.20; F, 7.65.

Ejemplo 88



3-hidroxi-N-[(1S)-2-metil-1-({4-[(3-metil-pirazin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

Ejemplo 88-1

[(1S)-2-metil-1-({4-[(3-metil-pirazin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo

Una solución al 40 por ciento en tolueno de azodicarboxilato de di-isopropilo (2.10 mililitros, 3.99 milimoles) se agregó a una solución en tolueno (15 mililitros) de {(1S)-1-[(4-hidroxi-piperidin-1-il)-carbonil]-2-metil-propil}-carbamato de terbutilo (1.00 gramos, 3.33 milimoles), 3-metil-pirazin-2-ol (403 miligramos, 3.66 milimoles), y trifenil-fosfina (1.05 gramos, 3.99 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a la misma temperatura durante la noche. Después de que la solución de la reacción se concentró, y el residuo resultante se diluyó con acetato de etilo, la capa orgánica se lavó en secuencia con una solución acuosa de hidróxido de sodio 1N, agua, y una solución salina, y se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, para proporcionar el [(1S)-2-metil-1-({4-[(3-metil-pirazin-2-il)-

oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (933 miligramos, rendimiento del 71 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.00 (1H, d, J=2.7 Hz), 7.90-7.88 (1H, m), 5.37-5.30 (2H, m), 4.54-4.50 (1H, m), 3.93-3.48 (4H, m), 2.47 (3H, d, J=6.3 Hz), 2.11-1.79 (5H, m), 1.44 (9H, s), 0.99 (3H, d, J=6.6 Hz), 0.90 (3H, d, J=6.6 Hz).

MS (ESI, m/z): 293 $(M+H)^+$.

Ejemplo 88-2

diclorhidrato de (2S)-3-metil-1-{4-[(3-metil-pirazin-2-il)-oxi]-piperidin-1-il}-1-oxobutan-2-amina

Se agregó ácido clorhídrico concentrado (2.4 mililitros) a una solución en etanol (4.8 mililitros) de [(1S)-2-metil-1-({4-[(3-metil-pirazin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (933 miligramos, 2.38 milimoles), a 0°C, y la agitación se llevó a cabo a temperatura ambiente durante la noche. La solución de la reacción se concentró, para proporcionar el diclorhidrato de (2S)-3-metil-1-{4-[(3-metil-pirazin-2-il)-oxi]-piperidin-1-il}-1-oxobutan-2-amina (920 miligramos, rendimiento del 100 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN (CD_3OD, 400 MHz) δ: 8.49-8.47 (1H, m), 8.18-8.16 (1H, m), 5.58-5.49 (1H, m), 4.39 (1H, d, J=4.7 Hz), 4.08-3.53 (4H, m), 2.66 y 2.63 (3H, s), 2.26-1.84 (5H, m), 1.12 (3H, d, J=7.0 Hz), 1.03 (3H, dd, J=7.0, 1.2 Hz).

MS (ESI, m/z): 293 $(M+H)^+$.

Ejemplo 88-3

3-hidroxi-N-[(1S)-2-metil-1-({4-[(3-metil-pirazin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

El clorhidrato de 1-etil-3-(3-dimetil-amino-propil)-carbodi-imida (157 miligramos, 0.821 milimoles) se agregó a una solución en cloruro de metileno (5.5 mililitros) de diclorhidrato de (2S)-3-metil-1-{4-[(3-metil-pirazin-2-il)-oxi]-piperidin-1-il}-1-oxobutan-2-amina (200 miligramos, 0.547 milimoles), ácido 3-hidroxi-quinoxalin-2-carboxílico (107 miligramos, 0.547 milimoles), monohidrato de 1-hidroxi-benzotriazol (88.8 miligramos, 0.657 milimoles), y N-metil-morfolina (0.301 mililitros, 2.74 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a temperatura ambiente durante la noche. Se agregó agua a la solución de la reacción, seguida por extracción con cloruro de metileno, y el extracto se lavó en secuencia con una solución acuosa saturada de carbonato ácido de sodio, agua, y una solución salina, y se secó sobre sulfato de sodio anhidro. Después de que la capa orgánica se concentró, y el residuo resultante se purificó mediante cromatografía en columna de gel de sílice, el residuo resultante se suspendió en un solvente mixto de etanol/dietil-éter, y subsiguientemente la sustancia sólida se recolectó mediante filtración, para proporcionar el compuesto del título deseado (181 miligramos, rendimiento del 71 por ciento) como un sólido amarillo.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 12.64 (1H, brs), 10.17 (1H, brs), 8.02-8.00 (2H, m), 7.91 (1H, dd, J=6.3 Hz, 2.7 Hz), 7.63-7.38 (3H, m), 5.41-5.34 (1H, m), 5.13-5.08 (1H, m), 4.06-3.68 (4H, m), 2.51 y

2.47 (3H, s), 2.36-1.92 (5H, m), 1.16-1.11 (6H, m).

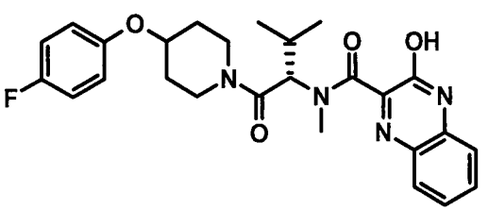
IR (KBr) cm^{-1}: 2960, 1690, 1640, 1540, 1415.

MS (ESI, m/z): 465 $(M+H)^+$.

HRMS (ESI, m/z): 465.2251 (Calculado para $C_{24}H_{29}N_6O_4$: 465.2250).

Análisis calculado para $C_{24}H_{28}N_6O_4$: C, 62.06; H, 6.08; N, 18.09. Encontrado: C, 61.70; H, 6.05; N, 17.90.

Ejemplo 89



N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-N-metil-quinoxalin-2-carboxamida

Ejemplo 89-1

[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-metil-carbamato de terbutilo

De una manera análoga al Ejemplo 2-1, el [(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-metil-carbamato de terbutilo (530 miligramos, rendimiento del 100 por ciento) se obtuvo a partir del clorhidrato de 4-(4-fluoro-fenoxi)-piperidina (300 miligramos, 1.29 milimoles), y N-(terbutoxi-carbonil)-N-metil-L-valina (300 miligramos, 1.29 milimoles) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.01-6.95 (2H, m), 6.88-6.83 (2H, m), 4.62 (1H, dd, J=10.8 Hz, 4.4 Hz), 4.52-4.35 (1H, m), 4.08-3.92

(1H, m), 3.84-3.75 (1H, m), 3.71-3.60 (1H, m), 3.55-3.31 (1H, m), 2.77 y 2.75 (3H, d, J=2.4 Hz), 2 42-2 31 (1H, m), 1.95-1.61 (4H, m), 1.48 y 1.46 (9H, s), 0.91-0.84 (6H, m).

MS (ESI, m/z): 409 $(M+H)^+$.

Ejemplo 89-2

N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-N-metil-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 2-2, el clorhidrato de (2S)-1-[4-(4-fluoro-fenoxi)-piperidin-1-il]-N,3-dimetil-1-oxobutan-2-amina (400 miligramos, 100 por ciento) se obtuvo a partir del [(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-metil-carbamato de terbutilo (530 miligramos, 1.29 milimoles) como un aceite incoloro. El compuesto resultante (100 miligramos, 0.290 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (60.0 miligramos, 0.290 milimoles), para proporcionar la N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-N-metil-quinoxalin-2-carboxamida (88.0 miligramos, rendimiento del 63 por ciento) como un sólido amarillo pálido.

^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.74 (1H, brs), 7.81 (1H, d, J=7.8 Hz), 7.67 (1H, d, J=7.3 Hz), 7.61 (1H, d, J=11.2 Hz, 7.3 Hz), 7.38-7.32 (1H, m), 7.15 -7.10 (2H, m), 7.05-7.02 (2H, m), 5.08 (1H, d, J=11.5 Hz), 4.65-4.55 (1H, m), 4.12-4.06 (2H, m), 3.96-3.79 (2H, m), 2.77 y 2.76 (3H, s), 2.07-1.24 (5H, m), 0.97 (3H, dd, J=6.4 Hz, 2.4 Hz), 0.92 (3H, dd, J=6.4 Hz, 3.2 Hz).

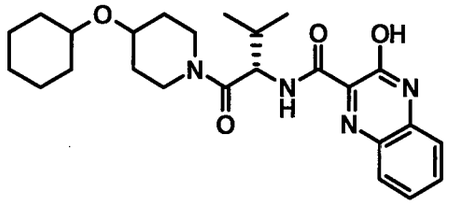
IR (ATR) cm^{-1}, 3460, 2960, 1685, 1640, 1505, 1455, 1205,

1055.

MS (ESI, m/z): 503 $(M+Na)^+$.

Análisis calculado para $C_{26}H_{29}FN_4O_4$: C, 64.99; H, 6.08; F, 3.95; N, 11.66. Encontrado: C, 64.69; H, 6.16; F, 4.14; N, 11.38.

Ejemplo 90



N-[(1S)-1-{[4-(ciclohexiloxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 90-1

4-(2-ciclohexen-1-iloxi)-piperidin-1-carboxilato de terbutilo

Se agregó óxido de plata (1.48 gramos) a una solución en tetrahidrofurano (10 mililitros) de 4-hidroxi-piperidin-1-carboxilato de terbutilo (1.00 gramos, 4.97 milimoles), y 3-bromo-ciclohexeno (300 miligramos, 1.29 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a 40°C durante la noche. Después de que el catalizador se filtró, el licor madre se concentró, y el material residual resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Yamazen Corporation, W-Prep 2XY), para proporcionar el compuesto del título (467 miligramos, rendimiento del 36 por ciento) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 5.86-5.82 (1H, m), 5.70 (1H, d, J=7.8 Hz), 4.00-3.95 (1H, m), 3.84-3.76 (2H, m), 3.62-3.56 (1H, m),

3.09-3.02 (2H, m), 2.07-1.50 (10H, m), 1.46 y 1.45 (9H, s).

MS (ESI, m/z): 262 $(M+H)^+$.

Ejemplo 90-2

4-(ciclohexiloxi)-piperidin-1-carboxilato de terbutilo

Se agregó un catalizador de paladio al 5 por ciento sobre carbón (60.0 miligramos) a una solución en etanol (10 mililitros) de 4-(2-ciclohexen-1-iloxi)-piperidin-1-carboxilato de terbutilo (360 miligramos, 1.29 milimoles), a temperatura ambiente, y la agitación se llevó a cabo a temperatura ambiente durante 5 horas bajo una atmósfera de hidrógeno. Después de que el catalizador se filtró, el licor madre se concentró, y el material residual resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Yamazen Corporation, W-Prep 2XY), para proporcionar el 4-(ciclohexiloxi)-piperidin-1-carboxilato de terbutilo (211 miligramos, rendimiento del 58 por ciento) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 3.82-3.75 (2H, m), 3.58-3.52 (1H, m), 3.36-3.30 (1H, m), 3.07-3.01 (2H, m), 1.88-1.70 (8H, m), 1.46 y 1.45 (9H, s), 1.32-1.15 (6H, m).

MS (ESI, m/z): 306 $(M+Na)^+$.

Ejemplo 90-3

[(1S)-1-{[4-(ciclohexiloxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 23-2, el clorhidrato de 4-(ciclohexiloxi)-piperidina (160 miligramos, 100 por ciento) se obtuvo

a partir del 4-(ciclohexiloxi)-piperidin-1-carboxilato de terbutilo (210 miligramos, 0.740 milimoles) como un aceite incoloro. El compuesto resultante (160 miligramos, 0.730 milimoles) se condensó con N-(terbutoxi-carbonil)-L-valina (160 miligramos, 0.730 milimoles), para proporcionar el [(1S)-1-{[4-(ciclohexiloxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo (280 miligramos, rendimiento del 100 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 5.36(1H, t, J=9.1 Hz), 4.50-4.46 (1H, m), 3.98-3.89 (1H, m), 3.80-3.71 (1H, m), 3.69-3.63 (1H, m), 3.34-3.28 (3H, m), 1.94-1.71 (7H, m), 1.63 -1.48 (4H, s), 1.43 (9H, s), 1.32-1.18 (4H, m), 0.96 (3H, dd, J=6.4 Hz, 2.4 Hz), 0.86 (3H, dd, J=6.4 Hz, 2.4 Hz).

IR (ATR) cm^{-1}: 2930, 1690, 1420, 1365, 1275, 1230, 1170, 1080.

MS (ESI, m/z): 383 $(M+H)^+$.

Ejemplo 90-4

N-[(1S)-1-{[4-(ciclohexiloxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 2-2, el clorhidrato de (2S)-1-[4-(ciclohexiloxi)-piperidin-1-il]-3-metil-1-oxobutan-2-amina (194 miligramos, 83 por ciento) se obtuvo a partir del [(1S)-1-{[4-(ciclohexiloxi)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo (280 miligramos, 0.730 milimoles) como una sustancia amorfa. El compuesto resultante (190 miligramos, 0.600 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (110 mili-

gramos, 0.600 milimoles), para proporcionar la N-[(1S)-1-{[4-(ciclohexiloxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida (219 miligramos, rendimiento del 81 por ciento) como un sólido amarillo pálido.

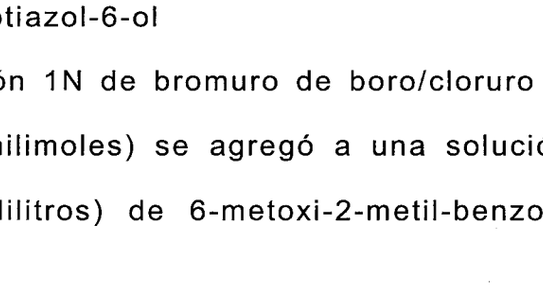
^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.81 (1H, brs), 9.45 (1H, t, J=8.3 Hz), 7.86 (1H, d, J=8.3 Hz), 7.63 (1H, t, J=7.5 Hz), 7.39-7.36 (1H, m), 4.86 (1H, dd, J=16.1 Hz, 9.3 Hz), 3.95-3.88 (2H, m), 3.70-3.63 (1H, m), 3.39-3.27 (3H, m), 3.19-3.06 (1H, m), 2.51-2.49 (4H, m), 1.92-1.11 (11H, m), 0.95-0.92 (6H, m).

IR (ATR) cm^{-1}: 2930, 1690, 1640, 1530, 1475, 1450, 1090.

MS (ESI, m/z): 455 $(M+H)^+$.

Análisis calculado para $C_{25}H_{34}N_4O_4$: C, 66.06; H, 7.54; N, 12.33. Encontrado: C, 65.77; H, 7.47; N, 12.33.

Ejemplo 91



3-hidroxi-N-[(1S)-2-metil-1-({4-[(2-metil-1,3-benzotiazol-6-il)-oxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

Ejemplo 91-1

2-metil-1,3-benzotiazol-6-ol

Una solución 1N de bromuro de boro/cloruro de metileno (8.4 mililitros, 8.40 milimoles) se agregó a una solución en cloruro de metileno (10 mililitros) de 6-metoxi-2-metil-benzotiazol (500 mili-

gramos, 2.79 milimoles), a -78°C, bajo una corriente de nitrógeno, y la agitación se llevó a cabo a 0°C durante 1 hora. Se agregó agua a la solución de la reacción, seguida por extracción con cloruro de metileno. El extracto se lavó en secuencia con una solución acuosa saturada de carbonato ácido de sodio y agua, y entonces se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Yamazen Corporation, W-Prep 2XY), para proporcionar el 2-metil-1,3-benzotiazol-6-ol (103 miligramos, rendimiento del 22 por ciento) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.66 (1H, d, J=8.8 Hz), 7.23 (1H, d, J=2.4 Hz), 6.94 (1H, dd, J=8.8 Hz, 2.4 Hz), 2.74 (3H, s).

MS (ESI, m/z): 166 $(M+H)^+$.

Ejemplo 91-2

[(1S)-2-metil-1-({4-[(2-metil-1,3-benzotiazol-6-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 1-2, el [(1S)-2-metil-1-({4-[(2-metil-1,3-benzotiazol-6-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (214 miligramos, rendimiento del 79 por ciento) se obtuvo a partir del 2-metil-1,3-benzotiazol-6-ol (100 miligramos, 0.610 milimoles), y {(1S)-1-[(4-hidroxi-piperidin-1-il)-carbonil]-2-metil-propil}-carbamato de terbutilo (200 miligramos, 0.670 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.83 (1H, d, J=8.8 Hz), 7.32 (1H, d, J=2.0 Hz), 7.05 (1H, dd, J=8.8 Hz, 2.0 Hz), 5.40-5.36 (1H, m),

4.61-4.50 (2H, m), 3.81-3.67 (2H, m), 3.59-3.47 (2H, m), 2.80 (3H, s), 1.99-1.86 (5H, m), 1.44 (9H, s), 0.98 (3H, d, J=6.4 Hz), 0.90 (3H, dd, J=6.4 Hz, 1.5 Hz).

IR (ATR) cm^{-1}: 2965, 1705, 1635, 1450, 1365, 1210, 1165.

MS (ESI, m/z): 448 $(M+H)^+$.

Ejemplo 91-3

3-hidroxi-N-[(1S)-2-metil-1-({4-[(2-metil-1,3-benzotiazol-6-il)-oxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 2-2, el clorhidrato de (2S)-3-metil-1-{4-[(2-metil-1,3-benzotiazol-6-il)-oxi]-piperidin-1-il}-1-oxobutan-2-amina (180 miligramos, 100 por ciento) se obtuvo a partir del [(1S)-2-metil-1-({4-[(2-metil-1,3-benzotiazol-6-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (210 miligramos, 0.470 milimoles) como un aceite incoloro. El compuesto resultante (180 miligramos, 0.470 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (90.0 miligramos, 0.470 milimoles), para proporcionar el 3-hidroxi-N-[(1S)-2-metil-1-({4-[(2-metil-1,3-benzotiazol-6-il)-oxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida (181 miligramos, rendimiento del 74 por ciento) como un sólido amarillo.

^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.78 (1H, brs), 10.20 (1H, brs), 7.99 (1H, s), 7.85 (1H, dd, J=8.8 Hz, 5.9 Hz), 7.61 (1H, brs), 7.51 (1H, brs), 7.34 (2H, dd, J=5.9 Hz, 2.0 Hz), 7.07 (1H, dt, J=9.1 Hz, 2.0 Hz), 5.09 (1H, t, J=7.3 Hz), 4.68-4.61 (1H, m), 4.02-3.73 (4H, m), 2.81 (3H, d, J=2.0 Hz), 2.40-2.17 (2H, m), 2.07-1.91 (3H, m),

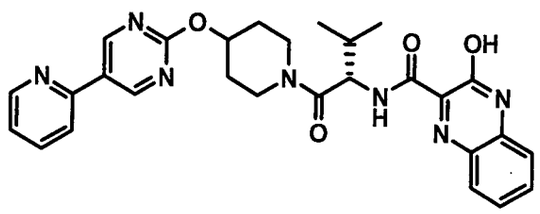
1.16-1.09 (6H, m).

IR (KBr) cm^{-1}: 2960, 1690, 1640, 1530, 1455, 1210.

MS (ESI, m/z): 520 $(M+H)^+$.

Análisis calculado para $C_{27}H_{29}N_5O_4S$: C, 62.41; H, 5.63; N, 13.48. Encontrado: C, 62.17; H, 5.79; N, 13.17.

Ejemplo 92



3-hidroxi-N-[(1S)-2-metil-1-({4-[(5-piridin-2-il-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

Ejemplo 92-1

4-[(5-piridin-2-il-pirimidin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo

Se agregó tetraquis-(trifenil-fosfina)-paladio (116 miligramos, 0.100 milimoles) a una solución en tolueno (6.0 mililitros) de 4-[(5-bromo-pirimidin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo (360 miligramos, 1.00 milimoles), y 2-(tributil-estanil)-piridina (555 miligramos, 1.51 milimoles), bajo una corriente de nitrógeno, y la agitación se llevó a cabo durante 7 horas bajo calentamiento a reflujo. Después de completarse la reacción, la solución de la reacción se enfrió a temperatura ambiente, y se vertió en agua helada, seguido por extracción con acetato de etilo. El extracto se lavó en secuencia con agua y una solución salina, y entonces se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró,

y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., 25+M), para proporcionar el 4-[(5-piridin-2-il-pirimidin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo (183 miligramos, rendimiento del 52 por ciento) como un sólido blanco.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 9.07 (2H, s), 8.67-8.66 (1H, m), 7.77-7.74 (1H, m), 7.63 (1H, d, J=7.2 Hz), 7.27-7.25 (1H, m), 5.27-5.21 (1H, m), 3.80-3.78 (2H, m), 3.33-3.27 (2H, m), 2.01-1.98 (2H, m), 1.83-1.80 (2H, m), 1.45 (9H, s).

MS (FAB, m/z): 357 $(M+H)^+$.

Ejemplo 92-2

[(1S)-2-metil-1-({4-[(5-piridin-2-il-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 23-2, el diclorhidrato de 2-(piperidin-4-iloxi)-5-piridin-2-il-pirimidina (169 miligramos) se obtuvo a partir del 4-[(5-piridin-2-il-pirimidin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo (183 miligramos, 0.513 milimoles) como un sólido blanco. El compuesto resultante (169 miligramos, 0.513 milimoles) se condensó con N-(terbutoxi-carbonil)-L-valina (167 miligramos, 0.770 milimoles), para proporcionar el [(1S)-2-metil-1-({4-[(5-piridin-2-il-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (212 miligramos, rendimiento del 91 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 500 MHz) δ: 9.15 (2H, s), 8.74 (1H, d, J=4.8 Hz), 7.85-7.82 (1H, m), 7.71 (1H, d, J=7.6 Hz), 7.34-7.32 (1H, m),

5.42-5.39 (2H, m), 4.56-4.54 (1H, m), 4.06-3.51 (4H, m), 2.19-1.91 (5H, m), 1.47 (9H, s), 1.01 (3H, d, J=6.8 Hz), 0.93 (3H, d, J=6.8 Hz).

MS (FAB, m/z): 456 $(M+H)^+$.

Ejemplo 92-3

3-hidroxi-N-[(1S)-2-metil-1-({4-[(5-piridin-2-il-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 23-3, el diclorhidrato de (2S)-3-metil-1-oxi-1-{4-[(5-piridin-2-il-pirimidin-2-il)-oxi]-piperidin-1-il}-butan-2-amina (200 miligramos) se obtuvo a partir del [(1S)-2-metil-1-({4-[(5-piridin-2-il-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (212 miligramos, 0.465 milimoles) como un sólido blanco.

El compuesto resultante (100 miligramos, 0.247 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (71.0 miligramos, 0.371 milimoles) bajo una corriente de nitrógeno, para proporcionar el compuesto del título deseado (70.0 miligramos, rendimiento del 54 por ciento) como un sólido amarillo pálido.

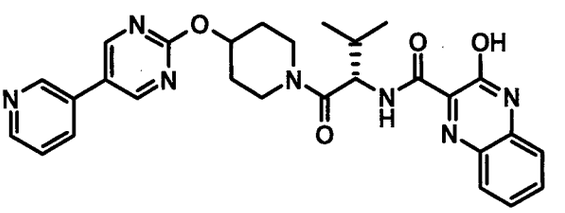
^{1}H-RMN (DMSO-d_6, 500 MHz) δ: 12.86 (1H, br s), 9.56 (1H, br s), 9.29 (2H, d, J=4.0 Hz), 8.72 (1H, d, J=4.4 Hz), 8.07 (1H, d, J=7.6 Hz), 7.96 (1H, t, J=7.6 Hz), 7.90 (1H, dd, J=8.0 Hz, 2.0 Hz), 7.67 (1H, t, J=7.6 Hz), 7.45-7.42 (3H, m), 5.37-5.35 (1H, m), 4.96 (1H, q, J=7.6 Hz), 4.08-4.00 (2H, m), 3.66-3.29 (2H, m), 2.09-1.75 (5H, m), 1.01-0.97 (6H, m).

IR (KBr) cm^{-1}: 2965, 1685, 1630, 1425, 1335.

MS (ESI, m/z): 528 $(M+H)^+$.

HRMS (ESI, m/z): 528.2371 (Calculado para $C_{28}H_{30}N_7O_4$: 528.2359).

Ejemplo 93



3-hidroxi-N-[(1S)-2-metil-1-({4-[(5-piridin-3-il-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

Ejemplo 93-1

4-[(5-piridin-3-il-pirimidin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo

De una manera análoga al Ejemplo 80-2, el 4-[(5-piridin-3-il-pirimidin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo (243 miligramos, rendimiento del 68 por ciento) se obtuvo a partir del [4-[(5-bromo-pirimidin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo (360 miligramos, 1.00 milimoles), y ácido 2-piridin-borónico (186 miligramos, 1.51 milimoles) como un sólido blanco.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.77 (1H, d, J=1.6 Hz), 8.69 (2H, s), 8.65-8.62 (1H, m), 7.81-7.78 (1H, m), 7.40-7.38 (1H, m), 5.22-5.21 (1H, m), 3.79-3.77 (2H, m), 3.33-3.26 (2H, m), 2.02-1.99 (2H, m), 1.86-1.80 (2H, m), 1.45 (9H, s).

Ejemplo 93-2

[(1S)-2-metil-1-({4-[(5-piridin-3-il-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 23-2, el diclorhidrato de 2-

(piperidin-4-iloxi)-5-piridin-3-il-pirimidina (225 miligramos) se obtuvo a partir del 4-[(5-piridin-3-il-pirimidin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo (243 miligramos, 0.682 milimoles) como un sólido blanco. El compuesto resultante (225 miligramos, 0.682 milimoles) se condensó con N-(terbutoxi-carbonil)-L-valina (222 miligramos, 1.02 milimoles), para proporcionar el [(1S)-2-metil-1-({4-[(5-piridin-3-il-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (227 miligramos, rendimiento del 73 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.79 (1H, d, J=2.4 Hz), 8.72 (2H, s), 8.66 (1H, d, J=4.8 Hz), 7.83 (1H, dt, J=7.6 Hz, 2.0 Hz), 7.42 (1H, dd, J=8.0 Hz, 4.8 Hz), 5.38-5.29 (2H, m), 4.50 (1H, dd, J=8.8 Hz, 5.8 Hz), 4.03-3.43 (4H, m), 2.13-1.86 (5H, m), 1.42 (9H, s), 0.96 (3H, d, J=6.8 Hz), 0.88 (3H, d, J=6.8 Hz).

MS (FAB, m/z): 456 $(M+H)^+$.

Ejemplo 93-3

3-hidroxi-N-[(1S)-2-metil-1-({4-[(5-piridin-3-il-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 23-3, el diclorhidrato de (2S)-3-metil-1-oxi-1-{4-[(5-piridin-3-il-pirimidin-2-il)-oxi]-piperidin-1-il}-butan-2-amina (213 miligramos) se obtuvo a partir del [(1S)-2-metil-1-({4-[(5-piridin-3-il-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (227 miligramos, 0.498 milimoles) como un sólido blanco. El compuesto resultante (106 miligramos, 0.249 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-

carboxílico (72.0 miligramos, 0.374 milimoles), para proporcionar el compuesto del título deseado (55.0 miligramos, rendimiento del 42 por ciento) como un sólido amarillo pálido.

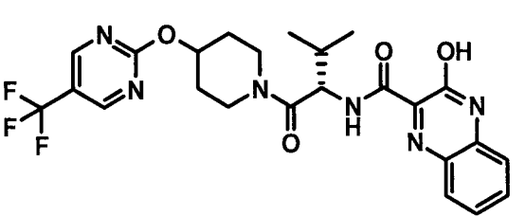
^{1}H-RMN (DMSO-d_6, 500 MHz) δ: 12.83 (1H, brs), 9.58 (1H, brs), 9.02 (2H, d, J=4.4 Hz), 8.96 (1H, s), 8.62 (1H, d, J=4.4 Hz), 8.17 (1H, dd, J=8.0 Hz, 2.0 Hz), 7.86 (1H, d, J=8.0 Hz), 7.63 (1H, t, J=7.6 Hz), 7.53 (1H, dd, J=7.6 Hz, 4.8 Hz), 7.37 (2H, t, J=7.6 Hz), 5.30-5.29 (1H, m), 4.93-4.90 (1H, m), 4.06-3.97 (2H, m), 3.62-3.25 (2H, m), 1.98-1.82 (5H, m), 0.98-0.92 (6H, m).

IR (KBr) cm^{-1}: 2965, 1690, 1640, 1525, 1440, 1335.

MS (ESI, m/z): 550 $(M+Na)^+$.

HRMS (ESI, m/z): 550.2174 (Calculado para $C_{28}H_{29}N_7NaO_4$: 550.2179).

Ejemplo 94



3-hidroxi-N-{(1S)-2-metil-1-[(4-{[5-(trifluoro-metil)-pirimidin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida

Ejemplo 94-1

4-[(5-yodo-pirimidin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo

Se agregaron en secuencia yoduro de sodio (336 miligramos,

2.24 milimoles), yoduro de cobre (213 miligramos, 1.12 milimoles), y N,N-dimetil-etilen-diamina (0.241 mililitros, 2.24 milimoles) a una solución en 1,4-dioxano (8.0 mililitros) de 4-[(5-bromo-pirimidin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo (400 miligramos, 1.12 milimoles), bajo una corriente de nitrógeno, y la agitación se llevó a cabo durante 5 horas bajo calentamiento a reflujo. Después de completarse la reacción, la solución de la reacción se enfrió a temperatura ambiente, y se vertió en agua helada, seguido por extracción con acetato de etilo. El extracto se lavó en secuencia con agua y una solución salina, y entonces se secó sobre sulfato de sodio anhidro. La capa orgánica resultante se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., 25+M), para proporcionar el 4-[(5-yodo-pirimidin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo (212 miligramos, rendimiento del 47 por ciento) como un sólido blanco.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.59 (2H, s), 5.10-5.06 (1H, m), 3.76-3.75 (2H, m), 3.29-3.23 (2H, m), 1.94-1.94 (2H, m), 1.77-1.74 (2H, m), 1.43 (9H, s).

MS (FAB, m/z): 406 $(M+H)^+$.

Ejemplo 94-2

4-{[5-(trifluoro-metil)-pirimidin-2-il]-oxi}-piperidin-1-carboxilato de terbutilo

Se agregaron en secuencia fluoruro de potasio (86.0 miligramos, 1.48 milimoles), yoduro de cobre (282 miligramos, 1.48

milimoles), y (trifluoro-metil)-trimetil-silano (0.219 mililitros, 1.48 mili-moles) a una solución en N,N'-dimetil-formamida (2.0 mililitros) de 4-[(5-yodo-pirimidin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo (120 miligramos, 0.296 milimoles), bajo una corriente de nitrógeno, y la agitación se llevó a cabo a 60°C durante la noche. Después de completarse la reacción, la solución de la reacción se enfrió a temperatura ambiente, y se vertió en agua helada, seguido por extracción con acetato de etilo. El extracto se lavó en secuencia con agua y una solución salina, y entonces se secó sobre sulfato de sodio anhidro. La capa orgánica resultante se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., 25+M), para proporcionar el 4-{[5-(trifluorometil)-pirimidin-2-il]-oxi}-piperidin-1-carboxilato de terbutilo (60.0 miligramos, rendimiento del 54 por ciento) como un sólido blanco.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.74 (2H, s), 5.29-5.21 (1H, m), 3.80-3.77 (2H, m), 3.31-3.27 (2H, m), 2.03-2.00 (2H, m), 1.82-1.77 (2H, m), 1.46 (9H, s).

MS (FAB, m/z): 347 $(M+H)^+$.

Ejemplo 94-3

{(1S)-2-metil-1-[(4-{[5-(trifluoro-metil)-pirimidin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-carbamato de terbutilo

De una manera análoga al Ejemplo 23-2, el clorhidrato de 2-(piperidin-4-iloxi)-5-(trifluoro-metil)-pirimidina (159 miligramos) se obtuvo a partir del 4-{[5-(trifluoro-metil)-pirimidin-2-il]-oxi}-piperidin-

1-carboxilato de terbutilo (195 miligramos, 0.561 milimoles) como un sólido blanco. El compuesto resultante (159 miligramos, 0.561 milimoles) se condensó con N-(terbutoxi-carbonil)-L-valina (183 miligramos, 0.842 milimoles), para proporcionar el {(1S)-2-metil-1-[(4-{[5-(trifluoro-metil)-pirimidin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-carbamato de terbutilo (217 miligramos, rendimiento del 87 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.73 (2H, s), 5.35-5.32 (2H, m), 4.47 (1H, dd, J=9.0 Hz, 5.6 Hz), 4.00-3.42 (4H, m), 2.03-1.88 (5H, m), 1.40 (9H, s), 0.94 (3H, d, J=6.8 Hz), 0.86 (3H, d, J=6.8 Hz).

MS (FAB, m/z): 447 $(M+H)^+$.

Ejemplo 94-4

3-hidroxi-N-{(1S)-2-metil-1-[(4-{[5-(trifluoro-metil)-pirimidin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 23-3, el clorhidrato de (2S)-3-metil-1-oxo-1-(4-{[5-(trifluoro-metil)-pirimidin-2-il]-oxi}-piperidin-1-il)-butan-2-amina (186 miligramos) se obtuvo a partir del [{(1S)-2-metil-1-[(4-{[5-(trifluoro-metil)-pirimidin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-carbamato de terbutilo (217 miligramos, 0.486 milimoles) como un sólido blanco. El compuesto resultante (93.0 miligramos, 0.243 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (70.0 miligramos, 0.365 milimoles), para proporcionar el compuesto del título deseado (60.0 miligramos, rendimiento del 48 por ciento) como un sólido amarillo pálido.

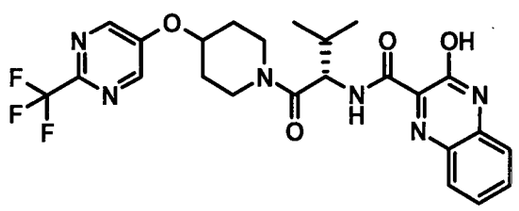
^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.78 (1H, brs), 10.21 (1H, brs), 8.78 (2H, d, J=7.6 Hz), 8.01 (1H, t, J=9.2 Hz), 7.63-7.54 (2H, m), 7.38 (1H, brs), 5.44-5.38 (1H, m), 5.12-5.08 (1H, m), 4.01-3.69 (4H, m), 2.26-2.09 (5H, m), 1.14-1.11 (6H, m).

IR (KBr) cm^{-1}: 2965, 1690, 1630, 1455, 1320, 1135.

MS (ESI, m/z): 541 $(M+Na)^+$.

HRMS (ESI, m/z): 541.1786 (Calculado para $C_{24}H_{25}F_3N_6NaO_4$: 541.1787).

Ejemplo 95



3-hidroxi-N-{(1S)-2-metil-1-[(4-{[2-(trifluoro-metil)-pirimidin-5-il]-oxi}-piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida

Ejemplo 95-1

5-bromo-2-(trifluoro-metil)-pirimidina

Se agregaron en secuencia yoduro de sodio (3.75 gramos, 25.0 milimoles), y una solución acuosa al 55 por ciento de ácido yodhídrico (1.48 gramos) a una solución en cloroformo (8.0 mililitros) de 5-bromo-2-cloro-pirimidina (2.90 gramos, 15.0 milimoles), a 0°C, y la agitación se llevó a cabo a temperatura ambiente durante 20 horas. Después de completarse la reacción, la solución de la reacción se vertió en agua helada, seguido por extracción con acetato de etilo. El extracto se lavó en secuencia con agua y una

solución salina, y entonces se secó sobre sulfato de sodio anhidro. La capa orgánica resultante se concentró, para proporcionar la 5-bromo-2-yodo-pirimidina (3.00 gramos) como una sustancia amorfa incolora. Este producto se utilizó en la siguiente reacción sin purificación.

Se agregaron en secuencia fluoruro de potasio (1.22 gramos, 21.1 milimoles), yoduro de cobre (4.01 miligramos, 21.1 milimoles), y (trifluoro-metil)-trimetil-silano (3.13 mililitros, 21.1 milimoles) a una solución en N,N-dimetil-formamida (20 mililitros) del compuesto resultante (3.00 gramos, 10.5 milimoles), y la agitación se llevó a cabo a 70°C durante 2 horas. Después de completarse la reacción, la solución de la reacción se enfrió a temperatura ambiente, y se vertió en agua helada, seguido por extracción con acetato de etilo. El extracto se lavó en secuencia con agua y una solución salina, y entonces se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., 25+M), para proporcionar la 5-bromo-2-(trifluoro-metil)-pirimidina (278 miligramos, rendimiento del 12 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.94 (2H, s).

MS (EI, m/z): 226 (M^+).

Ejemplo 95-2

2-(trifluoro-metil)-pirimidin-5-ol

Se agregaron en secuencia acetato de paladio (27.0

miligramos, 0.122 milimoles), bis-(pinacolato)-diboro (342 miligramos, 1.35 milimoles), y acetato de potasio (359 miligramos, 3.66 milimoles) a una solución en N,N-dimetil-formamida (3.0 mililitros) de 5-bromo-2-(trifluoro-metil)-pirimidina (278 miligramos, 1.22 milimoles), bajo una corriente de nitrógeno, y la agitación se llevó a cabo a 90°C durante 3 horas. Después de completarse la reacción, la solución de la reacción se enfrió a temperatura ambiente, y se vertió en agua helada, seguido por extracción con acetato de etilo. El extracto se lavó en secuencia con agua y una solución salina, y entonces la capa orgánica resultante se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se disolvió en una solución mixta de tetrahidrofurano-agua (8.0 mililitros, 1:1, volumen/volumen), seguida por la adición de tetrahidrato de perborato de sodio y agitación durante la noche. Después de completarse la reacción, la solución de la reacción se enfrió a temperatura ambiente, y se vertió en agua helada, seguido por extracción con acetato de etilo. El extracto se lavó en secuencia con agua y una solución salina, y entonces se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., 25+M), para proporcionar el 2-(trifluoro-metil)-pirimidin-5-ol (220 miligramos, 100 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.46 (2H, s).

MS (EI, m/z): 164 (M^+).

Ejemplo 95-3

{(1S)-2-metil-1-[(4-{[2-(trifluoro-metil)-pirimidin-5-il]-oxi}-piperidin-1-il)-carbonil]-propil}-carbamato de terbutilo

De una manera análoga al Ejemplo 1-2, el {(1S)-2-metil-1-[(4-{[2-(trifluoro-metil)-pirimidin-5-il]-oxi}-piperidin-1-il)-carbonil]-propil}-carbamato de terbutilo (320 miligramos, 49 por ciento) se obtuvo a partir del 2-(trifluoro-metil)-pirimidin-5-ol (240 miligramos, 1.46 milimoles), y {(1S)-1-[(4-hidroxi-piperidin-1-il)-carbonil]-2-metil-propil}-carbamato de terbutilo (527 miligramos, 1.76 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.50 (2H, s), 5.35 (1H, d, J=9.2 Hz), 4.80-4.72 (1H, m), 4.47 (1H, dd, J=9.2 Hz, 6.0 Hz), 3.91-3.50 (4H, m), 2.12-1.84 (5H, m), 1.41 (9H, s), 0.95 (3H, d, J=6.8 Hz), 0.89 (3H, d, J=6.8 Hz).

MS (FAB, m/z): 447 $(M+H)^+$.

Ejemplo 95-4

3-hidroxi-N-{(1S)-2-metil-1-[(4-{[2-(trifluoro-metil)-pirimidin-5-il]-oxi}-piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 23-3, el clorhidrato de (2S)-3-metil-1-oxo-1-(4-{[2-(trifluoro-metil)-pirimidin-5-il]-oxi}-piperidin-1-il)-butan-2-amina (274 miligramos) se obtuvo a partir del {(1S)-2-metil-1-[(4-{[2-(trifluoro-metil)-pirimidin-5-il]-oxi}-piperidin-1-il)-carbonil]-propil}-carbamato de terbutilo (320 miligramos, 0.717 milimoles) como un sólido blanco.

El compuesto resultante (137 miligramos, 0.360 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (103 miligramos, 0.538 milimoles) bajo una corriente de nitrógeno, para proporcionar el compuesto del título deseado (70.0 miligramos, rendimiento del 38 por ciento) como un sólido amarillo pálido.

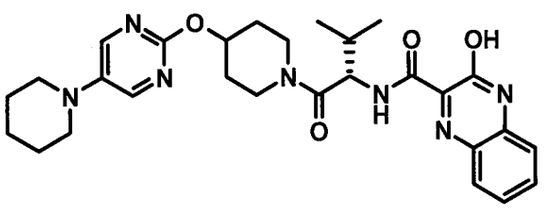
^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.84 (1H, brs), 9.55 (1H, brs), 8.85 (2H, d, J=3.6 Hz), 7.86 (1H, t, J=6.8 Hz), 7.64 (1H, t, J=8.0 Hz), 7.39-7.38 (2H, m), 5.04-5.02 (1H, m), 4.93-4.89 (1H, m), 4.01-3.99 (2H, m), 3.44-3.27 (2H, m), 2.08-2.04 (3H, m), 1.61 (2H, s), 0.96-0.95 (6H, m).

IR (KBr) cm^{-1}: 2965, 1685, 1640, 1535, 1350.

MS (ESI, m/z): 519 $(M+H)^+$.

HRMS (ESI, m/z): 519.1966 (Calculado para $C_{24}H_{26}F_3N_6O_4$: 519.1968).

Ejemplo 96



3-hidroxi-N-[(1S)-2-metil-1-({4-[(5-piperidin-1-il-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

Ejemplo 96-1

4-[(5-piperidin-1-il-pirimidin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo

Se agregaron en secuencia tris-(dibenciliden-acetona)-dipaladio (96.0 miligramos, 0.167 milimoles), 1,1'-bi-2-naftol (312 miligramos, 0.501 milimoles), piperidina (0.332 mililitros, 3.35 milimoles), y terbutóxido de sodio (324 miligramos, 3.35 milimoles) a una solución en tolueno (10 mililitros) de 4-[(5-bromo-pirimidin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo (600 miligramos, 1.67 milimoles), bajo una corriente de nitrógeno, y la agitación se llevó a cabo durante 5 horas bajo calentamiento a reflujo. Después de completarse la reacción, la solución de la reacción se enfrió a temperatura ambiente, y se vertió en agua helada, seguido por extracción con acetato de etilo. El extracto se lavó en secuencia con agua y una solución salina, y entonces se secó sobre sulfato de sodio anhidro. La capa orgánica resultante se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., 25+M), para proporcionar el 4-[(5-piperidin-1-il-pirimidin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo (600 miligramos, rendimiento del 98 por ciento) como un sólido blanco.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.14 (2H, s), 5.06-5.01 (1H, m), 3.77-3.73 (2H, m), 3.29-3.23 (2H, m), 3.02-3.01 (4H, m), 1.94 (2H, brs), 1.79-1.67 (6H, m), 1.57-1.51 (2H, m), 1.43 (9H, s).

MS (FAB, m/z): 363 $(M+H)^+$.

Ejemplo 96-2

[(1S)-2-metil-1-({4-[(5-piperidin-1-il-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 23-2, el diclorhidrato de 5-piperidin-1-il-2-(piperidin-4-iloxi)-pirimidina (556 miligramos) se obtuvo a partir del 4-[(5-piperidin-1-il-pirimidin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo (600 miligramos, 1.66 milimoles) como un sólido blanco. El compuesto resultante (556 miligramos, 1.66 milimoles) se condensó con N-(terbutoxi-carbonil)-L-valina (539 miligramos, 2.48 milimoles), para proporcionar el [(1S)-2-metil-1-({4-[(5-piperidin-1-il-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (567 miligramos, rendimiento del 74 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.15 (2H, s), 5.35-5.33 (1H, m), 5.15-5.11 (1H, m), 4.47 (1H, dd, J=8.8 Hz, 5.6 Hz), 3.91-3.40 (4H, m), 3.03 (4H, t, J=5.6 Hz), 2.04-1.78 (5H, m), 1.73-1.67 (4H, m), 1.57-1.51 (2H, m), 1.40 (9H, s), 0.93 (3H, dd, J=6.8 Hz, 2.4 Hz), 0.85 (3H, dd, J=6.8 Hz, 4.0 Hz).

MS (FAB, m/z): 462 $(M+H)^+$.

Ejemplo 96-3

3-hidroxi-N-[(1S)-2-metil-1-({4-[(5-piperidin-1-il-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 23-3, el diclorhidrato de (2S)-3-metil-1-oxo-1-{4-[(5-piperidin-1-il-pirimidin-2-il)-oxi]-piperidin-1-il}-butan-2-amina (534 miligramos) se obtuvo a partir del [(1S)-2-metil-1-({4-[(5-piperidin-1-il-pirimidin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (567 miligramos, 1.23 milimoles) como un sólido blanco. El compuesto resultante (283

miligramos, 0.614 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (175 miligramos, 0.921 milimoles), para proporcionar el compuesto del título deseado (105 miligramos, rendimiento del 32 por ciento) como un sólido amarillo pálido.

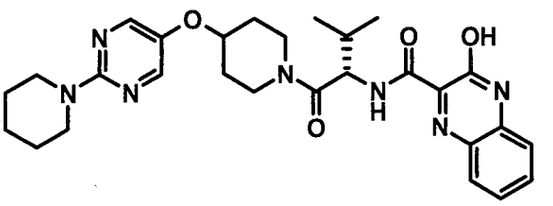
^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.84 (1H, brs), 9.56 (1H, brs), 8.32 (2H, d, J=3.6 Hz), 7.87 (1H, d, J=8.0 Hz), 7.64 (1H, t, J=8.0 Hz), 7.39-7.37 (2H, m), 5.10-5.09 (1H, m), 4.95-4.92 (1H, m), 4.00-3.95 (2H, m), 3.55-3.23 (2H, m), 3.07 (4H, t, J=5.2 Hz), 2.06-2.04 (3H, m), 1.62-1.52 (8H, m), 0.96-0.94 (6H, m).

IR (KBr) cm^{-1}: 2940, 1690, 1640, 1525, 1440, 1320.

MS (ESI, m/z): 556 $(M+Na)^+$.

HRMS (ESI, m/z): 556.2641 (Calculado para $C_{28}H_{35}N_7NaO_4$: 556.2648).

Ejemplo 97



3-hidroxi-N-[(1S)-2-metil-1-({4-[(2-piperidin-1-il-pirimidin-5-il)-oxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

Ejemplo 97-1

[(1S)-2-metil-1-({4-[(2-piperidin-1-il-pirimidin-5-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo

Se agregaron en secuencia piperidina (0.284 mililitros, 2.83

milimoles), y carbonato de potasio (330 miligramos, 4.78 milimoles) a una solución en N,N-dimetil-formamida (4.0 mililitros) de (1S)-1-({4-[(2-cloro-pirimidin-5-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-carbamato de terbutilo (300 miligramos, 0.956 milimoles), bajo una corriente de nitrógeno, y la agitación se llevó a cabo a 100°C durante 3 horas. Después de completarse la reacción, la solución de la reacción se enfrió a temperatura ambiente, y se vertió en agua helada, seguido por extracción con acetato de etilo. El extracto se lavó en secuencia con agua y una solución salina, y entonces se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., 25+M), para proporcionar el [(1S)-2-metil-1-({4-[(2-piperidin-1-il-pirimidin-5-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (400 miligramos, rendimiento del 91 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 8.04 (2H, s), 5.32 (1H, d, J=9.2 Hz), 4.46-4.44 (1H, m), 4.26-4.18 (1H, m), 3.89-3.59 (6H, m), 3.49-3.34 (2H, m), 1.97-1.49 (11H, m), 1.40 (9H, s), 0.93 (3H, dd, J=6.8 Hz, 5.2 Hz), 0.85 (3H, dd, J=6.8 Hz, 2.8 Hz).

Ejemplo 97-2

3-hidroxi-N-[(1S)-2-metil-1-({4-[(2-piperidin-1-il-pirimidin-5-il)-oxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 23-3, el diclorhidrato de (2S)-3-metil-1-oxo-1-{4-[(2-piperidin-1-il-pirimidin-5-il)-oxi]-piperidin-

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1-il}-butan-2- (376 miligramos) se obtuvo a partir del [(1S)-2-metil-1-({4-[(2-piperidin-1-il-pirimidin-5-il)-oxi]-piperidin-1-il}-carbonil)-propil]-carbamato de terbutilo (400 miligramos, 0.867 milimoles) como un sólido blanco. El compuesto resultante (188 miligramos, 0.433 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (125 miligramos, 0.650 milimoles), para proporcionar el compuesto del título deseado (70.0 miligramos, rendimiento del 30 por ciento) como un sólido amarillo pálido.

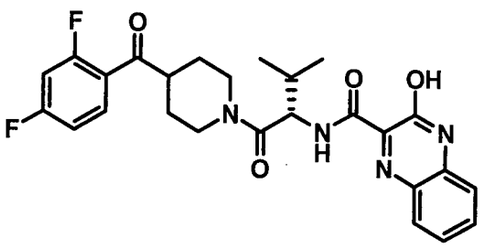
^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.84 (1H, brs), 9.52 (1H, brs), 8.23 (2H, d, J=6.4 Hz), 7.87 (1H, d, J=7.6 Hz), 7.64 (1H, t, J=7.6 Hz), 7.39-7.38 (2H, m), 4.92-4.89 (1H, m), 4.45-4.43 (1H, m), 3.93-3.88 (2H, m), 3.66 (4H, t, J=4.8 Hz), 3.47-3.22 (2H, m), 2.02-1.92 (3H, m), 1.60-1.51 (8H, m), 0.95 (6H, t, J=6.8 Hz).

IR (KBr) cm^{-1}: 2935, 1690, 1635, 1495, 1445, 1255.

MS (ESI, m/z): 556 $(M+Na)^+$.

HRMS (ESI, m/z): 556.2651 (Calculado para $C_{28}H_{35}N_7NaO_4$: 556.2648).

Ejemplo 98



N-[(1S)-1-{[4-(2,4-difluoro-benzoil)-piperidin-1-il]-carbonil}-2-metil-

propil]-3-hidroxi-quinoxalin-2-carboxamida

Ejemplo 98-1

[(1S)-1-{[4-(2,4-difluoro-benzoil)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo

De una manera análoga al Ejemplo 2-1, el clorhidrato de 4-(2,4-difluoro-benzoil)-piperidina (1.00 gramos, 3.82 milimoles) se condensó con N-(terbutoxi-carbonil)-L-valina (1.25 gramos, 5.73 milimoles), para proporcionar la N-[(1S)-1-{[4-(2,4-difluoro-benzoil)-piperidin-1-il]-carbonil}-2-metil-propil]-3,4-difluoro-2-hidroxi-benzamida (1.45 gramos, rendimiento del 90 por ciento) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.87-7.84 (1H, m), 6.97 (1H, t, J=8.0 Hz), 6.91-6.84 (1H, m), 5.33 (1H, t, J=8.0 Hz), 4.53-4.48 (2H, m), 4.02-3.98 (1H, m), 3.37-3.32 (1H, m), 3.26-3.16 (1H, m), 2.87-2.83 (1H, m), 2.01-1.85 (3H, m), 1.75-1.51 (2H, m), 1.41 (9H, s), 0.94 (3H, t, J=6.8 Hz), 0.86 (3H, d, J=6.8 Hz).

MS (FAB, m/z): 425 $(M+H)^+$.

Ejemplo 98-2

N-[(1S)-1-{[4-(2,4-difluoro-benzoil)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 23-3, el clorhidrato de (2,4-difluoro-fenil)-(1-L-valil-piperidin-4-il)-metanona (1.29 gramos) se obtuvo a partir del [(1S)-1-{[4-(2,4-difluoro-benzoil)-piperidin-1-il]-carbonil}-2-metil-propil]-carbamato de terbutilo (1.45 gramos, 3.44 milimoles) como un sólido blanco. El compuesto resultante (300

miligramos, 0.831 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (238 miligramos, 1.25 milimoles), para proporcionar el compuesto del título deseado (362 miligramos, rendimiento del 88 por ciento) como un sólido amarillo pálido.

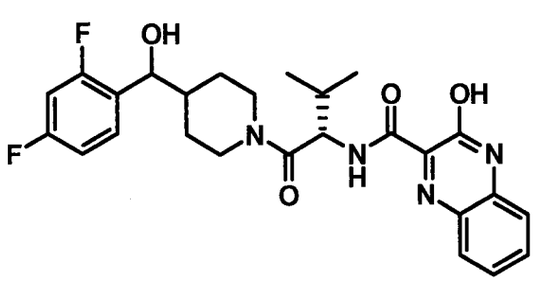
^{1}H-RMN (DMSO-d_6, 500 MHz) δ: 12.82 (1H, brs), 9.51 (1H, brs), 7.95-7.79 (2H, m), 7.63 (1H, t, J=8.0 Hz), 7.47-7.33 (3H, m), 7.28-7.24 (1H, m), 4.92-4.86 (1H, m), 4.44-4.40 (1H, m), 4.18-4.16 (1H, m), 3.39-3.26 (2H, m), 2.84-2.81 (1H, m), 2.00-1.83 (3H, m), 1.61-1.31 (2H, m), 0.95-0.93 (6H, m).

IR (KBr) cm^{-1}: 2965, 1685, 1610, 1530, 1270.

MS (ESI, m/z): 519 $(M+Na)^+$.

HRMS (ESI, m/z): 519.1812 (Calculado para $C_{26}H_{26}F_2N_4NaO_4$: 519.1820).

Ejemplo 99



N-[(1S)-1-({4-[(2,4-difluoro-fenil)-(hidroxi)-metil]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida

Se agregó borohidruro de sodio (183 miligramos, 0.483 milimoles) a una solución en metanol (2.0 mililitros) de N-[(1S)-1-{[4-(2,4-difluoro-benzoil)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida (218 miligramos, 0.439 milimoles),

a 0°C, y la agitación se llevó a cabo a la misma temperatura durante 1 hora. Después de completarse la reacción, la solución de la reacción se vertió en agua helada, seguido por extracción con acetato de etilo. El extracto se lavó en secuencia con agua y una solución salina, y entonces se secó sobre sulfato de sodio anhidro. La capa orgánica resultante se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., 25+M), para proporcionar el compuesto del título deseado (85.0 miligramos, rendimiento del 39 por ciento) como un sólido amarillo pálido.

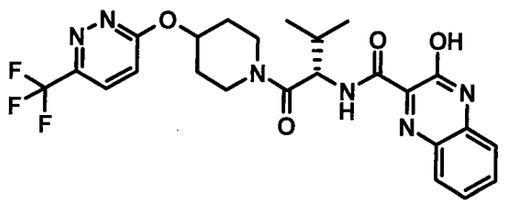
^{1}H-RMN (DMSO-d_6, 500 MHz) δ: 12.83 (1H, brs), 9.55 (1H, brs), 7.87-7.85 (1H, m), 7.63 (1H, q, J=8.0 Hz), 7.50-7.47 (1H, m), 7.38-7.36 (2H, m), 7.15-7.09 (2H, m), 5.44-5.42 (1H, m), 4.92-4.85 (1H, m), 4.60-4.55 (1H, m), 4.45-4.42 (1H, m), 4.16-4.01 (1H, m), 3.38-3.33 (1H, m), 3.03-3.01 (1H, m), 2.02-2.00 (1H, m), 1.86-1.79 (2H, m), 1.44-1.06 (2H, m), 0.93-0.89 (6H, m).

IR (KBr) cm^{-1}: 3425, 2965, 1685, 1620, 1525, 1455.

MS (ESI, m/z): 521 $(M+Na)^+$.

HRMS (ESI, m/z): 521.1965 (Calculado para $C_{26}H_{28}F_2N_4NaO_4$: 521.1976).

Ejemplo 100



3-hidroxi-N-{(1S)-2-metil-1-[(4-{[6-(trifluoro-metil)-piridazin-3-il]-oxi}-piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida

Ejemplo 100-1

3-cloro-6-(trifluoro-metil)-piridazina

Se agregaron en secuencia yoduro de sodio (1.31 gramos, 8.72 milimoles), y una solución acuosa al 55 por ciento de ácido yodhídrico (1.25 gramos) a una solución en cloroformo (4.0 mililitros) de 3,6-dicloro-piridazina (1.00 gramos, 6.71 milimoles), a 0°C, y la agitación se llevó a cabo a 40°C durante 5 horas. Después de completarse la reacción, a 0°C, se agregó hidróxido de sodio 2N para la neutralización, seguido por extracción con acetato de etilo. El extracto se lavó en secuencia con agua y una solución salina, y entonces se secó sobre sulfato de sodio anhidro. La capa orgánica resultante se concentró, para proporcionar la 3-cloro-6-yodo-piridazina (1.23 gramos) como un sólido blanco. Este producto se utilizó como estaba en la siguiente reacción sin purificación.

Se agregaron en secuencia fluoruro de potasio (889 miligramos, 15.3 milimoles), yoduro de cobre (2.92 gramos, 15.3 milimoles), y (trifluoro-metil)-trimetil-silano (2.27 mililitros, 15.3 milimoles) a una solución en N,N-dimetil-formamida (10 mililitros) del compuesto resultante (1.23 gramos, 5.11 milimoles), y la agitación se llevó a cabo a 60°C durante 2.5 horas. Después de completarse la reacción, la solución de la reacción se enfrió a temperatura ambiente, y se vertió en agua helada, seguido por extracción con acetato de etilo. El extracto se lavó en secuencia con agua y una

solución salina, y entonces se secó sobre sulfato de sodio anhidro. La capa orgánica se concentró, y el residuo resultante se purificó mediante un cromatógrafo de líquidos de preparación a presión media (fabricado por Biotage, Inc., 25+M), para proporcionar la 3-cloro-6-(trifluoro-metil)-piridazina (350 miligramos, rendimiento del 38 por ciento) como un sólido blanco.

^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 7.83 (1H, d, J=9.2 Hz), 7.76 (1H, d, J=9.2 Hz).

MS (EI, m/z): 182 (M^+).

Ejemplo 100-2

{(1S)-2-metil-1-[(4-{[6-(trifluoro-metil)-piridazin-3-il]-oxi}-piperidin-1-il)-carbonil]-propil}-carbamato de terbutilo

De una manera análoga al Ejemplo 64-1, el {(1S)-2-metil-1-[(4-{[6-(trifluoro-metil)-piridazin-3-il]-oxi}-piperidin-1-il)-carbonil]-propil}-carbamato de terbutilo (380 miligramos, rendimiento del 44 por ciento) se obtuvo a partir de la 3-cloro-6-(trifluoro-metil)-piridazina (350 miligramos, 1.92 milimoles), y {(1S)-1-[(4-hidroxi-piperidin-1-il)-carbonil]-2-metil-propil}-carbamato de terbutilo (634 miligramos, 2.11 milimoles) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$, 500 MHz) δ: 7.71 (1H, d, J=9.2 Hz), 7.11 (1H, dd, J=9.2 Hz, 3.2 Hz), 5.68-5.65 (1H, m), 5.34 (1H, t, J=9.2 Hz), 4.52-4.50 (1H, m), 4.13-3.79 (2H, m), 3.61-3.40 (2H, m), 2.21-2.13 (2H, m), 1.94-1.84 (3H, m), 1.44 (9H, s), 0.98 (3H, d, J=6.8 Hz), 0.90 (3H, t, J=6.0 Hz).

MS (FAB, m/z): 447 $(M+H)^+$.

Ejemplo 100-3

3-hidroxi-N-{(1S)-2-metil-1-[(4-{[6-(trifluoro-metil)-piridazin-3-il]-oxi}-piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida

De una manera análoga al Ejemplo 23-3, el clorhidrato de (2S)-3-metil-1-oxo-1-{4-{[6-(trifluoro-metil)-piridazin-3-il]-oxi}-piperidin-1-il}-butan-2-amina (299 miligramos) se obtuvo a partir del {(1S)-2-metil-1-[(4-{[6-(trifluoro-metil)-piridazin-3-il]-oxi}-piperidin-1-il)-carbonil]-propil}-carbamato de terbutilo (350 miligramos, 0.784 milimoles) como un sólido blanco. El compuesto resultante (150 miligramos, 0.392 milimoles) se condensó con ácido 3-hidroxi-quinoxalin-2-carboxílico (112 miligramos, 0.588 milimoles), para proporcionar el compuesto del título deseado (85.0 miligramos, rendimiento del 42 por ciento) como un sólido amarillo pálido.

^{1}H-RMN (DMSO-d_6, 400 MHz) δ: 12.79 (1H, brs), 9.57 (1H, brs), 8.17 (1H, dd, J=9.2 Hz, 4.0 Hz), 7.87-7.86 (1H, m), 7.66-7.62 (1H, m), 7.51 (1H, dd, J=9.2 Hz, 5.6 Hz), 7.39-7.37 (2H, m), 5.60-5.59 (1H, m), 4.95-4.93 (1H, m), 4.03-3.95 (2H, m), 3.63-3.32 (2H, m), 2.07-1.77 (5H, m), 0.96 (6H, t, J=6.0 Hz).

IR (KBr) cm^{-1}: 2960, 1690, 1630, 1525, 1450, 1300.

MS (ESI, m/z): 541 $(M+Na)^+$.

HRMS (ESI, m/z): 541.1788 (Calculado para $C_{24}H_{25}F_3N_6NaO_4$: 541.1787).

[Ejemplos de Preparación]

Ejemplo de Preparación 1

Solución para inyección

El 1.5 por ciento en peso del compuesto del Ejemplo 8 se agita en el 10 por ciento por volumen de propilenglicol, seguido por un ajuste hasta un volumen fijo con agua para inyección y esterilización, para obtener una solución para inyección.

Ejemplo de Preparación 2

Cápsula Dura

50 miligramos del compuesto del Ejemplo 12 en forma de polvo, 128.7 miligramos de lactosa, 70 miligramos de celulosa, y 1.3 miligramos de estearato de magnesio, se mezclan y se filtran con un tamiz de malla 60, seguido por el relleno con el polvo de una cápsula de gelatina Número 3 de 250 miligramos, para obtener una cápsula.

Ejemplo de Preparación 3

Tableta

50 miligramos del compuesto del Ejemplo 16 en forma de polvo, 124 miligramos de lactosa, 25 miligramos de celulosa, y 1 miligramo de estearato de magnesio, se mezclan y se forman en tabletas con una máquina formadora de tabletas, para obtener una tableta de 200 miligramos. Esta tableta se puede recubrir con azúcar como sea necesario.

[Ejemplos de Prueba]

(Ejemplo de Prueba 1) Medición de la acción inhibidora en una reacción de γ-glutamil-carboxilación

Se utilizaron células que expresaban Gas6 excretado hacia fuera de las células cuando se sometieron a la γ-glutamil-carboxilación, y se evaluó la acción inhibidora en la reacción de γ-glutamil-carboxilación mediante la medición de la cantidad secretada de Gas6 extracelular mediante el método ELISA.

(A) Preparación para la placa de ensayo que contenía el anticuerpo Gas6 anti-human en fase sólida

El anticuerpo Gas6 de cabra anti-humano (R&D Systems, Inc.) se diluyó hasta 1 microgramo/mililitro con suero regulado con fosfato de Dulbecco, y se dosificaron alícuotas de 40 microlitros del mismo en cada pozo de una microplaca de 384 pozos. Después de inmovilizar el anticuerpo en la fase sólida permitiéndole reposar a 4°C durante la noche o a temperatura ambiente durante 2 horas o más, cada pozo se lavó tres veces con regulador de lavado (Tris-HCl 10 mM, pH de 7.4, cloruro de sodio 150 mM, y Tween 20 al 0.05 por ciento). Después de remover el sobrenadante, se dosificaron alícuotas de 80 microlitros de una solución acuosa al 1 por ciento de Block Ace (Dainippon Sumitomo Pharma) en cada pozo, y se dejaron reaccionar a temperatura ambiente durante 1 hora o más.

(B) Exposición de los compuestos de prueba a células que expresaban establemente el Gas6 humano

Las células que expresaban establemente el Gas6 humano (Gas6-HEK293), las cuales se prepararon insertando el gen Gas6 humano (insertado entre SalI y NotI dentro de múltiples sitios de clonación del vector de expresión pCIneo) en las células HEK293, se

cultivaron y se sub-cultivaron utilizando el medio de Eagle modificado por Dulbecco (DMEM) que contenía el suero fetal de becerro al 10 por ciento (FCS). El día anterior a la medición ELISA, las células Gas6-HEK293 se desprendieron con tripsina-EDTA, se dispersaron en DMEM que contenía suero fetal de becerro al 10 por ciento (FCS), y se diseminaron en cada pozo de una placa recubierta con colágeno tipo I de 384 pozos (Becton-Dickinson) en alícuotas de 30 microlitros que contenían 1.0 x 10^4 células cada una, seguido por un cultivo durante 3 a 4 horas con CO_2 al 5 por ciento y a 37°C. A cada pozo se le agregaron alícuotas de 30 microlitros de DMEM que contenía las soluciones de los compuestos de prueba, preparadas en diferentes concentraciones mediante su disolución en sulfóxido de dimetilo, y vitamina K_2 al 0.1 por ciento y 100 nM, respectivamente (se indican las concentraciones finales en ambos casos), seguido por un cultivo adicional durante 18 a 20 horas.

(C) Cuantificación del Gas6 γ-glutamil-carboxilado mediante ELISA, y cálculo de las concentraciones inhibidoras del 50 por ciento de la reacción de γ-glutamil-carboxilación

Después de remover una solución acuosa al 1 por ciento de Block Ace a partir de las placas de ensayo preparadas preliminarmente que contenían el anticuerpo Gas6 anti-humano en fase sólida, se recolectó el sobrenadante del cultivo de las células Gas6-HEK293 expuestas a los compuestos de prueba, y se dosificaron alícuotas de 40 microlitros en cada pozo, seguido por permitir la reacción a temperatura ambiente durante 2 horas (paso

1). El sobrenadante del cultivo se removió, y cada pozo se lavó tres veces con regulador de lavado. Posteriormente, se llevó a cabo el mismo procedimiento de lavado entre los pasos 2 y 3 y entre los Pasos 3 y 4. Subsiguientemente, en cada pozo se dosificaron alícuotas de 40 microlitros de anticuerpo de ratón anti-γ-glutamil-carboxilasa humana (American Diagnostica inc.), ajustadas a 0.5 microgramos/mililitro con regulador de inmuno-reacción (Tris-HCl 100 mM, pH de 7.4, Tween 20 al 0.05 por ciento, Block Ace al 0.1 por ciento), y se dejaron reaccionar a temperatura ambiente durante 1 hora (paso 2). En seguida, en cada pozo se dosificaron alícuotas de 40 microlitros de anticuerpo anti-IgG de ratón conjugado con fosfatasa alcalina, ajustadas a 1.0 microgramos/mililitro con regulador de inmuno-reacción, y se dejaron reaccionar a temperatura ambiente durante 1 hora (paso 3). En cada pozo se dosificaron alícuotas de 40 microlitros de BluePhos Microwell (KPL), y después de incubar a temperatura ambiente durante 10 minutos (paso 4), se agregaron alícuotas de 20 microlitros de EDTA al 5 por ciento a cada pozo para detener la reacción de desarrollo de color, seguido por la medición de la absorbencia a 620 nanómetros (paso 5). El índice de inhibición de la reacción de γ-glutamil-carboxilación de cada compuesto de prueba se calculó asignando un valor del 100 por ciento para la reacción de γ-glutamil-carboxilación, a la absorbencia de los pozos en donde las células solamente se expusieron a vitamina K_2 y sulfóxido de dimetilo en ausencia del compuesto de prueba, y asignando un valor del 0 por ciento para la reacción de γ-

glutamil-carboxilación, a la absorbencia de los pozos en donde las células se expusieron a warfarina 10 μM en ausencia de vitamina K_2. Los valores de la concentración inhibidora del 50 por ciento (IC_{50}) para la reacción de γ-glutamil-carboxilación se calcularon a partir de los índices de inhibición de la reacción de γ-glutamil-carboxilación de los compuestos de prueba en cada concentración.

Los resultados se muestran en la Tabla 1.

(Tabla 1)

Número de Ejemplo del Compuesto de Prueba	**IC_{50} (nM)**
Ejemplo 1	8.4
Ejemplo 2	6.6
Ejemplo 3	3.5
Ejemplo 4	4.7
Ejemplo 6	74
Ejemplo 7	1.7
Ejemplo 8	1.8
Ejemplo 9	<0.6
Ejemplo 10	<0.6

Número de Ejemplo del Compuesto de Prueba	IC_{50} (nM)
Ejemplo 11	6.5
Ejemplo 12	4.2
Ejemplo 13	5.8
Ejemplo 14	25
Ejemplo 15	18
Ejemplo 16	7.0
Ejemplo 18	2.9
Ejemplo 19	4.7
Ejemplo 21	0.89
Ejemplo 23	<0.6
Ejemplo 29	7.2
Ejemplo 30	1.7
Ejemplo 34	12
Ejemplo 35	<0.6
Ejemplo 36	1.8

Número de Ejemplo del Compuesto de Prueba	IC_{50} (nM)
Ejemplo 37	5.4
Ejemplo 45	1.3
Ejemplo 49	4.3
Ejemplo 61	5.1
Ejemplo 62	3.6
Ejemplo 65	20
Ejemplo 67	0.75
Ejemplo 69	3.4
Ejemplo 74	5.5
Ejemplo 80	7.1
Ejemplo 81	4.6
Ejemplo 82	4.6
Ejemplo 84	5.5
Ejemplo 86	0.7
Ejemplo 91	3.8

Número de Ejemplo del Compuesto de Prueba	IC_{50} (nM)
Ejemplo 94	2.7
Ejemplo 96	9.6
Ejemplo 97	4.5
Ejemplo 98	3.5
Ejemplo 99	4.9
Ejemplo 100	10.4

(Ejemplo de Prueba 2) Medición de la actividad anti-coagulante *ex vivo*

(A) Dosificación y recolección de muestras de sangre

Las soluciones de dosificación (1 miligramo/mililitro), en donde los compuestos de prueba se disolvieron o se suspendieron en metil-celulosa al 0.5 por ciento (MC), se administraron oralmente a ratas (3 miligramos/kilogramo). 18 horas después de su administración, se muestrearon 0.5 mililitros de sangre (que contenía la solución acuosa de ácido cítrico) a partir de la vena yugular utilizando una jeringa para inyección con 50 microlitros de una solución acuosa de dihidrato de citrato trisódico al 3.13 por ciento (peso/volumen). La sangre citratada se centrifugó durante 10 minutos a 1500 x g para

separar el plasma. También se muestreó sangre de ratas no dosificadas con los compuestos de prueba, y se obtuvo el plasma a partir de la misma para utilizarse como un control.

(B) Medición del tiempo de protrombina y cálculo del índice de prolongación

Se midió el tiempo de protrombina (PT) utilizando un Micro-Coagulómetro Amelung KC-10A (MC Medical), que es un aparato de medición del tiempo de coagulación. Se agregaron 50 microlitros de solución salina a 50 microlitros de plasma, seguido por una incubación preliminar a 37°C durante 1 minuto. La reacción de coagulación se inició mediante la adición de 100 microlitros de Tromboplastina C Plus (Dade Behring), la cual se ajustó a 0.5 Unidades/mililitro mediante su suspensión en agua para inyecciones, seguido por la medición de la protrombina (PT). Los valores de protrombina (PT) de las ratas no dosificadas con los compuestos de prueba se utilizaron como un control, y los índices de prolongación de protrombina (PT) de las ratas dosificadas con los compuestos de prueba se expresaron como un porcentaje.

Los resultados se muestran en la Tabla 2.

(Tabla 2)

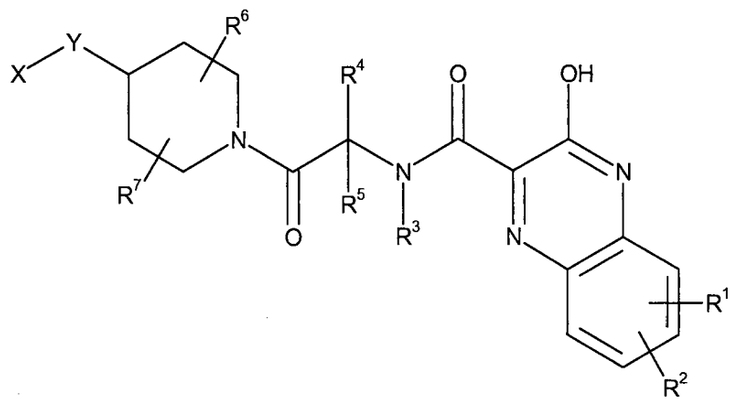
Número de Ejemplo del Compuesto de Prueba	**PT (%)**
Ejemplo 1	731

Número de Ejemplo del Compuesto de Prueba	PT (%)
Ejemplo 3	616
Ejemplo 4	790
Ejemplo 6	557
Ejemplo 7	732
Ejemplo 8	576
Ejemplo 9	751
Ejemplo 10	802
Ejemplo 12	725
Ejemplo 13	580
Ejemplo 15	663
Ejemplo 16	720
Ejemplo 18	709
Ejemplo 21	637
Ejemplo 23	681
Ejemplo 29	707

Número de Ejemplo del Compuesto de Prueba	PT (%)
Ejemplo 36	649
Ejemplo 37	644
Ejemplo 45	609
Ejemplo 49	750
Ejemplo 65	568
Ejemplo 69	798
Ejemplo 74	688
Ejemplo 80	616
Ejemplo 81	706
Ejemplo 86	582
Ejemplo 94	574
Ejemplo 98	623
Ejemplo 99	747

REIVINDICACIONES

1. Un compuesto representado por la fórmula general (i):



en donde:

cada uno de R^1 y R^2 representa independientemente un átomo de hidrógeno, un átomo de halógeno, un grupo ciano, un grupo alquilo de 1 a 4 átomos de carbono, o un grupo alcoxilo de 1 a 4 átomos de carbono,

R^3 representa un átomo de hidrógeno o un grupo alquilo de 1 a 4 átomos de carbono,

cada uno de R^4 y R^5 representa independientemente un átomo de hidrógeno, un átomo de halógeno, un grupo alquilo de 1 a 4 átomos de carbono, un grupo alquenilo de 2 a 4 átomos de carbono, un grupo alquinilo de 2 a 4 átomos de carbono, un grupo cicloalquilo de 3 a 5 átomos de carbono, o un grupo hidroxi-alquilo de 1 a 4 átomos de carbono,

cada uno de R^6 y R^7 representa independientemente un átomo de hidrógeno o un grupo alquilo de 1 a 4 átomos de carbono,

X representa un grupo cicloalquilo de 3 a 10 átomos de carbono monocíclico o bicíclico, un grupo arilo de 6 a 10 átomos de carbono monocíclico o bicíclico, o un grupo heterocíclico de 5 a 10 miembros monocíclico o bicíclico (en donde el grupo heterocíclico incluye heterociclos aromáticos y heterociclos no aromáticos, y contiene de 1 a 3 átomos seleccionados a partir del grupo que consiste en un átomo de nitrógeno, un átomo de azufre, y un átomo de oxígeno), el cual puede estar sustituido con 1 a 3 sustituyentes seleccionados a partir del grupo sustituyente α,

Y representa -CHRa-, -C(OH)Ra-, -CO-, -O-, -NRa-, -S-, -SO- o $-SO_2-$,

Ra representa un átomo de hidrógeno, un grupo alquilo de 1 a 4 átomos de carbono, un grupo halo-alquilo de 1 a 4 átomos de carbono, o un grupo alcanoílo de 1 a 4 átomos de carbono, o

en el caso en donde Ra en Y es un grupo alquilo de 1 a 4 átomos de carbono, un grupo halo-alquilo de 1 a 4 átomos de carbono, o un grupo alcanoílo de 1 a 4 átomos de carbono, Ra puede formar un anillo de 5 ó 6 miembros mediante su enlace con un átomo que sea un componente de X,

el grupo sustituyente α representa:

un átomo de halógeno, un grupo ciano, un grupo nitro, un grupo hidroxilo;

un grupo alquilo de 1 a 4 átomos de carbono, un grupo alquenilo de 2 a 4 átomos de carbono, un grupo alquinilo de 2 a 4 átomos de carbono, un grupo cicloalquilo de 3 a 6 átomos de

carbono, un grupo alcoxilo de 1 a 4 átomos de carbono, o un grupo cicloalcoxilo de 3 a 6 átomos de carbono, el cual puede estar sustituido con sustituyente(s) seleccionado(s) a partir del grupo sustituyente ß;

-OCORb, -CORb, -COORb, -CONRbRc, -NRbRc, -NRbCORc, -NRbSORc, -$NRbSO_2Rc$, -SRb, -SORb, -SO_2Rb;

un grupo fenilo, y

un grupo heterocíclico de 5 ó 6 miembros, el cual puede estar sustituido con un grupo alquilo de 1 a 4 átomos de carbono (en donde el grupo heterocíclico incluye heterociclos aromáticos y heterociclos no aromáticos, y contiene de 1 a 3 átomos seleccionados a partir del grupo que consiste en un átomo de nitrógeno, un átomo de azufre, y un átomo de oxígeno),

cada uno de Rb y Rc representa independientemente un átomo de hidrógeno, un grupo alquilo de 1 a 4 átomos de carbono o un grupo halo-alquilo de 1 a 4 átomos de carbono, y

el grupo sustituyente ß representa un átomo de halógeno, un grupo hidroxilo, un grupo alcoxilo de 1 a 4 átomos de carbono, y un grupo alcanoiloxilo de 1 a 4 átomos de carbono,

o una sal farmacológicamente aceptable del mismo.

2. Un compuesto o una sal farmacológicamente aceptable del mismo, de acuerdo con la reivindicación 1, en donde cada uno de R^1 y R^2 representa independientemente un átomo de hidrógeno o un átomo de halógeno.

3. Un compuesto o una sal farmacológicamente aceptable

del mismo, de acuerdo con la reivindicación 1, en donde cada uno de R^1 y R^2 representa independientemente un átomo de hidrógeno o un átomo de flúor.

4. Un compuesto o una sal farmacológicamente aceptable del mismo, de acuerdo con la reivindicación 1, en donde R^1 y R^2 representan ambos un átomo de hidrógeno.

5. Un compuesto o una sal farmacológicamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 4, en donde R^3 representa un átomo de hidrógeno o un grupo metilo.

6. Un compuesto o una sal farmacológicamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 4, en donde R^3 representa un átomo de hidrógeno.

7. Un compuesto o una sal farmacológicamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 6, en donde R^4 representa un átomo de hidrógeno, un átomo de flúor, un grupo alquilo de 1 a 4 átomos de carbono, un grupo alquenilo de 2 a 4 átomos de carbono, un grupo alquinilo de 2 a 4 átomos de carbono, un grupo cicloalquilo de 3 a 5 átomos de carbono, o un grupo hidroxi-alquilo de 1 a 4 átomos de carbono, y R^5 representa un átomo de hidrógeno.

8. Un compuesto o una sal farmacológicamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 6, en donde R^4 representa un grupo metilo, un grupo etilo, un grupo isopropilo, un grupo isobutilo, un grupo terbutilo, un grupo ciclopropilo, o un grupo 1-hidroxi-1-metil-etilo, y R^5 representa un

átomo de hidrógeno.

9. Un compuesto o una sal farmacológicamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 6, en donde R^4 representa un grupo metilo, un grupo etilo, un grupo isopropilo, un grupo terbutilo, un grupo ciclopropilo, o un grupo 1-hidroxi-1-metil-etilo, y R^5 representa un átomo de hidrógeno.

10. Un compuesto o una sal farmacológicamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 6, en donde R^4 representa un grupo etilo, un grupo isopropilo, un grupo ciclopropilo, o un grupo 1-hidroxi-1-metil-etilo, y R^5 representa un átomo de hidrógeno.

11. Un compuesto o una sal farmacológicamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 6, en donde cada uno de R^4 y R^5 representa independientemente un átomo de hidrógeno, un átomo de halógeno, un grupo alquilo de 1 a 4 átomos de carbono, un grupo alquenilo de 2 a 4 átomos de carbono, un grupo alquinilo de 2 a 4 átomos de carbono, o un grupo cicloalquilo de 3 a 5 átomos de carbono.

12. Un compuesto o una sal farmacológicamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 6, en donde R^4 representa un átomo de hidrógeno, un grupo metilo, un grupo etilo, un grupo isopropilo, un grupo isobutilo, un grupo terbutilo o un grupo ciclopropilo, y R^5 representa un átomo de hidrógeno.

13. Un compuesto o una sal farmacológicamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 12,

en donde cada uno de R^6 y R^7 representa independientemente un átomo de hidrógeno o un grupo metilo.

14. Un compuesto o una sal farmacológicamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 12, en donde R^6 y R^7 representan ambos un átomo de hidrógeno.

15. Un compuesto o una sal farmacológicamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 14, en donde X representa un grupo fenilo, un grupo naftilo, un grupo piridilo, un grupo piridazinilo, un grupo pirimidinilo, un grupo pirazinilo, un grupo quinolilo, un grupo isoquinolilo, un grupo bencimidazolilo, un grupo benzoxazolilo, o un grupo benzotiazolilo, el cual puede estar sustituido con 1 ó 2 sustituyentes seleccionados a partir del grupo sustituyente α, y

el grupo sustituyente α representa un átomo de halógeno, un grupo ciano, un grupo nitro, un grupo hidroxilo, un grupo metilo, un grupo etilo, un grupo propilo, un grupo isopropilo, un grupo terbutilo, un grupo hidroxi-metilo, un grupo fluoro-metilo, un grupo difluoro-metilo, un grupo trifluoro-metilo, un grupo metoxilo, un grupo etoxilo, un grupo propoxilo, un grupo isopropoxilo, un grupo acetoxilo, un grupo trifluoro-metoxilo, un grupo acetilo, un grupo metoxi-carbonilo, un grupo etoxi-carbonilo, un grupo dimetil-carbamoílo, un grupo piperidilo, un grupo pirrolidilo, un grupo morfolino, un grupo pirazolilo, un grupo metil-pirazolilo, un grupo oxadiazolilo, un grupo metil-oxadiazolilo, un grupo fenilo, y un grupo piridilo.

16. Un compuesto o una sal farmacológicamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 14, en donde X representa un grupo fenilo, un grupo naftilo, un grupo piridilo, un grupo piridazinilo, un grupo pirimidinilo, un grupo pirazinilo, un grupo quinolilo, o un grupo isoquinolilo, el cual puede estar sustituido con 1 ó 2 sustituyentes seleccionados a partir del grupo sustituyente α, y

el grupo sustituyente α representa un átomo de flúor, un átomo de cloro, un átomo de bromo, un grupo ciano, un grupo hidroxilo, un grupo metilo, un grupo etilo, un grupo propilo, un grupo isopropilo, un grupo terbutilo, un grupo hidroxi-metilo, un grupo fluoro-metilo, un grupo difluoro-metilo, un grupo trifluoro-metilo, un grupo metoxilo, un grupo etoxilo, un grupo propoxilo, un grupo isopropoxilo, un grupo trifluoro-metoxilo, un grupo piperidilo, un grupo pirrolidilo, un grupo fenilo, y un grupo piridilo.

17. Un compuesto o una sal farmacológicamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 14, en donde X representa un grupo fenilo, un grupo 2-piridilo, un grupo 3-piridilo, un grupo 3-piridazinilo, un grupo 2-pirimidinilo, o un grupo 5-pirimidinilo, el cual puede estar sustituido con 1 ó 2 sustituyentes seleccionados a partir del grupo sustituyente α, y

el grupo sustituyente α representa un átomo de flúor, un átomo de cloro, un átomo de bromo, un grupo ciano, un grupo hidroxilo, un grupo metilo, un grupo etilo, un grupo terbutilo, un grupo trifluoro-metilo, un grupo metoxilo, un grupo etoxilo, un grupo

trifluoro-metoxilo, un grupo fenilo, y un grupo piridilo.

18. Un compuesto o una sal farmacológicamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 14, en donde X representa un grupo fenilo o un grupo 2-piridilo, el cual puede estar sustituido con 1 ó 2 sustituyentes seleccionados a partir del grupo sustituyente α, y

el grupo sustituyente α representa un átomo de flúor, un átomo de cloro, un grupo trifluoro-metilo, un grupo metoxilo, y un grupo trifluoro-metoxilo.

19. Un compuesto o una sal farmacológicamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 14, en donde X representa 4-fluoro-fenilo, 2,4-difluoro-fenilo, 3,4-difluoro-fenilo, 4-cloro-fenilo, 2,4-dicloro-fenilo, 4-trifluoro-metil-fenilo, 4-trifluoro-metoxi-fenilo, 5-fluoro-piridin-2-ilo, 5-cloro-piridin-2-ilo, 5-trifluoro-metil-piridin-2-ilo o 6-metoxi-piridin-3-ilo.

20. Un compuesto o una sal farmacológicamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 14, en donde X representa un grupo fenilo, un grupo naftilo, un grupo piridilo, un grupo piridazinilo, un grupo pirimidinilo, un grupo pirazinilo, un grupo quinolilo, o un grupo isoquinolilo, el cual puede estar sustituido con 1 ó 2 sustituyentes seleccionados a partir del grupo sustituyente α, y

el grupo sustituyente α representa un átomo de flúor, un átomo de cloro, un átomo de bromo, un grupo ciano, un grupo hidroxilo, un grupo metilo, un grupo etilo, un grupo propilo, un grupo

isopropilo, un grupo terbutilo, un grupo hidroxi-metilo, un grupo fluoro-metilo, un grupo difluoro-metilo, un grupo trifluoro-metilo, un grupo metoxilo, un grupo etoxilo, un grupo propoxilo, un grupo isopropoxilo, un grupo trifluoro-metoxilo, un grupo fenilo, y un grupo piridilo.

21. Un compuesto o una sal farmacológicamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 14, en donde X representa un grupo fenilo, un grupo naftilo, un grupo piridilo, un grupo piridazinilo, o un grupo pirimidinilo, el cual puede estar sustituido con 1 ó 2 sustituyentes seleccionados a partir del grupo sustituyente α, y

el grupo sustituyente α representa un átomo de flúor, un átomo de cloro, un átomo de bromo, un grupo ciano, un grupo hidroxilo, un grupo metilo, un grupo trifluoro-metilo, un grupo metoxilo, un grupo trifluoro-metoxilo y un grupo fenilo.

22. Un compuesto o una sal farmacológicamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 14, en donde X representa un grupo fenilo o un grupo piridilo, el cual puede estar sustituido con 1 ó 2 sustituyentes seleccionados a partir del grupo sustituyente α, y

el grupo sustituyente α representa un átomo de flúor, un átomo de cloro, un grupo ciano, un grupo trifluoro-metilo, y un grupo trifluoro-metoxilo.

23. Un compuesto o una sal farmacológicamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 22,

en donde Y representa -CO-, -O- o -NRa-, Ra representa un átomo de hidrógeno, un grupo metilo, o un grupo etilo, y Ra puede formar un anillo de 5 miembros mediante su enlace con un átomo que sea un componente de X en el caso en donde Ra sea un grupo etilo en Y.

24. Un compuesto o una sal farmacológicamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 22, en donde Y representa -O- o -NRa-, y Ra representa un átomo de hidrógeno, un grupo metilo o un grupo etilo.

25. Un compuesto o una sal farmacológicamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 22, en donde Y representa -O-.

26. Un compuesto o una sal farmacológicamente aceptable del mismo, de acuerdo con la reivindicación 1, el cual se selecciona a partir del los siguientes:

N-{(1S)-2-[4-(2-fluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(3-fluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(4-fluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(4-cloro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-[(1S)-1-metil-2-oxo-2-{4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-etil]-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(4-ciano-fenoxi)-piperidin-1-il]-1-metil-2-oxo-

etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2-{4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-1-metil-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2-{4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-1-metil-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-[(1S)-1-metil-2-oxo-2-(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-etil]-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(2-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(3-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-cloro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-[(1S)-1-({4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-ciano-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-{(1S)-1-[(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(2-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(3-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-cloro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-[(1S)-2-metil-1-({4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-ciano-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-

carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-{(1S)-2-metil-1-[(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida,

3-hidroxi-N-[(1S)-1-({4-[(6-metoxi-piridin-3-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(2,4-difluoro-benzoil)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(2,4-difluoro-fenil)-(hidroxi)-metil]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-hidroxi-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-1-ciclopropil-2-[4-(2-fluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-1-ciclopropil-2-[4-(3-fluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-1-ciclopropil-2-[4-(4-fluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(4-cloro-fenoxi)-piperidin-1-il]-1-ciclopropil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-ciclopropil-2-oxo-2-{4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-etil]-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(4-ciano-fenoxi)-piperidin-1-il]-1-ciclopropil-

2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-1-ciclopropil-2-[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-1-ciclopropil-2-[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-ciclopropil-2-{4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2-{4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-1-ciclopropil-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-ciclopropil-2-oxo-2-(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-etil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2,2-dimetil-1-{[4-(2-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2,2-dimetil-1-{[4-(3-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2,2-dimetil-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-cloro-fenoxi)-piperidin-1-il]-carbonil}-2,2-dimetil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2,2-dimetil-1-({4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-carbonil)-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-ciano-fenoxi)-piperidin-1-il]-carbonil}-2,2-dimetil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-

2,2-dimetil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-2,2-dimetil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2,2-dimetil-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2,2-dimetil-propil]-3-hidroxi-quinoxalin-2-carboxamida, y

N-{(1S)-2,2-dimetil-1-[(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-3-hidroxi-quinoxalin-2-carboxamida.

27. Un compuesto o una sal farmacológicamente aceptable del mismo, de acuerdo con la reivindicación 1, el cual se selecciona a partir del los siguientes:

N-{(1S)-2-[4-(2-fluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(3-fluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(4-fluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(4-cloro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-[(1S)-1-metil-2-oxo-2-{4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-etil]-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(4-ciano-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2-{4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-1-metil-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2-{4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-1-metil-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-[(1S)-1-metil-2-oxo-2-(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-etil]-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(2-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(3-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-cloro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-[(1S)-1-({4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-ciano-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-

propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-{(1S)-1-[(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(2-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(3-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-cloro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-[(1S)-2-metil-1-({4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-ciano-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-{(1S)-2-metil-1-[(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida,

N-{(1S)-1-ciclopropil-2-[4-(2-fluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-1-ciclopropil-2-[4-(3-fluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-1-ciclopropil-2-[4-(4-fluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(4-cloro-fenoxi)-piperidin-1-il]-1-ciclopropil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-ciclopropil-2-oxo-2-{4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-etil]-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(4-ciano-fenoxi)-piperidin-1-il]-1-ciclopropil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-1-ciclopropil-2-[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-1-ciclopropil-2-[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-ciclopropil-2-{4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2-{4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-1-ciclopropil-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-ciclopropil-2-oxo-2-(4-{[5-(trifluoro-metil)-

piridin-2-il]-oxi}-piperidin-1-il)-etil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2,2-dimetil-1-{[4-(2-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2,2-dimetil-1-{[4-(3-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2,2-dimetil-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-cloro-fenoxi)-piperidin-1-il]-carbonil}-2,2-dimetil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2,2-dimetil-1-({4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-carbonil)-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-ciano-fenoxi)-piperidin-1-il]-carbonil}-2,2-dimetil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-2,2-dimetil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-carbonil}-2,2-dimetil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2,2-dimetil-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2,2-dimetil-propil]-3-hidroxi-quinoxalin-2-carboxamida, y

N-{(1S)-2,2-dimetil-1-[(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-3-hidroxi-quinoxalin-2-carboxamida.

28. Un compuesto o una sal farmacológicamente aceptable del mismo, de acuerdo con la reivindicación 1, el cual se selecciona a partir del los siguientes:

N-{(1S)-2-[4-(4-cloro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(2,4-difluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-{(1S)-2-[4-(3,4-difluoro-fenoxi)-piperidin-1-il]-1-metil-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2-{4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-1-metil-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-2-{4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-1-metil-2-oxo-etil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-[(1S)-1-metil-2-oxo-2-(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-etil]-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-cloro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-propil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-{(1S)-1-[(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida,

N-[(1S)-1-{[4-(4-fluoro-fenoxi)-piperidin-1-il]-carbonil}-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-[(1S)-2-metil-1-({4-[4-(trifluoro-metoxi)-fenoxi]-piperidin-1-il}-carbonil)-propil]-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-fluoro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

N-[(1S)-1-({4-[(5-cloro-piridin-2-il)-oxi]-piperidin-1-il}-carbonil)-2-metil-propil]-3-hidroxi-quinoxalin-2-carboxamida,

3-hidroxi-N-{(1S)-2-metil-1-[(4-{[5-(trifluoro-metil)-piridin-2-il]-oxi}-piperidin-1-il)-carbonil]-propil}-quinoxalin-2-carboxamida, y

N-{(1S)-1-ciclopropil-2-[4-(4-fluoro-fenoxi)-piperidin-1-il]-2-oxo-etil}-3-hidroxi-quinoxalin-2-carboxamida.

29. Una composición farmacéutica, la cual comprende, como un ingrediente activo, un compuesto o una sal farmacológicamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 28.

30. Una composición farmacéutica para prevenir y/o tratar un trastorno de la coagulación sanguínea, el cual comprende, como un ingrediente activo, un compuesto o una sal farmacológicamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 28.

31. Una composición farmacéutica para prevenir y/o tratar tromboembolismo, deficiencia congénita del factor anticoagulante, o anormalidad de plasminógeno, la cual comprende, como un ingrediente activo, un compuesto o una sal farmacológicamente

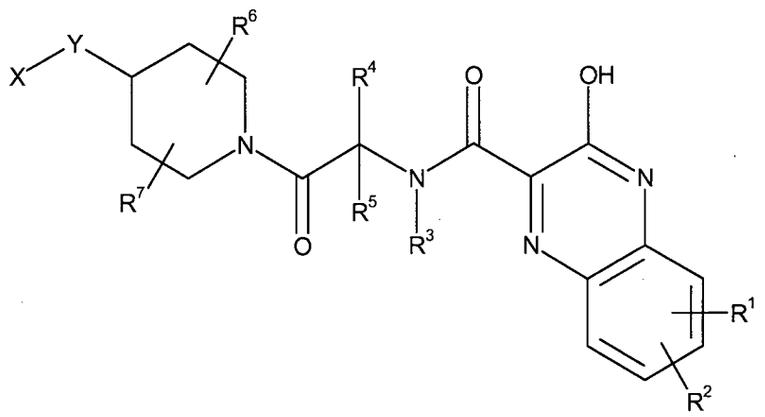
aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 28.

32. Una composición farmacéutica para prevenir trombogénesis en seguida de cirugía de reemplazo de válvula artificial, o trombogénesis causada por fibrilación auricular no valvular, o fibrilación auricular que acompaña a cardiopatía valvular, la cual comprende, como un ingrediente activo, un compuesto o una sal farmacológicamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 28.

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RESUMEN

La presente invención proporciona un derivado de hidroxi-quinoxalin-carboxamida novedoso que es útil para prevenir y/o tratar los trastornos de la coagulación sanguínea. Un compuesto representado por la fórmula (i), o una sal farmacológicamente aceptable del mismo:



en donde cada uno de R^1 y R^2 representa independientemente un grupo tal como un átomo de hidrógeno o un átomo de halógeno; R^3 representa un grupo tal como un átomo de hidrógeno; cada uno de R^4 y R^5 representa independientemente un grupo tal como un átomo de hidrógeno, un átomo de halógeno, o un grupo alquilo de 1 a 4 átomos de carbono; cada uno de R^6 y R^7 representa independientemente un átomo de hidrógeno o un grupo alquilo de 1 a 4 átomos de carbono; X representa un grupo tal como un grupo cicloalquilo de 3 a 10 átomos de carbono, un grupo arilo de 6 a 10

átomos de carbono, o un grupo heterocíclico de 5 a 10 miembros, el cual puede estar sustituido con los sustituyentes seleccionados a partir del grupo de sustituyentes α; Y representa un grupo tal como -CO-, -O- o -NRa-, y Ra representa un grupo tal como un átomo de hidrógeno o un grupo alquilo de 1 a 4 átomos de carbono.

* * * * *

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

(21) N° de solicitud:

22) Fecha de solicitud:

(30) Prioridad (31) ***Prioridad*** (32) ***Fecha*** (33) ***País***
2008-079919 **26/03/2008** **JP**
2008-332106 **26/12/2008** **JP**

(51) Int Cl: **C07D 401/012**

(71)Solicitante(s) **DAIICHI SANKYO CAMPANY, LIMITED**

(72) Inventor(es) **KAYOKO MOTOKI**
Y OTROS

(74) Apoderado: **LUZ CLEMENCIA DE PAEZ**

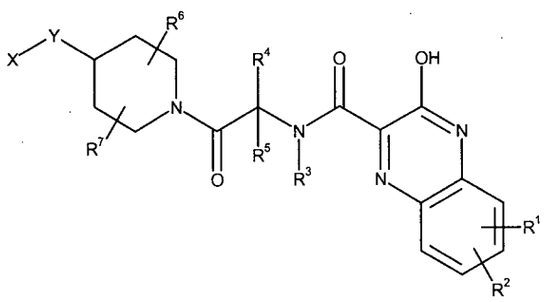
(85) Fecha limite inicio fase nacional: 26/10/2010
(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 24/03/2009
No. de solicitud PCT/JP2009/055741

(87) Publicación internacional
Fecha: 01/10/2009
N° publicación: ***WO 2009/119537 A1***

(54) Titulo: **DERIVADO DE HIDROXI-QUINOXALIN-CARBOXAMIDA**

Reivindicación(es):

1. Un compuesto representado por la fórmula general (i):



en donde:

cada uno de R^1 y R^2 representa independientemente un átomo de hidrógeno, un átomo de halógeno, un grupo ciano, un grupo alquilo de 1 a 4 átomos de carbono, o un grupo alcoxilo de 1 a 4 átomos de carbono,

R^3 representa un átomo de hidrógeno o un grupo alquilo de 1 a 4 átomos de carbono,

cada uno de R^4 y R^5 representa independientemente un átomo de hidrógeno, un átomo de halógeno, un grupo alquilo de 1 a 4 átomos de carbono, un grupo alquenilo de 2 a 4 átomos de carbono, un grupo alquinilo de 2 a 4 átomos de carbono, un grupo cicloalquilo de 3 a 5 átomos de carbono, o un grupo hidroxi-alquilo de 1 a 4 átomos de carbono,

cada uno de R^6 y R^7 representa independientemente un átomo de hidrógeno o un grupo alquilo de 1 a 4 átomos de carbono,

X representa un grupo cicloalquilo de 3 a 10 átomos de carbono monocíclico o bicíclico, un grupo arilo de 6 a 10 átomos de carbono monocíclico o bicíclico, o un grupo heterocíclico de 5 a 10 miembros monocíclico o bicíclico (en donde el grupo heterocíclico incluye heterociclos aromáticos y heterociclos no aromáticos, y contiene de 1 a 3 átomos seleccionados a partir del grupo que consiste en un átomo de nitrógeno, un átomo de azufre, y un átomo de oxígeno), el cual puede estar sustituido con 1 a 3 sustituyentes seleccionados a partir del grupo sustituyente α,

Y representa -CHRa-, -C(OH)Ra-, -CO-, -O-, -NRa-, -S-, -SO- o $-SO_2-$,

Ra representa un átomo de hidrógeno, un grupo alquilo de 1 a 4 átomos de carbono, un grupo halo-alquilo de 1 a 4 átomos de carbono, o un grupo alcanoílo de 1 a 4 átomos de carbono, o

en el caso en donde Ra en Y es un grupo alquilo de 1 a 4 átomos de carbono, un grupo halo-alquilo de 1 a 4 átomos de carbono, o un grupo alcanoílo de 1 a 4 átomos de carbono, Ra puede formar un anillo de 5 ó 6 miembros mediante su enlace con un átomo que sea un componente de X,

el grupo sustituyente α representa:

un átomo de halógeno, un grupo ciano, un grupo nitro, un grupo hidroxilo;

un grupo alquilo de 1 a 4 átomos de carbono, un grupo alquenilo de 2 a 4 átomos de carbono, un grupo alquinilo de 2 a 4 átomos de carbono, un grupo cicloalquilo de 3 a 6 átomos de carbono, un grupo alcoxilo de 1 a 4 átomos de carbono, o un grupo cicloalcoxilo de 3 a 6 átomos de carbono, el cual puede estar sustituido con sustituyente(s) seleccionado(s) a partir del grupo sustituyente β;

-OCORb, -CORb, -COORb, -CONRbRc, -NRbRc, -NRbCORc, -NRbSORc, $-NRbSO_2Rc$, -SRb, -SORb, $-SO_2Rb$;

un grupo fenilo, y

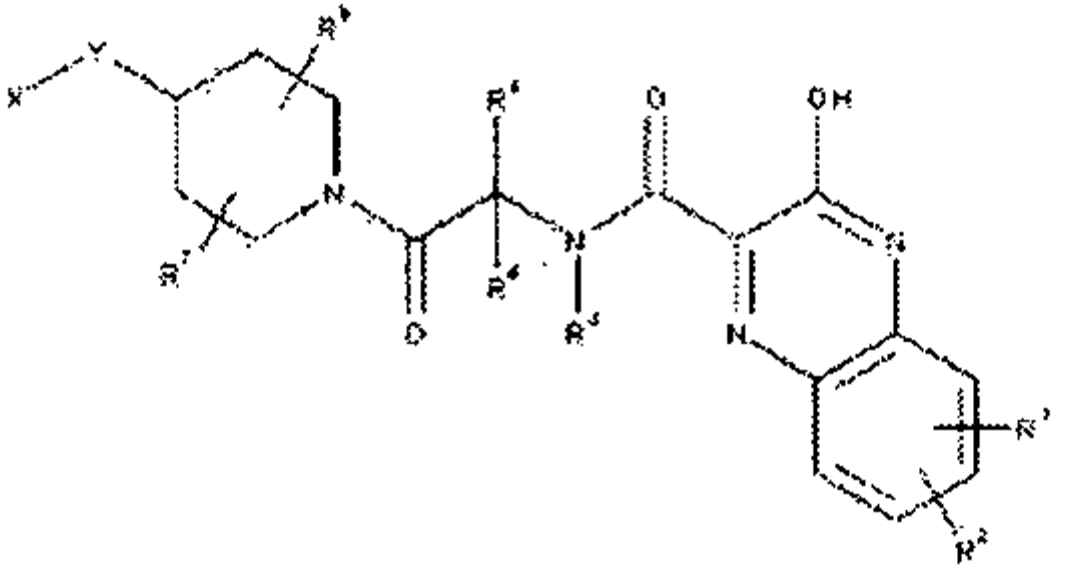
un grupo heterocíclico de 5 ó 6 miembros, el cual puede estar sustituido con un grupo alquilo de 1 a 4 átomos de carbono (en donde el grupo heterocíclico incluye heterociclos aromáticos y heterociclos no aromáticos, y contiene de 1 a 3 átomos seleccionados a partir del grupo que consiste en un átomo de nitrógeno, un átomo de azufre, y un átomo de oxígeno),

cada uno de Rb y Rc representa independientemente un átomo de hidrógeno, un grupo alquilo de 1 a 4 átomos de carbono o un grupo halo-alquilo de 1 a 4 átomos de carbono, y

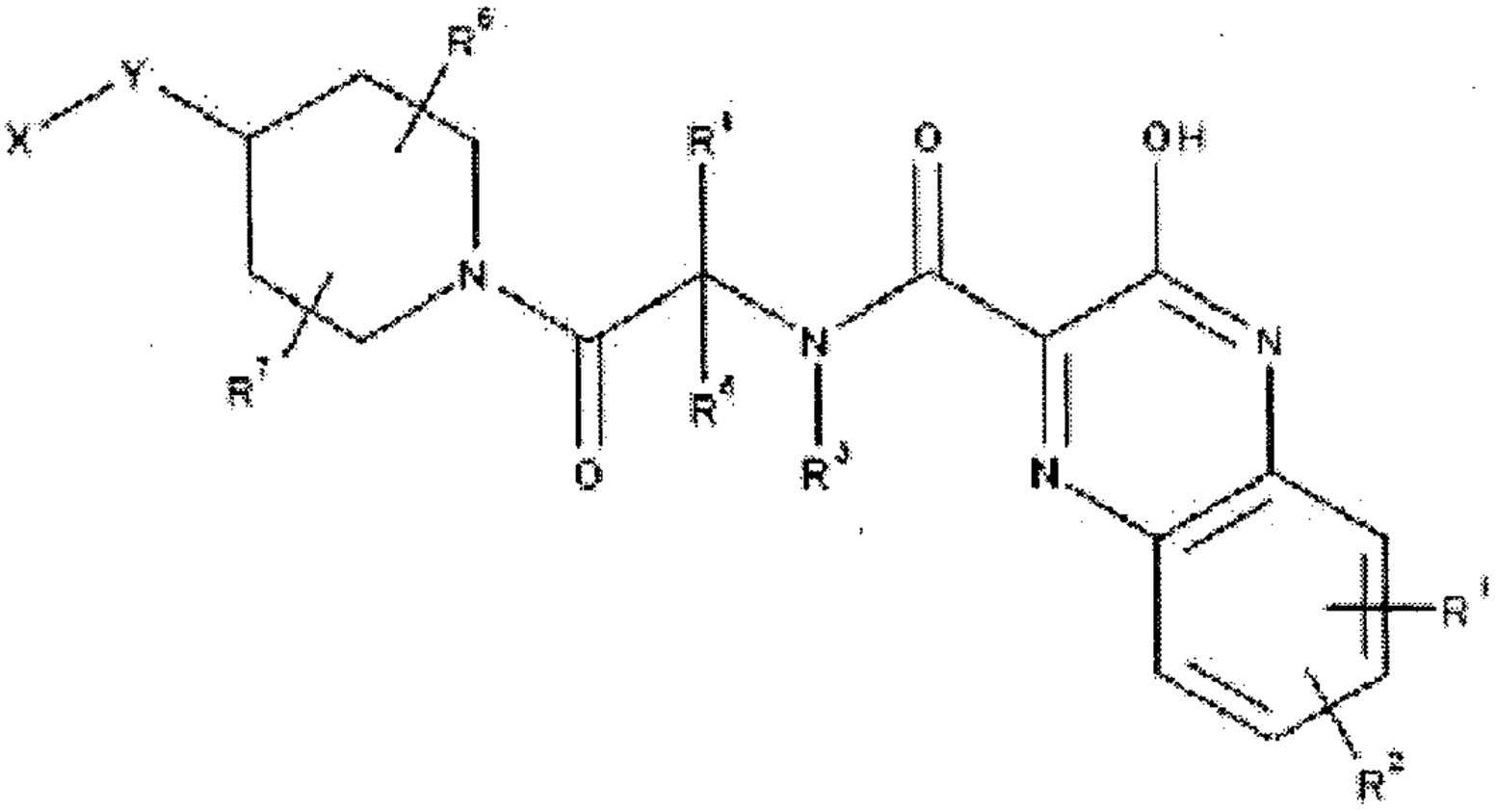
el grupo sustituyente β representa un átomo de halógeno, un grupo hidroxilo, un grupo alcoxilo de 1 a 4 átomos de carbono, y un grupo alcanoiloxilo de 1 a 4 átomos de carbono,

o una sal farmacológicamente aceptable del mismo.

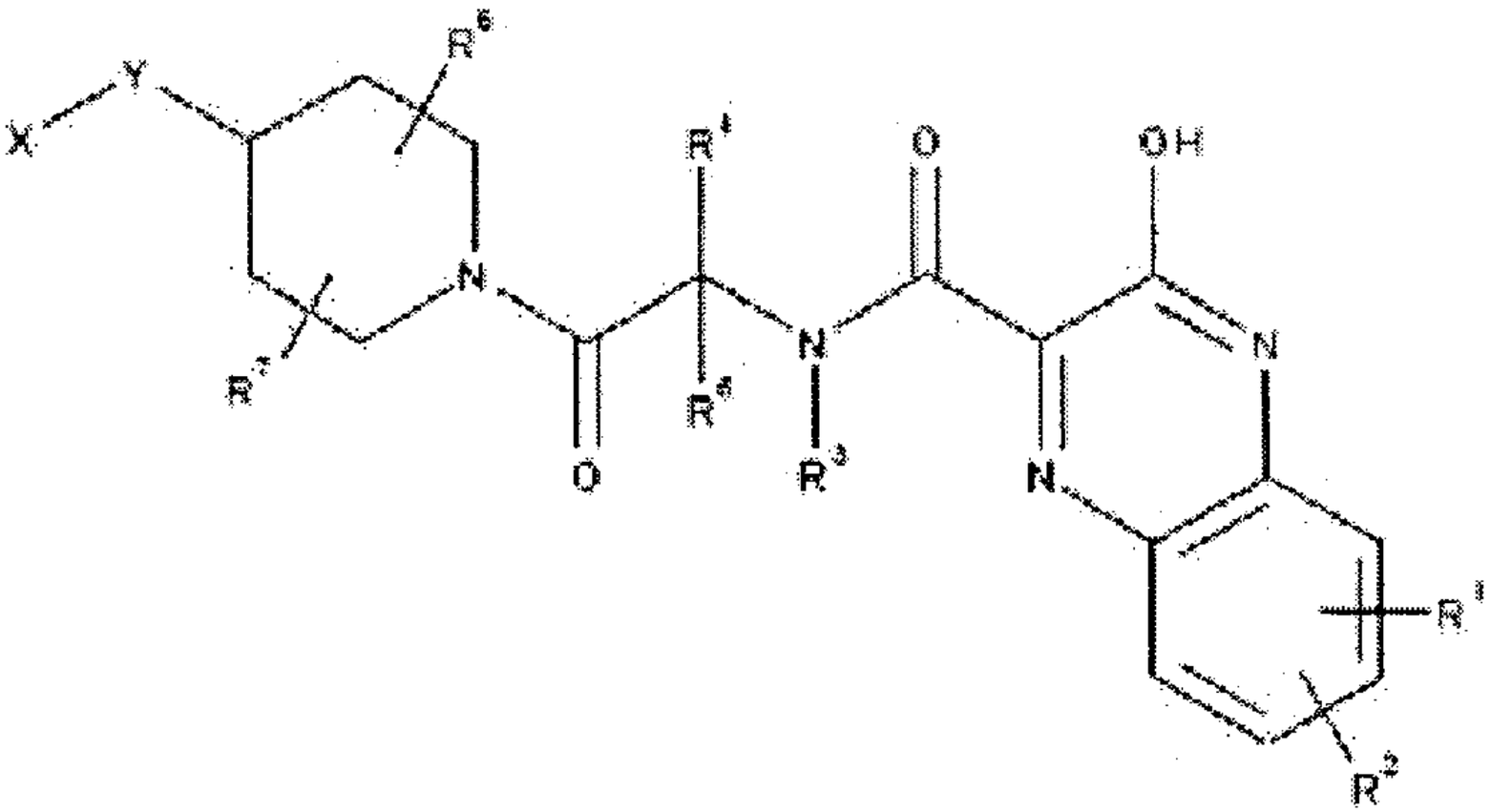
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615

NIT : 80017

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-132362- -00000-0000

Fecha: 2010-10-26 10:31:28 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 619

RECIBO OFICIAL DE CAJA : 10 - 87,900
FECHA : OCTUBRE 20 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	146325060	19/10/2010	84,872,000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	21	CERTIFICACIONES	13,000.00
			TOTAL : $	13,000.00

SON: TRECE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL ASUNTO No.

COLO: 15869-841-824-4

616

NIT : 800176089-7

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RECIBO OFICIAL DE CAJA : 10 - 87,905
FECHA : OCTUBRE 20 DE 2010

No. 10-132362- -00000-0000
Fecha: 2010-10-26 10:31:28 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 619

***** 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	146325060	19/10/2010	84,872,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	*** REIVINDICACION UNITARIA ADICIONAL	26,000.00
		TOTAL : $	26,000.00

SON: VEINTISEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL ASUNTO No.

COLO: 15869-841-024-4

617

NIT : 8C SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-132362- -00000-0000

Fecha: 2010-10-26 10:31:28 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 619

RECIBO OFICIAL DE CAJA : 10 - 87,906
FECHA : OCTUBRE 20 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	146325060	19/10/2010	84,872,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	*** REIVINDICACION UNITARIA ADICIONAL	26,000.00
		TOTAL : $	26,000.00

SON: VEINTISEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL ASUNTO No.

COLO: 15869-841-024-4

618

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-132362- -00000-0000

Fecha: 2010-10-26 10:31:28 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 619

RECIBO OFICIAL DE CAJA : 10 - 87,932
FECHA : OCTUBRE 20 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	146325060	19/10/2010	84,872,000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	82	INVOCACION DE UNA PRIORIDAD EN NU	155,000.00
			TOTAL : $	155,000.00

SON: CIENTO CINCUENTA Y CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

COLO: 15869 - 84-024-4

619

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RECIBO OFICIAL DE CAJA : 10 - 88,078
FECHA : OCTUBRE 20 DE 2010

No. 10-132362- -00000-0000
Fecha: 2010-10-26 10:31:28 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 619

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	146325060	19/10/2010	84,872,000.00

C O N C E P T O

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	### TASA ANUAL A#OS 17 a 20 PARA MANT	907,000.00

##########

TOTAL : $ 907,000.00

SON: NOVECIENTOS SIETE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

CO10:15869-841-024-4

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-132362- -00000-0000
Fecha: 2010-10-26 10:31:28 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 619

PATENTE DE INVENCIÓN ☐ MODELO DE UTILIDAD ☐ Art 35 Decis...

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☐ MODELO DE UTILIDAD PCT ☐ Art.33 Decisión 486/00, Circular Única

- ☐ Indicación que se solicita una PCT
- ☐ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☐ Incompleta ☐

DISEÑO INDUSTRIAL ☐ (Art. 119 Decisión 486/00)

- ☐ Indicación que se solicita Diseño industrial
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ (Art. 92 Decisión 486/00)

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
SUAREZ DE PAEZ LUZ CLEMENCIA
Apoderado(a) y/o Representante de
DAIICHI SANKYO COMPANY LIMITED

REFERENCIA	Radicación No.	10 132362
	Solicitud internacional	pct/jp2009/055741
	Fecha inicio fase nacional	26/10/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	№ 14743

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 12 NOV. 2010
adpa11